



## “Parkinson Disease, Movement Disorders and Dementia”<sup>☆,☆☆</sup>

### SESSION 1 “Connectivity and synaptic plasticity: the contribution of neurophysiology and neuroimaging”

#### L1

#### Exploration of the cortical connectivity by means of transcranial magnetic stimulation

*Antonio Suppa*

Department of Neurology and Psychiatry, “Sapienza”, University of Rome, Rome and Neuromed Institute, “Sapienza”, University of Rome, Rome

Over recent years, an increasing number of studies in humans have investigated the functional connectivity between the primary motor cortex (M1) and non-primary motor areas with the transcranial magnetic stimulation (TMS) technique. One experimental approach consisted of delivering repetitive TMS (rTMS) over the dorsal premotor cortex (PMd) and measuring post-intervention changes in motor evoked potential (MEP) amplitude elicited by TMS over M1 [1]. By applying PMd-rTMS in patients with Parkinson's Disease (PD), we have demonstrated that altered M1 responses also reflect abnormal PMd-to-M1 functional connectivity in parkinsonian patients on and off L-dopa therapy [2,3]. The functional connectivity between M1 and non-motor cortical areas has been also investigated by modifying the original paired associative stimulation (PAS) protocol. PAS implies rTMS over M1 paired with repetitive electric stimulation of a mixed peripheral nerve at specific interstimulus intervals (ISIs). According to the specific ISI used, PAS can increase or decrease MEP amplitudes through functional sensori-motor connectivity (sensori-motor integration). We have recently developed two PAS protocols able to investigate the functional connectivity between M1 and sensory areas other than those activated by the original PAS. Laser-PAS implies rTMS paired with the nociceptive system activation elicited by the laser evoked potential technique. Laser-PAS is able to induce long-term changes in MEP amplitudes through functional connectivity between brain regions involved in pain processing and M1 (pain-motor integration) [4]. Laser-PAS can be helpful to investigate pain-motor integration processes in patients with different types of movement disorders including PD and dystonia. Finally, Visual-PAS consists of rTMS paired with the activation of the visual system as elicited by the visual evoked potential technique. Visual-PAS induces long-term changes in MEP

amplitudes through functional visuo-motor connectivity (visuo-motor integration). Recent observations have found altered responses to Visual-PAS in patients with photoparoxysmal response (PPR) suggesting that abnormal visuo-motor integration may contribute to the pathophysiology of PPR.

#### References

- [1] Suppa A, Bologna M, Gilio F, Lorenzano C, Rothwell JC, Berardelli A. Preconditioning rTMS of premotor cortex can reduce but not enhance short-term facilitation of primary motor cortex. *J Neurophysiol* 2008; 99:564-570.
- [2] Suppa A, Iezzi E, Conte A, Belvisi D, Marsili L, Modugno N, Fabbri G, Berardelli A. Dopamine influences primary motor cortex plasticity and dorsal premotor-to-motor connectivity in Parkinson's disease. *Cereb Cortex* 2010; 20:2224-2233.
- [3] Suppa A, Marsili L, Belvisi D, Conte A, Iezzi E, Modugno N, Fabbri G, Berardelli A. Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. *Exp Neurol*. 2011; 227:296-301.
- [4] Suppa A, Biasiotto A, Belvisi D, Marsili L, La Cesa S, Truini A, Cruccu G, Berardelli A. Heat-evoked experimental pain induces long-term potentiation-like plasticity in human primary motor cortex. *Cereb Cortex* 2012; doi:10.1093/cercor/bhs182.

#### L2

#### Plasticity, adaptation and compensation: studies with functional MRI

*Alessandro Tessitore*

Dipartimento di Scienze Neurologiche, Seconda Università degli Studi di Napoli, Napoli

Functional MRI (fMRI), whereby a time series of MRI volumes is collected over several minutes while the patient lies quietly in the scanner or performs a cognitive or motor task, is used to assess regions of altered activation or functional connectivity between brain regions, or both. Changes in functional connectivity between brain regions might underlie many of the clinical impairments seen in PD, such as in the performance of simultaneous movements. Changes in functional connectivity to or from the supplementary motor area are associated with impaired motor performance in PD and with difficulties in automatic movement. Furthermore, functional connectivity assessed with fMRI might be important for assessing systems-wide compensatory mechanisms in PD. On motor tasks of increasing levels of difficulty, it seems that individuals with PD tap into a motor reserve and activate normal motor networks to a greater degree and at an earlier (simpler)

<sup>☆</sup> Joint Congress LIMPE/DISMOV-SIN.

<sup>☆☆</sup> XXXIX LIMPE National Congress VI DISMOV-SIN National Meeting Pisa, Italy, November 7-10, 2012.

stage than healthy controls. fMRI has also shown common compensatory activity in the rostral SMA and premotor cortex in individuals who are heterozygous for mutations in *PARK2* and *PINK1*. In recent years, resting-state imaging has been more extensively used in the investigation of neurodegenerative disorders. This technique might be useful in PD. The resting-state motor network is disrupted in PD patients with decreased functional connectivity between the posterior putamen and the inferior parietal cortex, and an increase in functional connectivity with the anterior putamen. Assessment of resting-state fMRI is closely related to studies examining the default mode network (DMN; including the precuneus, medial, lateral and inferior parietal cortex, medial temporal lobe, medial prefrontal, and posterior cingulate cortex), which is active during wakeful rest. However, few studies have addressed the DMN connectivity in PD reporting conflicting results, with some authors detecting reduced deactivation of posterior midline areas (PCC and precuneus) and mPFC during different cognitive tasks, while others found no altered deactivation during an executive task or a complex visual scene-encoding task. Such discrepancy across studies may be due to methodological differences in the fMRI analyses or heterogeneity in patient characteristics.

#### References:

- [1] Raichle ME, Snyder AZ A default mode of brain function: a brief history of an evolving idea. *Neuroimage*. 2007 Oct 1;37(4): 1083-90
- [2] Stoessel AJ, et al. Advances in imaging in Parkinson's disease. *Lancet Neurol*. 2011 Nov;10(11):987-1001
- [3] Wu T et al. Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. *Hum Brain Mapp* 2011 32:1443-1457
- [4] Van Eimeren T, et al. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Arch Neurol*. 2009 Jul;66(7):877-83.

### L3

#### Functional correlates of motor and non-motor symptoms in early Parkinson's disease

*Roberto Ceravolo*

Department of Neuroscience, Azienda Ospedaliero-Universitaria Pisana, Pisa

The brain functional imaging by means of both functional MRI and PET or SPECT allows to explore the network of synaptic connectivity and/or the neurochemical changes even in the early or prodromic phases of Parkinson's Disease (PD). Moreover this approach is useful for detecting the neurobiological basis of motor and non motor symptoms of PD. Several studies have consistently demonstrated that putaminal uptake of 18F-Dopa as well as DAT density inversely and strongly correlates with rigidity and bradykinesia but not with tremor. These evidences could suggest that parkinsonian tremor is not directly due to degeneration of nigro-striatal pathway. However the severity of dopaminergic degeneration is time and disease related, since at the disease onset the pallidal 18F-dopa uptake might be increased up to 50%, and with disease progression pallidal uptake might be much decreased as expression of compensatory phenomena with increased dopamine turnover. In a very recent report the finding of lower levels of DAT availability in PD patients with tremor than in patients without tremor suggested the internal pallidum could be the main driver of parkinsonian tremor [1]. Finally the investigation of cortical and subcortical arrangements following the dopamine depletion in the long preclinical phase of PD by means

of fMRI could help to understand and support the compensatory mechanisms in PD. Depression affects 40-50% PD patients and may antedate the motor onset. It is long known that depression in PD is related to change in monoaminergic systems, and a significant reduction of uptake of CTI-32, a PET ligand selective for dopamine and noradrenaline, has been observed in the thalamus, ventral striatum, locus coeruleus and amigdala in PD with depression with respects to PD without depression [2]. The correlation of dopaminergic dysfunction with affective disorders has been confirmed in some SPECT studies with DATSCAN, even in the presence of mild affective symptoms. Up to 15% of PD patients may develop after dopamine replacement therapy impulse control disorders. An increase of availability and release of dopamine in the ventral striatum has been consistently demonstrated in PET and SPECT studies [3], as well as an hyperactivation of frontal lobes and anterior cingulate, other than ventral striatum has been reported in fMRI studies [4]. The next step will be to define in vivo which neurochemical or functional pattern is related to the risk to develop these complications in order to better tailor the therapy since the early phases of PD.

#### References

- [1] Helmich RC, Janssen MJ, Oyen WJ, Bloem BR, Toni I. Pallidal dysfunction drives a cerebello thalamic circuit into Parkinson tremor. *Ann Neurol*. 2011 Feb;69(2):269-81.
- [2] Remy P, Doder M, Lees AJ, Turjanski N, Brooks DJ. Depression in Parkinson disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 2005; 128: 1314-1322
- [3] Steeves TD, Miyasaki J, Zurowski M et al. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a 11C-raclopride PET study. *Brain* 2009; 132: 1376-1385.
- [4] Frosini D, Pesaresi I, Cosottini M. et al. Parkinson's disease and pathological gambling: results from a functional MRI study. *Mov Disord*. 2010 30;25(14):2449-53.

### SESSION 2 "Molecular and clinical markers in Parkinson's disease: preclinical diagnosis and disease progression"

#### L4

#### Molecular markers in Parkinson's disease

*Paolo Calabresi*

Clinica Neurologica, Università degli Studi di Perugia, Perugia

Parkinson's disease (PD) is a common neurodegenerative disorder, in which the diagnosis is primarily based on clinical criteria. The required clinical criteria suggest the presence of a full-blown disease, while the neurodegenerative process in the PD brain occurs much earlier than the clinical onset. Therefore, the formulation of an early clinical diagnosis may be very difficult, impeding an accurate and focused therapeutical approach.

Accumulation and aggregation of  $\alpha$ -synuclein, lysosome dysfunction, and the dynamic interaction taking place along the course of the disease between  $\alpha$ -synuclein and other misfolding proteins (such as tau protein and beta amyloid) should be considered the key pathogenetic events in PD.

There is a high need of identifying peripheral biomarkers - specifically, cerebrospinal fluid (CSF) biomarkers - mirroring the molecular changes occurring in the brain, which might allow both an earlier diagnosis and a better prognosis. To this respect, CSF  $\alpha$ -synuclein-related markers, beta amyloid, and lysosomal enzymes (namely, beta-glucocerebrosidase) deserve attention, according to the evidences collected so far about their role in PD. Moreover, the role of beta amyloid 1-42 as predictive factor for cognitive

impairment in PD has consistently been reported. CSF biomarkers are of value in PD diagnostic and prognostic work-up. To this respect, it is important to combine different biomarkers for improving the diagnostic approach to this neurodegenerative disease.

## L5

### Sleep Disorders

#### Claudio Pacchetti

Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia and Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

Synucleinopathies as Parkinson's disease (PD), Multisystem Atrophy (MSA) and Dementia with Lewy Bodies (DLB) are typically characterized by motor and non motor symptoms. Among sleep alterations, REM sleep behavior disorder (RBD) is notable for its identity as a "preclinical" sign of synuclein-mediated neurodegenerative disease. In these pathologies the main suspected cause of RBD is the degeneration of pontomedullary brainstem structures. Longitudinal studies show that idiopathic RBD harbinger synucleinopathies with a rate of conversion of 46-60% within 5-10 years. There are a number of studies in which RBD is also considered a reliable marker of disease progression. When PD patients present RBD, they have a significantly higher risk (odd's ratio 2.7) of having concomitant visual hallucinations. Further, RBD might be indicative of a subtype of PD with more rapid progression to cognitive impairment and dementia. Other sleep disorders investigated as premotor sign are RLS, insomnia and excessive daytime sleepiness; however, sleepiness and sleep attacks, probably due both to dysfunction of hypothalamic hypocretin neurons (Hcr) and dopaminergic treatment are commonly correlated with disease severity and cognitive decline. The Sleep Disordered Breathing (SDB) refers to momentary, often cyclical, cessation in breathing rhythm (apneas) or sustained reductions in the breath amplitude (hypopneas). They potentially increase the risk of paroxysmal nocturnal motor events during both REM sleep (RBD) and during NREM sleep (confusional arousal). Indeed, SDB could predispose to well documented neuropsychological deficits in PD, involving the short- and long-term memory, logical abilities and frontal functions. Finally, there are ongoing studies on sleep structure in PD with associated dementia (PDD) and in DLB. In these latter patients we observe a severe disruption of sleep pattern; high percentage of "arousal" with confusional episodes of long duration, often associated to delirium which arising from NREM sleep (NREM parasomnias).

### References

- [1] Postuma RB, Montplaisir JY, Pelletier A, Dauvilliers Y, Oertel W, Iranzo A, Ferini-Strambi L, Arnulf I, Hogl B, Manni R, Miyamoto T, Mayer G, Stiasny-Kolster K, Puligheddu M, Ju Y, Jennum P, Sonka K, Santamaria J, Fantini ML, Zucconi M, Leu-Semenescu S, Frauscher B, Terzaghi M, Miyamoto M, Unger MM, Cochen De Cock V, Wolfson C. Environmental risk factors for REM sleep behavior disorder: A multicenter case-control study. *Neurology*. 2012 Jun 27.
- [2] Postuma RB, Lang AE, Gagnon JF, Pelletier A, Montplaisir JY. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. *Brain*. 2012 Jun;135(Pt 6):1860-70. Epub 2012 May 4.
- [3] Arnulf I. REM sleep behavior disorder: Motor manifestations and pathophysiology. *Mov Disord*. 2012 May;27(6):677-89. Epub 2012 Mar 22.

- [4] Sinforiani E, Pacchetti C, Zangaglia R, Pasotti C, Manni R, Nappi G. REM behavior disorder, hallucinations and cognitive impairment in Parkinson's disease: a two-year follow up. *Mov Disord*. 2008 Jul 30;23(10):1441-5
- [5] Postuma RB, Bertrand JA, Montplaisir J, Desjardins C, Vendette M, Rios Romenets S, Panisset M, Gagnon JF. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: A prospective study. *Mov Disord*. 2012 May;27(6):720-6. Epub 2012 Feb 9
- [6] Manni R, Terzaghi M, Repetto A, Zangaglia R, Pacchetti C. Complex paroxysmal nocturnal behaviors in Parkinson's disease. *Mov Disord*. 2010 Jun 15;25(8):985-90.
- [7] Ratti PL, Terzaghi M, Minafra B, Repetto A, Pasotti C, Zangaglia R, Pacchetti C, Manni R. REM and NREM sleep enactment behaviors in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. *Sleep Med*. 2012 Jun 13.

## L6

### Early Parkinson biomarkers: abnormalities of mood and of the sensory system

#### Angelo Antonini

Department for Parkinson's disease, IRCCS San Camillo, Venice

The early identification of Parkinson's disease is complex and the inaccuracy of using current clinical diagnostic is well recognized raising the demand for a diagnostic biomarker. Markers reflecting pathology may allow the earliest presymptomatic diagnosis but based on our current understanding of the disorder we recognize that several systems may be affected before nigral dopaminergic neurons start degenerating. Moreover genetic forms of parkinsonism may not share the same neuropathological hallmark and do not develop Lewy bodies ad for idiopathic PD.

There is already evidence that this is possible to some extent using PET or SPECT imaging of the dopamine system, but an appealing alternative would be to gain insight into the pathological changes from a continuously variable biochemical marker that can be assayed economically and easily.

Overall, it is clear that not a single but rather a combination biomarker may be able to do it all in Parkinson's disease. Given the heterogeneity of disease, it is likely that a biomarker will only prove useful in certain situations, whilst the strength of the clinical examination is its breadth and ability to detect non-dopaminergic symptoms. In the search for improved diagnostic fidelity it may be that a stepwise approach is required despite the potential pitfalls in combining diagnostic tests. For example, clinical assessment might be supplemented by a specific neuropsychological questionnaire or physiological test, with subsequent confirmation by imaging or a biochemical marker. Finally, any biomarker used in clinical trials as a surrogate end-point requires extensive evaluation over years in different populations of Parkinson's disease patients to ensure its validity. The key in each situation is to appreciate the limitations of the biomarker and what it actually measures.

### Affective disorders

Prior to developing motor disability many PD patients complain a series of rather non-specific behavioral symptoms, such as depression, anxiety and musculoskeletal pain that might herald subsequent disease development but have the disadvantage to be highly prevalent in the general population. Depression is probably the most suitable and it has been extensively studied. Specific scales are available and could be applied to capture the relevant early depressive symptoms although these scales have not been designed specifically for PD.

An alternative might be to develop tests that focus on certain features of the depression that are more specific to Parkinson's

disease patients, such as apathy or anhedonia and are likely underlined by dopamine deficiency. Therefore a personality questionnaire looking at such traits may go some way to predicting mood disorder and support early diagnosis in potentially at-risk individuals.

### Olfaction

The loss of smell detection, identification or discrimination often goes unnoticed early in PD and generally occurs before the development of extrapyramidal signs. In Parkinson's disease this may in part reflect neurodegeneration within the olfactory bulb since there is evidence that this might precede both nigral degeneration and symptoms. Support for the presymptomatic deterioration of olfaction has been also provided who showed olfactory dysfunction in first-degree relatives of patients with Parkinson's disease together with reduced striatal dopamine transporter binding, as assessed by  $^{123}\text{I}$ - $\beta$ -CIT in four out of 25 SPECT scans of these hyposmic relatives. Two of the relatives with hyposmia and reduced striatal dopamine transporter binding subsequently developed Parkinson's disease, suggesting that olfaction might be a useful presymptomatic biomarker.

Once symptoms have developed, it has been suggested that olfactory dysfunction might help distinguish patients with idiopathic Parkinson's disease from healthy subjects. Similarly, it may be that alterations in the sense of smell may help distinguishing true cases of Parkinson's disease from atypical parkinsonism. In a recent study it was found that patients with idiopathic Parkinson's disease were either anosmic or hyposmic, whereas all but one of the patients with MSA or progressive supranuclear palsy had only mild to moderate hyposmia, and patients with corticobasal degeneration or psychogenic movement disorders were found to be normosmic.

### Vision

Vision might be variably affected in Parkinson's disease. For example, it has been suggested that colour vision and contrast sensitivity might be abnormal as a result of a change in intraretinal dopaminergic transmission in amacrine and interplexiform cells, and colour vision has indeed been found to be abnormal in some PD patients. Furthermore, there seem to be differences in contrast sensitivity, visual evoked responses and electroretinograms in Parkinson's disease patients compared with controls, but the diseased and normal values overlap. Given that the pathological process in Parkinson's disease affects retinal cells, it may be that tests of retinal function will correlate more closely with pathological changes in the basal ganglia than clinical phenotype.

Abnormalities of eye movement may be more closely related to motor phenotype than pathology since, for example, it seems that visual landmarks improve antisaccade performance (a saccade made in the opposite direction to a stimulus) in Parkinson's disease more than controls, in a fashion analogous to target-directed pointing. Several studies have recorded eye movements in Parkinson's disease compared with controls, and although there does seem to be some difference between Parkinson's disease patients and controls during voluntary saccade paradigms their potential as biomarkers is not fully characterized.

### Hearing

Hearing impairment and loss is frequent in elderly people but it has been only marginally investigated in PD. The Brain Auditory Evoked Potentials were reported both normal or prolonged but little knowledge was available about auditory function until recently. A case control study measured auditory function in over 100 PD patients vs. an age matched cohort of healthy controls and found that PD patients are affected by high-frequency age-

dependent, unilateral or bilateral hearing impairment compared to healthy controls. The relevance of these findings needs to be evaluated but certainly it expands the clinical spectrum of non-motor disturbances in PD.

### References

- [1] Antonini A, Barone P, Marconi R et al. The progression of non-motor symptoms in Parkinson's disease and their contribution to motor disability and quality of life. *J Neurol* 2012
- [2] Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. *Neurology*. 2004 Jan 27;62(2):177-80
- [3] Braak H, Del Tredici K, Bratzke H, Hamm-Clement J, Sandmann-Keil D, Rüb U. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). *J Neurol*. 2002 Oct;249 Suppl 3:III/1-5
- [4] Doty RL. Olfactory dysfunction in Parkinson disease. *Nat Rev Neurol*. 2012 May 15;8(6):329-39.
- [5] Vitale C, Marcelli V, Allocca R et al Hearing impairment in Parkinson's disease: expanding the non-motor phenotype. *Movement Disorders* 2012 (in press)

## SESSION 3 "Cognitive abnormalities in movement disorders"

### L7

#### Epidemiology of cognitive disturbances in movement disorders

Giovanni Defazio

Department of Neuroscience and Sensory Organs, "Aldo Moro" University of Bari, Bari

The common belief that primary forms of movement disorders are purely motor disorder with no other accompanying neurological dysfunction has recently been challenged. Anatomical and imaging evidence have documented changes in several cortical and subcortical regions of patients with different forms of Movement Disorders. Moreover, there is also clinical evidence suggesting that the basal ganglia, besides motor control, may also play a role in emotional and cognitive functioning, and several studies have demonstrated the presence of cognitive impairment in the most common forms of Movement Disorders. In Parkinson's disease, mild cognitive impairment has been detected in 15% of newly diagnosed patients whereas the prevalence of dementia is between 20 and 40%, with estimates increasing with disease duration. In Essential Tremor, cognitive abnormality is characterized by mild frontal dysfunction that may have a functional impact, or by an association with dementia particularly evident among those with late onset of tremor (>65 years). In Dystonia, a few studies observed that patients with either early onset dystonia or late onset blepharospasm performed significantly worse on some cognitive tests than healthy controls. To date, however, no systematic cognitive performance evaluation has been carried out in patients with the various forms of primary adult-onset dystonia and the frequency of the phenomenon remains unknown

### L8

#### Cognitive dysfunction in movement disorders: clinical evaluation

Marianna Amboni

CEMAND, Università di Salerno, Salerno and IDC Hermitage-Capodimonte, Napoli

Cognitive impairment is common in Parkinson's disease (PD) and can already be detected in patients with early-stage PD [1,3].

Executive, attention, memory and visuospatial functions have been shown as the cognitive domains more affected with a prevalent impairment in executive functions. Memory impairment might be related to executive and attentional disturbances rather than to primary memory domain dysfunctions but this point is debated.

Williams-Gray and coll. [4] have reported that two distinct cognitive syndromes could be recognized in PD, based on genetic variations in catechol-O-methyltransferase (COMT) gene (Val-Met polymorphism) or in microtubule-associated protein tau (MAPT) gene (H1-H2 polymorphism). The dementing process in PD has resulted associated with more posterior cortically based cognitive deficits heavily depending on MAPT genotype, while frontal-executive dysfunctions, with a more dopaminergic basis linked to COMT gene variations, have resulted to display no correlation with the development of dementia.

The construct of mild cognitive impairment (MCI) is considered a transition state between normal aging and dementia. Originally, it was conceptualized as the transitional state between normalcy and Alzheimer's disease. More recently, it has been used to identify a pre-dementia state in PD patients.

Most studies exploring cognition in nondemented PD patients have employed selected neuropsychological tests rather than comprehensive batteries/scales. A number of neuropsychological tools are available for testing cognitive function in PD. Very recently, specific guidelines to assess cognition and diagnose MCI in PD have been published [2]. These guidelines include: 1) an abbreviated assessment that provides a practical but with reduced positive predictive value neuropsychological tool; 2) a comprehensive assessment that offers an extensive evaluation of the whole spectrum of the cognitive domains commonly affected in PD. The abbreviated assessment is based on the use of global scales validated in PD like Montreal Cognitive Assessment (MoCA), Parkinson's disease Cognitive Rating Scale (PD-CRS), Scales for Outcomes of Parkinson's disease–cognition (SCOPA-COG), Mattis Dementia Rating Scale (MDRS). The comprehensive assessment should include at least two selected neuropsychological tests for each of the typical cognitive domains (attention and working memory, executive function, language, memory, visuospatial function).

Mood disorders, apathy, psychosis, sleep disorders are common in PD and may impair cognitive performances. Similarly, anxiety and cognitive slowing during off periods can adversely affect neuro-psychological test performance. Thus, patients with motor fluctuations should ideally be assessed in the on state, be devoid of any drug potentially interfering with cognition and not display other nonmotor features judged so severe to invalidate the results of the neuropsychological assessment.

## References:

- [1] Aarsland D, et al. Norwegian ParkWest Study Group. Cognitive impairment in incident, untreated Parkinson Disease: the Norwegian ParkWest study. *Neurology* 2009;72:1121–1126.
- [2] Litvan I, et al. Diagnostic criteria for Mild Cognitive Impairment in Parkinson's Disease: Movement Disorder Society Task Force Guidelines. *Mov Disord* 2012;27(3):349–356.
- [3] Muslimovic D, et al. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005;65:1239–45.
- [4] Williams-Gray CH, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIG cohort. *Brain* 2009;132:2958–2969.

## L9

### Default mode network in Dementia/Parkinson

R. Franciotti<sup>1,2,3</sup>, N.W. Falasca<sup>4</sup>, L. Bonanni<sup>1,2,5</sup>, S. Comani<sup>1,4</sup>, A. Thomas<sup>1,2</sup>, Marco Onofri<sup>1,2</sup>.

<sup>1</sup>Department of Neuroscience and Imaging, G. d'Annunzio University, Chieti, Italy

<sup>2</sup>Aging Research Centre, Ce.S.I., "G. d'Annunzio" University Foundation, Chieti

<sup>3</sup>ITAB, "G. d'Annunzio" University Foundation, Chieti

<sup>4</sup>BIND – Behavioral Imaging and Neural Dynamics Center, University of Chieti-Pescara, Chieti

<sup>5</sup>Leonardo Foundation, Abano Terme (PD), Italy

During resting state, functional magnetic resonance imaging (fMRI) shows synchronous activity of brain regions involving ventral anterior and posterior cingulate cortex/precuneus, medial prefrontal cortex and bilateral lateral and inferior parietal cortex. This network is defined "default mode network" (DMN) because it is typically deactivated during processing of external stimuli, being active instead in resting condition. Research on resting state brain activity offers a novel approach for understanding brain organization and dysfunction in presence of neurological disorders [2]. Recent studies have shown the DMN to be dysfunctional in Alzheimer's disease (AD) (Greicius et al., 2004; Zhang et al., 2010). Spontaneous fMRI signal were measured to investigate connectivity between key brain regions in the DMN of AD and patients affected by dementia with Lewy bodies (DLB) (Galvin et al., 2011; Kenny et al., 2012). Compared to controls, greater connectivity was found between the right posterior cingulate cortex (PCC) and other brain areas in DLB patients and in left hippocampus in AD patients [1]. A definitive clarification of the DMN dysfunction in dementia could come from studies assessing both task and rest conditions, evidencing whether DMN as well as dorsal and ventral attention systems are not inhibited in patients during task execution. Indeed a previous study [2] proposed that visual misperception and hallucinations in Parkinson Disease are related to a failure occurring in competing complementary neural networks that normally regulate attention and thereby the accurate perception of visual stimuli. Specifically, perceptual errors arise in the context of impaired signaling between both a "task negative" DMN and a "stimulus-driven" ventral attentional network (VAN). Normally these perceptual errors would be corrected by a "goal-directed" dorsal attentional network (DAN) which probably is impaired in patients with visual misperception and hallucinations, allowing the reinforcement of false images.

If the patient is unable to activate the DAN, it is proposed that the conflict resolution is processed by neural networks unprepared for this task, such as the DMN and/or the VAN [4]. In accordance with this hypothesis, a previous study [3] investigating visual task related neural changes in DLB found reduced DMN inhibition during a series of visual tasks.

Given the greater attentional deficits in DLB than AD (Calderon et al., 2001; Collerton et al., 2003) and the link between DMN deactivation and attentional demand (McKiernan et al., 2003), one would predict that the DMN will be more dysfunctional in DLB than AD. Based on this hypothesis we performed a resting state fMRI study on DLB patients with fluctuating cognition, AD patients without fluctuating cognition and age-matched healthy controls. Our findings showed a preservation of PCC activity and connectivity inside the DMN in DLB patients and a reduced PCC activity and connectivity in AD patients. Our hypothesis is that DMN dysfunction might have a role in determining different phenotypes in dementia.

**References:**

- [1] Kenny, E.R., Blamire, A.M., Firbank, M.J., O'Brien, J.T. 2012. Functional connectivity in cortical regions in dementia with Lewy bodies and Alzheimer's disease. *Brain* 135, 569-581.
- [2] Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. 2011. Functional network disruption in the degenerative dementias. *Lancet Neurol.* 10, 829-43. Review.
- [3] Sauer, J., ffytche, D.H., Ballard, C., Brown, R.G., Howard, R. 2006. Differences between Alzheimer's disease and dementia with Lewy bodies: an fMRI study of task-related brain activity. *Brain* 129, 1780-1788.
- [4] Shine, J.M., Halliday, G.M., Naismith, S.L., Lewis, S.J. 2011. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? *Mov. Disord.* 26, 2154-2159.

**L10****Therapy**Daniela Frosini

Dipartimento di Neuroscienze, Università di Pisa, Pisa

Cognitive impairment consistent with a diagnosis of Mild Cognitive Impairment (MCI) is detectable already in newly diagnosed drug-naïve Parkinson's Disease (PD) patients and prospective studies showed that up to 75-80% of PD patients may develop dementia (PDD) during the course of the disease. At different disease stages dopaminergic and cholinergic deficit have been implicated in cognitive dysfunction and from a pathological point of view cortical Lewy body diffusion, Alzheimer like pathology and vascular lesion are detected in PD-MCI and PDD patients.

On the basis of the evidence of a severe cholinergic dysfunction in PDD cholinesterase inhibitors have been proposed as treatment of cognitive dysfunction in PD. Very recently the Cochrane Library has reviewed the effect of cholinesterase inhibitors in PDD and the examination of literature supports the use of such drugs because of a positive impact on global assessment, cognitive functions, behavioural disturbances and activities of daily living rating scales with lower tolerability than placebo but no serious adverse events and non-significant effect on motor symptoms [1].

Memantine, a low-affinity antagonist to glutamate NMDA receptors, has been tested in three parallel-group, randomized placebo-controlled trials in PDD but due to conflicting results the Movement Disorders Society evidence-based review concluded for insufficient evidence for memantine to be rated for the treatment of dementia in PD [2].

To date, clinical research trials and therapeutic interventions specifically for PD-MCI are limited. Cholinesterase inhibitors have been tested in PD-MCI only once and although with positive results newer and larger studies are needed to provide a conclusive opinion [1].

Dopaminergic medications such as levodopa or dopamine agonists may have variable effects on cognition, with improvement in some executive function tasks in PD patients and in others, worsening or no effect. The "Dopamine overdose hypothesis", suggests that the administration of dopaminergic medication to PD patients may replete dopamine depleted circuits, but overdose relatively intact ones. The treatment with levodopa has a beneficial effect on Dorso Lateral Prefrontal Cortex related functions, including planning, attention, set-switching, working memory but has a detrimental effect on Orbito Frontal Cortex related functions causing poor performances in tasks evaluating decision making and reversal learning [3]. Recently the beneficial effect of Rasagiline on cognitive functions in PD has been tested in a

randomized, double blind, placebo-controlled, multi-center study in non-demented PD patients. Rasagiline has been reported to improve performance in tasks exploring executive and attentional functions when compared to placebo. Larger placebo controlled studies are ongoing in PD-MCI patients to confirm beneficial effect of Rasagiline. Atomoxetine, a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder, has been studied in a pilot trial in 12 non-demented PD patients with moderate executive dysfunction with beneficial effect on Clinical Global Impression-Change Scale and on behavioral measures of executive dysfunction.

Treatment of co-morbid conditions such as hallucinations, depression, apathy and sleep dysfunction may play a role in treating PDD and PD-MCI as well as the withdrawal of PD and non PD related drugs with possible detrimental effect on cognition such as anti-cholinergics should be evaluated in patients with cognitive impairment. Moreover emerging literature on cognitive rehabilitation in Alzheimer disease and PD showed the beneficial effect of cognitive training on neuropsychological performance however in preliminary reports [4].

**References:**

- [1] Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *The Cochrane Library* 2012, Issue 3.
- [2] Seppi K, Weintraub D, Coelho M et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease. *Mov Disord*, 2011; 26:S42-S80.
- [3] Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev* 2006;30:1-23.
- [4] Burn D. The Treatment of Cognitive Impairment Associated with Parkinson's Disease. *Brain Pathology* 2010; 20:672-678

**SESSION 4 "Choreic Syndromes"****L11****Hereditary choreas: when and which test?**Giuseppe De Michele

Departments of Neurological Sciences and of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples

Chorea is a not uncommon movement disorder characterised by abnormal involuntary movements that are irregularly timed, randomly distributed and abrupt. Chorea can be inherited or acquired and can be caused by structural, neurochemical, or metabolic disturbances to basal ganglia function.

Advances in molecular genetics medicine have identified the causes of many inherited choreic disorders and have expanded the phenotype of recognized conditions. The pattern of inheritance provides a guide to possible diagnoses, however, the absence of a family history does not exclude a genetic cause.

Huntington's disease (HD), a progressive autosomal dominant neurodegenerative disorder, represents the most common inherited cause of chorea. Onset is usually in adult life although juvenile and elderly onset are described. HD is caused by an expanded trinucleotide CAG repeat, encoding for a polyglutamine stretch, within the *HIT* gene on chromosome 4p16.3. This gene encodes for the protein huntingtin whose function is not yet known, but the expanded polyglutamine tract appears to interfere with a number of cellular functions. The CAG repeat ranges between 10 and 29 copies on normal chromosomes, and is expanded to 36-121 on HD

chromosomes. CAG repeats above 40 are fully penetrant, with a borderline range between 36 and 39 associated with reduced penetrance. Abnormal CAG repeats are liable to expand in subsequent generations, particularly when transmitted through the paternal lineage. There is an inverse correlation between CAG repeat size and age of onset.

Huntington's disease-like 2 (HDL2), another autosomal dominant disorder, is caused by a CTG/CAG expansion within junctophilin-3 (*JPH3*). HDL2 has only been reported in families of African ancestry. Symptoms develop in adulthood, with an age of onset inversely related to size of the trinucleotide repeat expansion, and look very similar to those of HD.

Among the autosomal dominant spinocerebellar ataxias (SCAs), SCA17 may cause parkinsonism, dystonia, and chorea, in addition to the typical phenotype of ataxia, dementia, and psychiatric symptoms. Also SCA1, SCA2, and SCA3 are possible cause of chorea. Chorea and myoclonus can be seen in dentatorubro-pallidolusian atrophy (DRPLA), usually in addition to ataxia and dementia.

Benign hereditary chorea is a dominantly inherited disorder caused by mutations in *TITF1* gene, which encodes thyroid transcription factor 1. It is usually of young-onset with very slowly progressive chorea without cognitive decline. It may be also associated with congenital hypothyroidism.

Abnormal brain iron accumulation in the basal ganglia is seen in an increasing number of disorders. Neuroferritinopathy is an autosomal-dominant form of neurodegeneration with brain iron accumulation (NBIA). The disorder is due to a mutation of the gene for the light chain of ferritin. Onset is in adulthood with a variety of movement disorders, including chorea, dystonia, parkinsonism, and occasional cognitive impairment.

Pantothenate-kinase-associated neurodegeneration (PKAN), once known as Halleorden-Spatz syndrome, is an autosomal recessive form of NBIA caused by mutations in *PANK2* (encoding pantothenate-kinase 2). Chorea may be associated to the typical phenotype characterized by pigmentary retinopathy, dystonia, intellectual decline, and neuropsychiatric features.

Ataxia-telangiectasia and ataxia with oculomotor apraxia types 1 and 2 are autosomal recessive diseases caused by mutations in genes involved in DNA repair. They typically present with ataxia during infancy and childhood, and may present with or develop chorea. Serum levels of  $\alpha$ -fetoprotein, albumin, and cholesterol may be abnormal and may suggest the diagnosis.

Chorea-acanthocytosis (ChAc) is an autosomal recessive disorder due to mutations of *VPS13A*, which codes for chorein. It presents in young or middle adulthood with tics, chorea, lingual-buccal-facial dystonia, psychiatric disturbances, cognitive dysfunction, seizures, peripheral neuropathy. Elevated creatine kinase and liver enzymes are common. Detection of acanthocytosis may be enhanced by use of a standard protocol, but a negative result does not exclude the diagnosis. Aceruloplasminemia is an autosomal recessive disorder due to mutations of the gene for ceruloplasmin, with onset in adulthood, usually characterized by retinal degeneration, diabetes mellitus, cognitive impairment, ataxia, orofacial dystonia, parkinsonism, and chorea.

McLeod neuroacanthocytosis syndrome (MLS) is similar in presentation to autosomal-recessive ChAc, with the additional involvement of other organ systems. It is diagnosed by decreased expression of Kell and Kx antigens on erythrocytes, caused by mutation of the *XK* gene. The neurologic symptoms of MLS develop in middle-aged males with neuropsychiatric changes, chorea, dystonia, tics, parkinsonism, peripheral neuropathy, and seizures. Cardiac involvement is often seen. As in ChAc, liver enzymes and CK are often elevated and acanthocytosis may be detected.

## References:

- [1] Bhidayasiri R, Truong DD. Chorea and related disorders. *Postgrad Med J*. 2004 Sep;80(947):527-34.
- [2] Schneider SA, Walker RH, Bhatia KP. The Huntington's disease-like syndromes: what to consider in patients with a negative Huntington's disease gene test. *Nat Clin Pract Neurol*. 2007 Sep;3(9):517-25.
- [3] Wild EJ, Tabrizi SJ. The differential diagnosis of chorea. *Pract Neurol*. 2007 Nov;7(6):360-73.
- [4] Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol*. 2011 Jan;10(1):83-98. Review.

## L12

### Autoimmune and dysmetabolic chorea

*Roberta Marchese*

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DINOGLI) – Università di Genova, Genova

Patients with sporadic chorea require a thorough diagnostic work up because numerous causes can lead to this condition. Stroke (ischemic or hemorrhagic) is the main cause of sporadic chorea. Streptococcal infection in children can cause, in a small percentage of cases, neurological and psychiatric symptoms: Sydenham's chorea (or rheumatic chorea) is the result of an autoimmune response that occurs following infection by group A  $\beta$ -hemolytic streptococci destroying cells in the corpus striatum of the basal ganglia.

Sydenham's chorea is characterised by the acute onset (sometimes a few hours) of neurologic symptoms, classically chorea, usually affecting all limbs. Other neurologic symptoms include behavioral changes, dysarthria, gait disturbances, headache, slowed cognition, facial grimacing and hypotonia. Fifty percent of patients with acute Sydenham's chorea spontaneously recover after 2 to 6 months, whilst mild or moderate chorea or other motor symptoms can persist for up to and over 2 years. Sydenham's chorea may be also associated with psychiatric symptoms, obsessive compulsive disorder being the most frequent manifestation.

The PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections) syndrome has some similarities with Sydenham's chorea, but differs from it for the type of motor dysfunction. PANDAS usually presents with tics and/or with psychological disturbances (OCD) occurring earlier, days to weeks after GABHS infection rather than 6–9 months. It may be confused with other conditions such as SLE and Tourette syndrome. Likewise Sydenham's chorea, PANDAS is thought to involve autoimmunity directed to the basal ganglia. Unlike Sydenham's chorea, PANDAS is not associated with other manifestations of acute rheumatic fever, such as inflammation of the heart. In addition to OCD or tics, children may have other symptoms associated with exacerbations such as emotional lability, enuresis, anxiety, and deterioration in handwriting.

Other causes of autoimmune chorea include: systemic lupus erythematosus, antiphospholipid syndrome, chorea gravidarum and paraneoplastic syndromes. The neoplasms most often associated with choreic syndrome are: small cell lung cancer (60%), other pulmonary cancer, kidney cancer, testicular germi-noma and lymphoma.

Secondary choreas may recognize also infectious or endocrine causes. Among infectious agents HIV is often implicated in the genesis of chorea, while among endocrine causes hyperthyroidism is the most frequent condition; possibly related to an increased

response of striatal dopamine receptors to dopamine. Other endocrine causes are: parathyroid dysfunctions (hypo- or hyperparathyroidism) and ketotic hyper-glycemia; choreic syndromes can occur in association with hepatic encephalopathy (acquired hepato-cerebral degeneration) and renal failure.

Finally, there is a growing list of drugs associated with chorea, including: lamotrigine, methadone, lithium, neuroleptics, antiparkinsonian drugs, alcohol, cotrimossazole and oral contraceptive.

### L13

#### New frontiers in the treatment of Huntington's disease

*Silvia Piacentini*

Dipartimento di Scienze Neurologiche e Psichiatriche, Facoltà di Medicina, Università degli Studi di Firenze, Firenze

Huntington disease (HD) is a genetic neurodegenerative disorder characterized by choreo-dystonic movements, psychiatric disorders and dementia. The therapies most widely used are symptomatic treatments to control abnormal movements, mainly chorea, as haloperidol or tetrabenazine, and psychiatric symptoms, as SSRI, olanzapine and quetiapine. Recent and growing advances in the knowledge of the molecular and cellular pathways underlying the disease, are prompting the development of new compounds that are currently tested in cellular and transgenic animal models with the aim of downregulate the expression of the expanded alleles or to interfere with the pathological mechanism of neuro-degeneration. In the last years several multicentre clinical trials have been carried out with drugs either for the control of motor or cognitive symptoms. A clinical trial, testing an inhibitor of sirtuine, which plays a role in neurodegeneration in HD, is ongoing. Other non pharmacological approaches in HD have been proposed in these years and are currently experimented in various European countries, mainly fetal neurons transplants and DBS for the control of severe chorea.

#### References:

- [1] W.G. Ondo et al.: Tetrabenazine treatment for Huntington's disease-associated chorea Clin Neuropharmacol, 25(2002),pp 300-302
- [2] T. Mestre et al.: Therapeutic intervention for symptomatic treatment in Huntington's disease -Cochrane Database Syst Rev, 3 (2009) CD006456
- [3] M.L. Lombardi et al.: A majority of Huntington's disease patients may be treatable by individualized allele-specific RNA interference - Experimental Neurology, 217 (2009), pp312-319
- [4] J. Garcia de Yébenes: Pridopidine for treatment of motor function in patient with Huntington's disease (MermaiHD): a phase 3, randomized, double-blind, placebo- controlled trial The Lancet Neurology,10(2011),pp 10049-1057

### SESSION 5 "Posture and gait disorders"

#### L14

#### Pathophysiology of postural abnormalities in Parkinson's disease

*Michele Tinazzi*

Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie, Università di Verona, Verona

Postural abnormalities of the trunk are frequent and often disabling complications of Parkinson's disease (PD) and atypical parkinsonisms. These abnormalities include camptocormia,

anterocollis and Pisa Syndrome. Although the pathophysiology of these abnormalities is not fully understood, there is evidence suggesting that they may account for a multifactorial pathophysiology. Contributing factors include muscular rigidity, axial dystonia, weakness caused by myopathy, body scheme defects due to dysfunction of proprioceptive and vestibular systems, and finally structural changes in the spine. The relative contribution of these different factors varies between patients and across specific syndromes. A better understanding of the pathophysiology of these postural abnormalities in PD might ultimately lead us to more effective management strategies for these disabling and drug-refractory complications.

#### References:

- [1] Tiple D, Fabbri G, Colosimo C, Ottaviani D, Camerota F, Defazio G, Berardelli A. Camptocormia in Parkinson's disease: an epidemiological and clinical study. JNNP 2009; 80: 145-148.
- [2] Di Matteo A, Fasano A, Squintani G, Ricciardi L, Bovi T, Fiaschi A, Barone P, Tinazzi M. Lateral trunk flexion in Parkinson's disease: EMG features disclose two different underlying pathophysiological mechanisms. J Neurol 2011; 258: 740-5.
- [3] Fasano A, Di Matteo A, Vitale C, Squintani G, Ferigo L, Bombieri F, Santangelo G, Amboni M, Barone P, Tinazzi M. Reversible Pisa syndrome in patients with Parkinson's disease on rasagiline therapy. Mov Disord 2011; 26: 2578-80.
- [4] Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanic OS, Bloem BR. Postural deformities in Parkinson's disease. Lancet Neurol 2011; 10: 538-549.

#### L15

#### Semeiology and diagnosis of gait disorders

*Alfonso Fasano*

Department of Neurology Catholic University, Rome

Human gait appears to be a simple innate ability, but it is an extraordinarily complex motor behavior with multiple contributions from all parts of the brain [1]. Indeed, locomotion requires the automatic and coordinate intervention of functional modules controlling: 1. Anti-gravity support of the body; 2. Stepping; 3. Dynamic stability; and 4. Body propulsion [2]. Normal gait requires a delicate balance between various interacting systems: three major afferent systems (visual, proprioception, and vestibular), a locomotor efferent system (including nerves, muscles, bones, joints and tendons) and the strict surveillance of several structures of central nervous system.

Gait disorders are one of the most common problems encountered in neurological patients, being present in more than half of 493 consecutive, non-bed-bound patients admitted to a neurological service [3]. It is now well recognized that gait impairment is a major determinant of quality of life. Gait disorders have devastating consequences: the most notorious corollary is falling and reduced mobility, which leads to loss of independence.

Clinical experience and lesions in humans indicate that, though being integrated in a complex interplay, functional domains corresponding to less anatomically defined structures may actually being hypothesized. In the Patla's model [4], a control system (placed into the central nervous system) controls an effector system (muscles, tendons, ligaments, and skeletal structures). The pathophysiology of gait disorders is tightly connected with their clinical features: phenomenology will guide our classification, thus representing our contribute to the ongoing debate on the nosology of gait disorders.

Several classifications of gait disorders have been proposed as well as a plethora of names for specific conditions. The many definitions of high level gait disorders (HLGD) or of freezing of gait are good examples and certainly have delayed gait research [5]. The seminal paper by Nutt and colleagues hierarchically classified gait disorders into lowest level (affecting one afferent system), middle level (more afferent system involvement), and highest level (characterized by planning deficits) disorders. This effort has certainly highlighted the relevance of nosology but has introduced too many terms of HLGD, leading to a more recent revision of them. Other clinical classifications have been based on anatomy (e.g. frontal gait disorder) or on etiology (e.g. vascular), thus introducing the bias of terms that cannot refer to clinic per se. Every classification has its own limits and, as recently pointed out, a classification based on clinical phenomenology appears as a good compromise between specificity and sensibility of a diagnosis based on the naked eye assessment.

#### References:

- [1] Hallett M. The intrinsic and extrinsic aspects of freezing of gait. *Mov Disord* 2008;23 Suppl 2:S439-443.
- [2] Martin JP, Hurwitz LJ. Locomotion and the basal ganglia. *Brain* 1962;85:261-276.
- [3] Stolze H, Klebe S, Baecker C, et al. Prevalence of gait disorders in hospitalized neurological patients. *Mov Disord* 2005;20:89-94.
- [4] Patla AE. Understanding the control of human locomotion: A 'Janus' perspective. In: Patla AE, ed. *Adaptability of Human Gait: Implication for the Control of Locomotion*. New York: Elsevier Publishers, 1991: 3-17.
- [5] Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology* 1993;43:268-279.

#### L16

#### Diagnosis and clinical evaluation of postural abnormalities in Parkinson's disease

*Carmine Vitale*<sup>1,2</sup>, *Paolo Barone*<sup>2,3</sup>

<sup>1</sup>University of Naples "Parthenope", Naples

<sup>2</sup>IDC Hermitage-Capodimonte, Naples

<sup>3</sup>Neurodegenerative Diseases Center, University of Salerno, Salerno

Posture is often affected in Parkinson's disease (PD) and atypical parkinsonism. Postural abnormalities are related to disease progression, neurochemical alterations, and antiparkinsonian treatment [1].

These deformities include marked anterior flexion of thoracolumbar spine which is called camptocormia, lateral flexion of the trunk or Pisa syndrome, and dropped head as a form of extreme anterior flexion of the neck. The broad variability with which these abnormal postures occur with regard to clinical presentation, temporal course, and clinical evolution renders their nosological characterization uncertain and complicates the identification of a pathophysiological explanation.

The evidence to date suggests that postural deformities have a multifactorial pathophysiology. Contributing factors include muscular rigidity; axial dystonia; weakness caused by myopathy [2]. Posture also depends on the appropriate integration of visual, proprioceptive, and vestibular signals that leads to the generation of an optimal motor response to counteract postural perturbation [3]. It has been recently established that motor deficits are not isolated deficits and that PD is also associated with impairments in sensory-motor integration [4]. Therefore, it seemed worth investigating the possibility that sensorimotor integration deficits

may be also at least in part responsible for the postural abnormalities observed in PD patients.

The relative contribution of these different factors varies between patients and across specific clinical pictures. Further studies are warranted aiming at understanding the mechanisms underlying postural deformities in PD and identifying more specific treatment strategies for these often disabling and drug-refractory complications.

#### References:

- [1] Yokochi F. Lateral flexion in Parkinson's disease and Pisa syndrome. *J Neurol* 2006;253(Suppl 7):VII17-VII20
- [2] Doherty KM, van de Warrenburg BP, Peralta MC, Silveira-Moriyama L, Azulay JP, Gershanik OS, Bloem BR. Postural deformities in Parkinson's disease. *Lancet Neurol* 2011; 10: 538-49
- [3] Vitale C, Marcelli V, Furia T, Santangelo G, Cozzolino A, Longo K, Allocca R, Amboni M, Marciano E, Barone P. Vestibular impairment and adaptive postural imbalance in parkinsonian patients with lateral trunk flexion. *Movement Disorder* 2011; 26(8): 1458-63
- [4] Vaugoyeau M, Viel S, Assaiante C, Amblard B, Azulay JP. Impaired vertical postural control and proprioceptive integration deficits in Parkinson's disease. *Neuroscience* 2007;146:852-863

#### SESSION 6 "Therapies in Parkinson's disease"

#### L17

#### Treatment of motor symptoms in Parkinson's disease

*Ubaldo Bonuccelli* Department of Clinical and Experimental Medicine, University of Pisa, Pisa

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder, characterized by the progressive loss of substantia nigra pars compacta dopamine neurons and the consequent decrease in the neurotransmitter dopamine. Patients exhibit a range of clinical symptoms, with the most common affecting motor function and including resting tremor, rigidity, akinesia, bradykinesia and postural instability. Current pharmacological interventions are palliative and largely aimed at increasing either dopamine levels through increased production and/or inhibition of metabolism of this key neurotransmitter or dopaminergic activity through increased stimulation of dopaminergic receptors. Initial treatment aims at replacing dopamine through the administration of oral levodopa or dopamine agonists. Although oral therapy can significantly improve clinical features for many years, motor response complications, characterized by "wearing off" and dyskinesias (potentially associated with OFF-period dystonia), emerge in up to 80-100% of patients. Their development leads to worsening disability with a significant impact on patient and caregiver quality of life. Moreover, axial motor symptoms like gait problems, freezing and postural instability, may not respond to dopamine replacement therapy as these symptoms are related to non dopaminergic neuron degeneration. The concept of continuous dopaminergic stimulation or continuous dopaminergic delivery has guided during the more recent years the treatment of PD. Levodopa shows a peculiar pharmacokinetics because of it is absorbed only in the small intestine and lasts shortly in the plasma (half life of about 100 min). Long term failure of levodopa due to the appearance of motor complications has been attributed to the intermittent and pulsatile dopaminergic stimulation operated by levodopa itself and dopamine agonists, used firstly as add on therapy to advanced PD patients under levodopa treatment, subsequently have replaced levodopa as

initial PD treatment specially in younger patients. Common clinical experience and several long term studies [1,2] have clearly shown a lower propensity of dopamine agonist to provoke fluctuations and dyskinesias, but after more or less 3 years levodopa needs to be added due to the loss of efficacy of dopamine agonists monotherapy. In any case the concept of continuous dopaminergic stimulation is proven only *ex contrario*: levodopa has a short half-life and provokes fluctuations and dyskinesias, dopamine agonists have a long half life and do not determine fluctuations and dyskinesias, thereby the cause of motor complications is represented by the short half life of dopaminergic agent. It is possible that also the pharmacological differences between levodopa and dopamine agonists may explain their different propensity to induce motor complications. In any case, continuous dopaminergic delivery may effectively reduce motor complications in PD patients already showing these problems. New formulations of ropinirole and pramipexole have been recently introduced and these agents together with the rotigotine transdermal patch ensure a constant delivery of the dopamine agonist throughout 24 hours. Apomorphine is the most potent dopamine agonist and its administration can provide symptom relief comparable to levodopa. The drug has a rapid absorption after subcutaneous injection (Cmax 20 min), and a short half-life (almost 40 min): clinical studies support a role for continuous subcutaneous apomorphine infusion as an effective option for patients with advanced PD poorly controlled by oral drug treatment. Constant levodopa infusion aims to achieve continuous delivery with an optimised dose that can be kept stable within the patient's individual therapeutic window but for reaching this goal gastric emptying must be bypassed. The development of a stable concentrated levodopa-carbidopa gel (Duodopa®) (levodopa/carbidopa 20/5 mg/ml in a carboxymethylcellulose mix) combined with progress in the construction and application of portable duodenal infusion systems using percutaneous endoscopic gastrostomy (PEG), has introduced it in the clinical arena [3]. The levodopa-carbidopa gel, which is administered inside the upper intestine via a small tube inserted via PEG into the duodenum to facilitate permanent use, has proven to be a successful therapeutic strategy. It provides constant plasma levodopa levels, reducing motor fluctuations and dyskinesias ensuring more continuous and predictable clinical benefits for patients.

Chronic high-frequency stimulation of the ventral intermediate nucleus was first described in 1991 with the demonstration of effectiveness of the technique, especially on the symptom tremor, in PD. In the following years new DBS-targets have been studied and the Bilateral Subthalamic Nucleus (STN) DBS has showed to represent the more powerful treatment for complicated PD especially in patients with disabling akinetic-rigid and severe motor fluctuations [4]. Another DBS-target is represented by the globus pallidus internal, with an improvement in bradykinesia, rigidity and mainly in dyskinesias. STN-DBS is however limited by strict inclusion criteria and although the scores in the off-medication state improve by an average of 50%, the L-dopa dose loads reduced by 50–60% and on medication dyskinesias by 90% after 12 months of STN-DBS a higher incidence of depression, cognitive decline, speech difficulty, and gait disturbance has been reported. Thus, despite improved motor control, quality of life in patients treated with DBS is significantly hampered by the risk of non-motor complication such as cognitive and behavioural problems. This limitation of the procedure must be considered when these treatment is proposed to PD patients.

#### References:

- [1] Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with

ropinirole or levodopa. 056 Study Group. *N Engl J Med.* 2000;342(20):1484–91

- [2] Parkinson Study Group- Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group. *JAMA.*2000;284(15):1931–8)
- [3] Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology.* 2005; 64(2):216–23.
- [4] Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the Subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;339:1105–11

#### L18

##### Treatment of non motor symptoms in Parkinson's disease

*Giovanni Fabbrini*

Department of Neurology and Psychiatry, Sapienza University of Rome, Rome

Non motor symptoms are a significant problem in Parkinson disease. Non motor symptoms may precede the appearance of the typical motor signs, and more frequently complicate the advanced phases of the disease. The most important non motor symptoms are: sleep disturbances (excessive daytime somnolence, sleep attacks, insomnia, parasomnias), neuropsychiatric disturbances (anxiety, depression, hallucinations, psychosis, impulse control disorder), cognitive disturbances (changes in executive functions, dementia), vegetative disturbances (urinary disturbances, constipation, sexual dysfunction, orthostatic hypotension) and sensory disturbances (particularly pain). The treatment of non motor symptoms is mostly based on small, uncontrolled, open studies. Some of the non motor disturbances are clearly correlated with the dopaminergic deficit and improve with a better control of motor symptoms. Other non motor symptoms are completely independent of the dopaminergic stimulation, and the correct treatment depends particularly on the correct diagnosis. Controlled studies are however needed to improve our ability to treat non motor symptoms in Parkinson disease.

#### References:

- [1] Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord.* 2000 Mar;15(2):201–11.
- [2] Emre M, Aarsland D, Albanese A et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004; 351:2509–18.
- [3] Poewe W, Hogl B. Parkinson's disease and sleep. *Curr Opin Neurol* 2000;13:423–26.
- [4] Pfeiffer RF: Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2003;2:107–116

#### L19

##### How Parkinson's disease changed and how it may change in the future

*Fabrizio Stocchi*

IRCCS San Raffaele Pisana, Roma

The introduction of levodopa in the treatment of Parkinson's disease (PD) in 1970 was one of the most extraordinary success in medicine. However quite soon levodopa therapy showed limitations like motor complications and dyskinesia.

To treat or avoid motor complications dopamine agonists (DA) were introduced. This class of drugs showed to be effective in monotherapy in mild to moderate patients, to delay motor complications and dyskinesia and to improve levodopa therapy when administered in combination. New formulations of DA agonists (slow release and patch) produced very interesting results in clinical trials and have advantage compared to the immediate release formulations.

Meanwhile more attention has been given to non motor symptoms of PD therefore drugs with potential effect on motor symptoms have been explored. DA can improve some non motor symptoms such as depression or sleep problems.

These drugs have been extensively used but in the recent years the use of DA has been limited by the appearance of side effects such as somnolence, hypotension but especially impulse control disorders.

The research also focused on disease progression and treatments that may modify disease progression. Many trial had been conducted but the results were disappointing. Recently a study showed that the MAOB-I rasagiline may modify disease progression in PD, however the effect has been showed only with 1 mg day but not with 2 mg day.

MAOB-I, selegiline, rasagiline were introduced in the treatment because they can improve symptoms of the disease in monotherapy and ameliorate levodopa therapy when administered in combination.

Levodopa remain the most effective drug but it is limited by its short half-life. Slow release formulations introduced in late eighties are not very efficacious and their effect is unpredictable.

Levodopa half life can be improved adding to the dopadecarboxylase inhibitors a COMT inhibitor. Tolcapone and entacapone showed to be efficacious in improving and optimize levodopa treatment. Unfortunately, tolcapone use is limited by its potential liver toxicity, whereas entacapone can be administered in a single tablet containing levodopa, carbidopa and entacapone. The research for a better levodopa lead to a new formulation of levodopa (IPX066) with a longer half life and stable plasma level. IPX066 has been tested in different clinical trials and may be used in the next future.

Other drugs may change PD therapy looking to new mechanisms and pathways.

Safinamide is an  $\alpha$ -aminoamide with MAO-B and dopamine reuptake inhibition action. Safinamide (100 mg day) improved motor performance added to a dopamine agonist (DA). More recently, safinamide reduced L-dopa-induced dyskinesia in parkinsonian monkeys.

A2A antagonists provide benefit for patients with motor complications based on their capacity to decrease overactive firing in striatal neurons that bear dopamine D2 receptors and comprise the indirect pathway. In MPTP monkeys Preladenant reduced dyskinesias associated with the introduction of levodopa. Istradefylline showed improvement in off time on patients with motor complications. Preladenant is now going in the phase III program.

AFQ056 is a novel, selective mGluR5 antagonist. Two randomized, double-blind, placebo-controlled, proof-of-concept studies of AFQ056 demonstrated anti-dyskinetic efficacy in moderate-to-severe PD-LID.

Talampanel, a non-competitive, selective antagonist of the  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) glutamate receptor has been reported to significantly reduce L-dopa-induced dyskinesia in Parkinsonian monkeys.

Gene therapy is producing interesting results and may change the treatment of PD in the future.

Of course brain surgery and in particular deep brain stimulation has been a major change in the treatment of PD and this topic will be extensively discussed in other part.

## SESSION 7 “Overlaps in movement disorders”

### L20

#### Phenotypic and genotypic overlaps in Parkinson's disease and parkinsonisms

*Enza Maria Valente* Istituto CSS-Mendel, Roma and Università di Messina, Messina

Over the past few years, several genes have been identified that cause mendelian forms of Parkinson's disease with autosomal dominant or recessive inheritance, as well as genetic factors that significantly increase the risk to develop the disease. The identification of a growing number of subjects carrying mutations in these genes has allowed on one hand to demonstrate that mutations in the same gene may cause a wide array of distinct phenotypes in terms of age at onset, progression, disease severity and prevalence of non-motor symptoms, on the other hand it has shown a marked clinical overlap in patients carriers of mutations in distinct genes. This phenomenon, known in genetics as “splitting and lumping”, is typical of several clinically and genetically heterogeneous disorders, and it is well represented in PD and parkinsonisms. For instance, duplications of the SNCA gene, encoding for the protein alpha-synuclein, can cause a wide spectrum ranging from a late onset clinical presentation indistinguishable from idiopathic PD to earlier onset, clinically aggressive forms of parkinsonism, with rapid onset of non-motor symptoms such as dysautonomia, psychiatric disturbances and cognitive impairment, that overlap with the diagnosis of PD-dementia or even Lewy Body Dementia. These severe phenotypes are often associated to triplications of the SNCA gene, but are also found with relative frequency in patients who are heterozygous carriers of GBA mutations. Another relevant example of “splitting and lumping” is represented by autosomal recessive parkinsonisms. Indeed, mutations in the Parkin or PINK1 genes have been associated to several clinical presentations, with variable age at onset, response to therapy and presence of atypical features (such as hyper-reflexia, dystonia, psychiatric disturbances), it is also true that the phenotypic spectrum of the three recessive genes (Parkin, PINK1 and DJ-1) tends to be similar, being often characterized by early onset (<40 years), slow progression and good response to levodopa therapy. Such marked clinical and genetic variability still remains largely unexplained by the known mechanisms of neurodegeneration associated to specific gene mutations. The complexity of our genome, that is clearly emerging in these years thanks to the many projects of massive resequencing, suggests that the definition of “monogenic PD and parkinsonisms” is over-simplistic, while we are facing a more complex scenario in which, besides the main mutation, several genetic variations (including common polymorphisms and rare variants) may interplay with environmental factors to influence the phenotypic presentation of the disease. The identification of such variants and the definition of their role in determining the parkinsonian phenotype represent one of the most interesting challenges of genetic research of these days.

### L21

#### Tremor in primary adult-onset dystonia

*Alfredo Berardelli*

Department of Neurology and Psychiatry, Sapienza Università di Roma, Roma

Tremor, defined as a rhythmic, involuntary, oscillatory movement in a body part, is frequent in patients with dystonia. Its clinical features in dystonic patients may be clinically indistinguishable from those in patients with essential tremor. We

investigated the frequency and the main phenotypic features of tremor in 429 patients with primary adult-onset dystonia from eight movement disorder centres. Of the 429 dystonic patients, 72 (16.7%) had tremor (43 dystonic tremor, 23 tremor associated with dystonia, 6 both tremor types, according to Deuschl's classification). Although sex and age at dystonia onset were similar in dystonic patients who had tremor and those who did not, patients who had tremor were more frequently affected by focal cervical dystonia and less frequently affected by focal blepharospasm; dystonia also had a greater tendency to spread in patients with tremor. Taking into account potential confounding by age at onset and body distribution of the corresponding dystonia type, all the clinical features in patients with dystonic tremor and in those with tremor associated with dystonia were comparable except the tendency of dystonia to spread, which was greater in patients with dystonic tremor. In conclusion tremor is relatively frequent in primary adult-onset dystonia and its main phenotypic features differ from those of essential tremor. Numerous clinical/demographic similarities suggest that dystonic tremor and tremor associated with dystonia are manifestations of the same disease, though dystonic tremor seems to be characterized by a greater tendency of dystonia to spread.

To investigate whether psychophysical techniques assessing temporal discrimination could help in differentiating patients who have tremor associated with dystonia or essential tremor we tested somatosensory temporal discrimination thresholds (TDT) and temporal discrimination movement thresholds (TDMT) in 39 patients who had tremor associated with dystonia or essential tremor presenting with upper-limb tremor of comparable severity and compared their findings with those from a group of 25 sex- and age-matched healthy control subjects. TDT and TDMT testing proved to be a useful tool for differentiating tremor associated with dystonia and essential tremor. These findings imply that the pathophysiological mechanisms underlying tremor associated with dystonia differ from those for essential tremor.

#### References:

- [1] Abbruzzese G, Berardelli A, Girlanda P, et al. Long-term assessment of the risk of spread in primary late-onset focal dystonia. *J Neurol Neurosurg Psychiatry* 2008; 79:392-396.
- [2] Conte A, Rocchi L, Nardella A, et al. Theta-burst stimulation-induced plasticity over primary somatosensory cortex changes somatosensory temporal discrimination in healthy humans. *PLoS One* 2012;7:e32979. Epub 32012 Mar 32977.
- [3] Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. *Ad Hoc Scientific Committee. Mov Disord* 1998;13 Suppl 3:2-23.
- [4] Scontrini A, Conte A, Defazio G, et al. Somatosensory temporal discrimination in patients with primary focal dystonia. *J Neurol Neurosurg Psychiatry* 2009;80:1315-1319

## L22

### Overlaps in Tauopathies

*Helen Ling*

Reta Lila Weston Institute of Neurological Studies and Queen Square Brain Bank for Neurological Studies, Institute of Neurology, University College London, London, UK

Normal tau protein binds to microtubules in axons in the brain, but in some neurodegenerative diseases it accumulates in the cell body to form insoluble, fibrillary deposits. Diseases with accumulation of pathological tau protein are known as tauopathies. More than 20 different disorders are characterized by tau-positive neurofibrillary tangle pathology [1], most of which cause dementia

and abnormalities in the motor system. Common tauopathies include Alzheimer's disease, progressive supranuclear palsy [2,3], corticobasal degeneration [4], frontotemporal dementia with parkinsonism linked to chromosome 17, Pick's disease, post-encephalitic parkinsonism, dementia pugilistica and argyrophilic grain disease. This talk will highlight the clinical and pathological similarities and differences between some of these tauopathies.

#### References:

- [1] Kara E, Ling H, Pittman AM, et al. The MAPT p.A152T variant is a risk factor associated with tauopathies with atypical clinical and neuropathological features. *Neurobiology of aging* 2012;33:2231 e2237-2231 e2214.
- [2] Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain* 2005;128:1247-1258.
- [3] Ling H, Massey LA, Lees AJ, Brown P, Day BL. Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. *Brain: a journal of neurology* 2012;135:1141-1153.
- [4] Ling H, O'Sullivan SS, Holton JL, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* 2010;133:2045-2057.

## L23

### Overlap in $\alpha$ -synucleinopathies

*Gregor K. Wenning*

Division of Neurobiology, Department of Neurology, Medical University, Innsbruck, Austria

There is increasing recognition that the  $\alpha$ -synucleinopathies Parkinson's disease and multiple system atrophy overlap at multiple levels. Both disorders are characterized by deposition of abnormally phosphorylated fibrillar  $\alpha$ -synuclein within the central nervous system supporting the notion that these two diseases are causally linked. Moreover, there is a well-established clinical overlap causing difficulties in the differential diagnosis, particularly early in the disease. I will review emerging evidence suggesting that multiple system atrophy and Parkinson's disease as well as related Lewy body disorders represent similar phenotypes within the spectrum of  $\alpha$ -synucleinopathies. Recognizing the links between multiple system atrophy and Lewy body disorders has fundamental implications for accelerated therapeutic discoveries including  $\alpha$ -synuclein immunization programs.

## COURSE "Diagnosis and treatment of autonomic system disorders"

### C1

#### Why and how to evaluate the cardiovascular system in Parkinson disease

*Pietro Cortelli*

Department of Neurological Sciences, Alma Mater Studiorum, IRCCS, Institute of Neurological Sciences, University of Bologna, Bologna

A dysfunction of the Autonomic Nervous System (ANS) is frequently observed in patients with Parkinson disease (PD). Besides the typical motor signs and symptoms, PD patients can develop during the disease course a wide spectrum of autonomic disorders, including gastrointestinal, urogenital, cardiovascular, sudomotor, thermoregulatory and respiratory dysfunctions, autonomic disorders during sleep and pupillary abnormalities.

The overall prevalence of the autonomic disturbances in PD is considerably variable, ranging from 2% for urinary incontinence to 30% for orthostatic hypotension and 72% for constipation. Further autonomic impairment may be related to disease duration and severity as well as to use of antiparkinsonian drugs.

The development of the neurodegenerative process responsible for PD has been supposed to follow a distinct caudal-rostral pathway throughout the brain. This process also progressively involves in an ascending manner several areas of the nervous system implicated in the control of autonomic functions: from the post-ganglionic sympathetic neurons of the intermediate cells columns, to the dorsal glossopharyngeal nerve nucleus, the dorsal motor nucleus of the vagus nerve and eventually to the anterior-medial temporal cerebral mesocortex and the prefrontal areas. Therefore, the occurrence of autonomic disturbances in PD can precede the onset of motor symptoms, increases in frequency with disease progression and becomes nearly a constant finding in advanced disease stages.

A prompt recognition of these disturbances is useful not only for diagnostic purposes, e.g. the differential diagnosis of the parkinsonian syndromes, but also to choose the most correct therapeutic approach and formulate a reliable prognosis. The instrumental diagnosis of the autonomic dysfunction could in fact help in the differential diagnosis between PD and atypical parkinsonisms but could also allow to disclose the iatrogenic aetiology of the autonomic disturbance.

The majority of ANS functions cannot be directly evaluated, therefore the assessment on ANS integrity frequently relies on indirect methods, which measure the reflex responses of the target organs to physiological and pathological stimuli. The cardiovascular reflex testing represents the most useful approach in clinical practice to evaluate the integrity of the ANS branch which controls heart rate and blood pressure response. These tests are easy to perform, non-invasive, reproducible, sensitive and specific and suitable for longitudinal ANS evaluations.

The present teaching course aims to provide clinical and physiopathological basis for understanding the results of standard cardiovascular reflex tests in patients with movement disorders. The course comprises also a practical section during which participants will be taught correct methods of cardiovascular reflex tests' execution and interpretation, including recognition of specific artefacts.

The final section will deal with the treatment of orthostatic hypotension - supine hypertension, a condition that represents an important cause of PD patient disability.

#### References:

- [1] Ziemssen T, Reichmann H. Cardiovascular autonomic dysfunction in Parkinson's disease. *J Neurol Sci.* 2010;289:74-80
- [2] Low PA. *Clinical Autonomic Disorders*, 2nd edition. Lippincott-Raven 1997
- [3] Lahrman H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurol.* 2006; 13: 930-6
- [4] Weimer LH. Autonomic testing: common techniques and clinical applications. *Neurologist.* 2010;16:215-22

## C2

### Clinical features and management of "orthostatic hypotension - supine hypertension"

Giovanna Calandra-Buonaura

Department of Neurological Sciences, Alma Mater Studiorum, IRCCS, Institute of Neurological Sciences, University of Bologna, Bologna, Italy

Orthostatic Hypotension (OH) is defined as a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table [1]. Orthostatic hypotension can be the first clinical sign of a dysfunction of the autonomic nervous system and may be symptomatic or asymptomatic. OH occurs in patients with neurodegenerative disorders such as Parkinson disease (PD), Multiple System Atrophy (MSA), Lewy Body Dementia and pure autonomic failure. This condition affects approximately 30% of patients with PD being symptomatic in 18% of these patients and therefore representing an important cause of disability. Usually the treatment of OH follows an integrated approach, consisting of both non-pharmacological and pharmacological interventions [2-4]. It is important to state that treatment of OH should not be focused on normalizing blood pressure values; instead it should be directed toward improving symptoms and patient functional status, and reducing the risk of falls and syncope.

First of all patients must be educated to avoid factors which precipitate OH, like sudden postural changes from clinostatic to orthostatic position, standing still for long periods, large meals rich of carbohydrates, alcohol intake, hot showers and excessive heat, straining during micturition or defecation and excessive physical efforts. Drugs that can exacerbate OH (e.g. alpha-blockers, diuretics, dopaminergic antiparkinsonian drugs) should be discontinued or the dosage should be reduced. The second step of non-pharmacological treatment is to educate patient about the use of physical manoeuvres that contribute to raise blood pressure by increasing venous return and peripheral resistance (e.g. crossing legs on standing, squatting). The rapid ingestion of approximately 500 cc of tap water is recommended as a rescue measure when patients are symptomatic to raise blood pressure values and improve symptoms. Finally patients should follow some suggestions to increase blood volume (e.g. addition of salt and water to the diet, use of custom fitted elastic stockings).

Pharmacological treatment should be implemented only in case of symptoms' persistence.

First line treatment intervention includes drugs which induce volume expansion (fludrocortisone acetate) and peripherally acting alpha-1-adrenoceptor agonist (midodrine). The noradrenaline precursor, Droxidopa, has also been demonstrated to effectively improve orthostatic blood pressure values and OH related symptoms in both PD and MSA patients.

Supplementary agents (e.g. acetylcholinesterase inhibitor, erythropoietin, caffeine, ocreotide, acarbose) could provide an additive therapeutic effect in patients, which do not respond to first line treatment interventions.

Finally supine hypertension is frequently observed in patients with neurogenic OH and could be aggravated by the treatment of OH. This condition increases the risk of developing ventricular cardiac hypertrophy and cerebrovascular and cardiovascular events.

As for OH, treatment of supine hypertension should start with non-pharmacological interventions (e.g. avoid the use of pressor agents or water intake close to bedtime, raise the head of the bed by 20-25 cm during night-time, allow sweet snack or minimal alcohol consumption before bedtime). If the non-pharmacological approach failed to control blood pressure, the use during bedtime of short active antihypertensive drugs or of phosphodiesterase inhibitors should be suggested [4].

#### References:

- [1] Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011; 21:69-72.

- [2] Lahrmann H, Cortelli P, Hilz M, et al. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurol* 2006; 13:930-6.
- [3] Low PA and Singer W. Update on management of neurogenic orthostatic hypotension. *Lancet Neurol* 2008; 7:451-8.
- [4] Shibao C, Okamoto L, Biaggioni I. Pharmacotherapy of autonomic failure. *Pharmacol Ther* 2012;134:279-86.

### C3

#### Gastrointestinal and genitourinary dysfunction in Parkinson's disease

*Giuseppe Pelliccioni, B. Gobbi, D. Sabbatini, O. Scarpino*

Neurology Unit, INRCA, Ancona

Parkinson's disease (PD) is a chronic-progressive neurodegenerative disorder with varying patterns of impairment in dopaminergic and non-dopaminergic (cholinergic, noradrenergic and serotonergic) neuronal systems. Bradykinesia, muscular rigidity, resting tremor, postural reflex impairment and gait disturbances are the most relevant motor dysfunctions. Rarely in the very beginning and frequently with disease progression, the patients affected by PD develop non-motor disabling autonomic symptoms due to cardiovascular, bladder, sexual and gastrointestinal dysfunctions. The prevalence of overactive bladder symptoms in PD was found to be 27% to 39%. The most common complaint is nocturia followed by frequency, urgency and urge-incontinence. Winge et al., [1] demonstrated that the presence of bladder symptoms is related to the decrease in the total number of dopaminergic neurones in the striatum and that relative degeneration of the caudate correlates to the severity of bladder symptoms. Urodynamic evaluation suggests that the most common abnormality is detrusor overactivity, presumably as a result of loss of normal inhibition exerted by the basal ganglia on the sacral spinal cord [2]. L-dopa treatment improves storage urodynamic parameters in *de novo* patients but the results are less consistent in patients with L-dopa related motor fluctuations. Sexual dysfunctions are common and distressing symptoms in PD patients of both genders. Women reported difficulties with arousal (87%) and reaching orgasm (75%), and low sexual desire (47%); men referred erectile dysfunction (68%), premature ejaculation (40%) and sexual dissatisfaction (65%). Typically erectile dysfunction affects men several years after the diagnosis and the risk increases with advancing Hoehn-Yahr stage and contributes to deterioration of their quality of life. Intermittent subcutaneous apomorphine improves erectile function, probably through central D2 receptors stimulation. However the phosphodiesterase-5 selective inhibitors (sildenafil, vardenafil and tadalafil) are the most commonly used drugs for the treatment of erectile dysfunction also in these patients [3]. Hypersexuality and compulsive sexual behaviour are side effects of dopaminergic therapy, particularly by dopaminergic agonists. Gastrointestinal motility is frequently disturbed in PD, manifesting chiefly as dysphagia, esophageal dysmotility with achalasia, impaired gastric emptying and constipation [4]. Dysphagia is usually identified by its consecutive symptom sialorrhea, though salivation is not increased. In the late stage of the disease defective swallowing induces aspiration pneumonia. Impaired gastric motility leads to nonspecific symptoms such as sensation of fullness, belching and heartburn. An important consequence of delayed gastric emptying is impaired delivery of L-dopa to the absorptive sites in the duodenum. Constipation is the most prominent manifestation of lower gastrointestinal dysfunction, resulting primarily from decreased transport and/or disturbed anorectal evacuation. A major mechanism of constipation is defecatory dysfunction which

results in dyschezia and outlet-type constipation. In conclusion, impairment of gastrointestinal and genitourinary functions frequently represent clinically relevant, pervasive problem, with considerable impact in daily life activities in all stages of the disease.

#### References:

- [1] Winge K, Friberg L, Werdelin L, Nielsen KK, Stimpel H. Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's disease. *Eur J Neurol* 2005;12(11):842-50.
- [2] Blackett H, Walker R, Wood B. Urinary dysfunction in Parkinson's disease: a review. *Parkinsonism Relat Disord* 2009;15(2):81-7.
- [3] Papatsoris AG, Deliveliotis C, Singer C, Papapetropoulos S. Erectile dysfunction in Parkinson's disease. *Urology* 2006;67(3):447-51.
- [4] Jost WH. Gastrointestinal dysfunction in Parkinson's Disease. *J Neurol Sci* 2010;289(1-2):69-73.

#### COURSE "Semeiologic evaluation of patients with movement disorders"

### C4

#### Examination of eye movements

*Silvia Ramat<sup>1</sup>, Stefano Ramat<sup>2</sup>*

<sup>1</sup>SOD Neurologia 1, Dipartimento di Neuroscienze, AOU Careggi, Firenze

<sup>2</sup>Dipartimento di Ingegneria Industriale e dell'Informazione, Università di Pavia, Pavia

Oculomotor abnormalities can be observed in all Parkinsonian syndromes. Nevertheless, due to the considerable overlap of oculomotor pathology in Parkinsonism, oculomotor changes are not generally considered to contribute substantially to the differential diagnosis of PS. There are subtle differences between apparently similar oculomotor alterations in Parkinson's disease and atypical neurodegenerative PS that can contribute to the early differential diagnosis of these entities.

Parkinson's disease is the most common movement disorder, and the most frequently reported neuro-ophthalmological findings include square wave jerks, hypometric saccades, mild impairment of upgaze, convergence insufficiency, and visual hallucinations. Most of these disturbances are best detected through electrophysiologic testing rather than by neurological examination.

Progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA) share many clinical and neuropathologic features. Of the three, progressive supranuclear palsy has the most neuro-ophthalmologic manifestations, often present early in the disease course. PSP patients develop slowed saccades (vertical before horizontal), frequent square-wave jerks, loss of convergence, and tend to have an initially preserved vestibulo-ocular reflex. Corticobasal degeneration does not usually cause slow saccades, but is associated with increased saccadic latency. Even at an early stage of the disease, CBD patients could be differentiated from PSP patients by increased horizontal saccadic latency and lack of impairment of vertical saccades. Multiple system atrophy patients differ from PSP patients by having normal vertical saccadic velocities.

Saccades may be also impaired in Parkinson's disease dementia and in dementia with Lewy bodies where cortical and subcortical neurodegeneration coexist.

**References:**

- [1] Pinkhardt EH, Jan Kassubek J Ocular motor abnormalities in Parkinsonian syndromes Parkinsonism and Related Disorders 17 (2011) 223-230.
- [2] Ramat S, Leigh RJ, Zee DS, Optican LM. What clinical disorders tell us about the neural control of saccadic eye movements. Brain 2007 Jan;130(Pt 1):10-35.
- [3] Archibald NK, Clarke MP, Mosimann UP, Burn DJ Visual symptoms in Parkinson's disease and Parkinson's disease dementia Mov Disord. 2011 Nov;26(13):2387-95.
- [4] Mosimann UP, Muri RM, Burn DJ, Felblinger J, O'Brien JT, McKeith IG Saccadic eye movement changes in Parkinson's disease dementia and dementia with Lewy bodies Brain (2005), 128, 1267–1276

**C5****Tremor evaluation**

Paolo Martinelli

Department of Neurological Sciences University of Bologna, Bologna

Tremor is the commonest movement disorder detected in neurological practice, encountered in more than a hundred neurological diseases. Tremor can be defined as an involuntary oscillation of a body segment around a central axis in both the space and time domains. Tremor should be differentiated from hyperkinesias without a constant periodic oscillation, i.e. pseudo-periodic myoclonic jerks. A correct tremor evaluation requires not only the appropriate clinical assessment, but also personal and family history-taking and, in a few cases, electrophysiologic study.

Clinical classification is largely linked to the phenomenology observed: rest, postural, and kinetic types of tremor are the first diagnostic hallmarks in the classification of a rhythmic hyperkinesia. More details however, are required: the body segment involved, the frequency of the hyperkinetic movement, the onset, disappearance or increase in the tremor during specific actions are all key pieces of information for a correct semeiotical and hence clinical diagnosis. Clinical rating scales and electrophysiologic investigations, e.g. electromyographic recordings, power and frequency spectra analysis, may add further details to clinical assessment.

The present review describes the clinical features of the following tremors: i) para-physiologic tremor, i.e. accentuated physiological tremor; ii) essential tremor; iii) tremors due to cortical, sub-cortical, cerebellar, brainstem involvement; iv) tremors associated with neuronal and neural diseases; v) tremor non directly linked to specific structures or systems, i.e. so-called psychogenic tremor.

**References:**

- [1] Fahn S. Classification of movement disorders. Mov Disord 2011 May 26 (6):947-57.
- [2] Elble R, Deusch G. Milestones in tremor research Mov Disord 2011may (26):1096-105
- [3] Lang AE, Voon V. Psychogenic movement disorders: past developments, current status, and future directions. Mov Disord 2011 May 26(6):1175-86.
- [4] Bain PG. Task-specific tremor Handb Clin Neurol 2011; 100:711-8.

**C6****Rating scales in Parkinson's disease**

Maria Teresa Pellecchia

Center for Neurodegenerative Disorders, University of Salerno, Salerno

Several rating scales are available to evaluate different motor and non motor signs and symptoms of Parkinson's disease, quality of life and disease severity. They are useful to objectively monitor disease progression and assess the efficacy of either pharmacological or non-pharmacological treatments.

Some new rating scales for PD have been recently developed and validated. The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease rating scale (MDS-UPDRS) has been available in English since 2008 and its Italian translation has been recently validated in 377 Italian PD patients, showing a Comparative Fit Index relative to the English version higher than 0.94 [1]. The Italian version of the Parkinson's disease sleep scale (PDSS) has been recently validated in 221 patients showing a satisfactory internal consistency and a good validity to assess sleep disturbances [2]. A patients self-rated 19-item wearing-off questionnaire (WOQ-19) was shown to be a potent screening tool for wearing off in PD patients. The Italian version of WOQ-19 showed an excellent linguistic validity and psychometric properties [3].

The Snaith-Hamilton Pleasure Scale (SHAPS) has been validated in 274 Italian PD patients and then administered to more than 1300 patients with different types of parkinsonism to evaluate relationship between anhedonia and clinical features. SHAPS score were related to type of parkinsonism, apathy, depression and cognitive impairment [4].

**References:**

- [1] Antonini A, Abbruzzese G, Ferini-Strambi L, et al. Validation of the Italian version of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale. Neurol Sci 2012 Jun 8. [Epub ahead of print]
- [2] Pellecchia MT, Antonini A, Bonucelli U, et al. Observational study of sleep-related disorders in Italian patients with Parkinson's disease: usefulness of the Italian version of Parkinson's disease sleep scale. Neurol Sci 2012;33:689-694.
- [3] Abbruzzese G, Antonini A, Barone P, et al. Linguistic, psychometric validation and diagnostic ability assessment of an Italian version of a 19-item wearing-off questionnaire for wearing-off detection in Parkinson's disease. Neurol Sci 2012 Feb 4. [Epub ahead of print]
- [4] Santangelo G, Morgante L, Savica R, et al. Anhedonia and cognitive impairment in Parkinson's disease: Italian validation of the Snaith Hamilton Pleasure Scale and its application in the clinical routine practice during the PRIAMO study. Parkinsonism Relat Disord 2009; 15:576-581.

**COURSE "Rehabilitation in movement disorders"****C7****Rehabilitation in Parkinson's disease: when, what, how much?**

Maria Gabriella Ceravolo

Dipartimento di Medicina Sperimentale e Clinica, Sezione Neuroscienze Cliniche, Università Politecnica delle Marche, Ancona

Parkinson's Disease (PD) shows a multifaceted progressive course, whose severity and clinical manifestations vary so much across individuals and, especially, over time, that, in the advanced phase, unpredictable shifts from a well-being condition to complete dependence may often alternate in the same subject, within few minutes.

Although replacement therapy may provide an effective control of motor symptoms throughout the disease course, disability onset cannot be averted in any patient due to both levodopa-refractory symptoms and late complications of dopaminergic treatment.

International guidelines underscore the usefulness, for PD patients, of receiving a tailored program of education, psychological support, exercise and nutritional interventions aimed at improving social interaction, reducing psychological distress, increasing fitness and independence in activities of daily life, and promoting relearning of motor and communication skills [1].

By contrast, reports addressing the unmet needs of these subjects highlight an unbalanced access to specialists (i.e. neurologists), with respect to non-medical providers of health care, with physiotherapists, occupational therapists and speech and language therapists seen less often than wanted.

Such discrepancy has different likely sources: a) the striking anti-symptomatic effect of drug treatment, releasing patients from motor troubles in the very short time of tablet assumption, drives individual attention towards passive ways of coping with disability, thus reducing their motivation to engage themselves in demanding proactive behaviour, as required by the rehabilitation concept; b) the neurodegenerative mechanism underlying the occurrence of movement disorder in PD is also assumed to be responsible for the loss of initiative that often characterise these subjects, thus further contributing to their inactivity; c) the lack of evidence supporting rehabilitation effectiveness at improving motor, swallowing or communication abilities in PD subjects has so far hindered the standardization of non pharmacological care provision and reduced the confidence of the stakeholders (carers, patients, public health system administrators) in allocating resources to this purpose.

Therefore, even if a few recent reports underscored the potential benefits of exercise with regard to physical functioning, quality of life, balance and gait speed, no guidelines have yet disclosed what is the recommended content (dosing, techniques) and timing of exercise interventions (when to start, how long to continue) for PD patients.

Some Authors described an improvement in either gait parameters or motor symptoms and physical fitness in PD patients that did supported-body-weight treadmill aerobic training in comparison to conventional physical therapy. Other studies showed that regular aerobic exercise helps preventing brain tissue loss, thus prompting some researchers to check whether even PD people would benefit from a similar advantage and improve their executive functions after prolonged generalised exercise [2].

Parallel to the development of evidences concerning endurance training, a wide range of studies focused on the efficacy of cued exercises. The rationale of applying sensory cues is linked to their ability in directing subject's attention to the task of walking. Cognitive strategies (internally generated cues such as thinking about step length) are equally as effective as external visual spatial cues. However, attention strategies potentially have a high cost in terms of mental effort and fatigue as a result of using cognitive resources to generate the internal cue. External cues may thus require less effort and attention, and their use during more complex activities could facilitate walking. Dance therapy has been referred to as a valuable method of combining the different key components of a rehabilitation program designed for PD people. Dance is an integrated approach including cued movements (music supplies auditory cues, while the dance partner gives rhythmic somatosensory inputs), cognitive movement strategies, joint motion and muscle strength and endurance exercises. Furthermore, it has the adjunct value of training subjects while amusing them thus potentially increasing their adherence to the exercise program [3].

An important pitfall of even high-quality randomised controlled trials of rehabilitation efficacy in PD concerns the demonstration of a carryover effect long after treatment end.

It has been extensively studied as an intact striatum is required to retain newly learned motor skill over the long-term, as it were

part of a motor skill consolidation system. It has also been postulated that the striatum and other cerebral regions including the premotor area, supplementary motor area, and cerebellum probably collaborate in the acquisition of new skills, and even when the striatum is abnormal, the other regions may support motor skill performance. According to some Authors, however, improvements in motor performance would not be retained unless the striatum is intact. Such a conclusion bears important consequences on rehabilitation provision to subjects whose basal ganglia suffer from a degenerative process [4].

#### References:

- [1] Keus SH, Munneke M, Nijkrake MJ, Kwakkel G, Bloem BR. Physical therapy in Parkinson's disease: evolution and future challenges. *Mov Disord.* 2009 Jan 15;24(1):1-14.
- [2] Herman T, Giladi N, Hausdorff JM. Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *J Neural Transm.* 2009 Mar;116(3):307-18. Epub 2008 Nov 4.
- [3] Earhart GM. Dance as therapy for individuals with Parkinson disease. *Eur J Phys Rehabil Med.* 2009 Jun;45(2):231-8.
- [4] Rochester L, Baker K, Hetherington V, Jones D, Willems AM, Kwakkel G, Van Wegen E, Lim I, Nieuwboer A. Evidence for motor learning in Parkinson's disease: acquisition, automaticity and retention of cued gait performance after training with external rhythmical cues. *Brain Res.* 2010 Mar 10;1319:103-11. Epub 2010 Jan 11.

#### C8

#### Rehabilitation of dystonia

*Cristina Tassorelli*

Unit of Neurorehabilitation, National Institute of Neurology Foundation "C. Mondino", Pavia and Department of Public Health, Neurosciences, Experimental and Forensic Medicine, Section of Neurological Sciences, University of Pavia, Pavia

Rehabilitation represents one of the most direct and effective treatments for several forms of dystonia. Quality of life is improved by reducing general disability, increasing range of motion, recovering normal gait or voice, reduction of tremors, rigidity, pain and fighting depression.

Dystonia rehabilitation strategies should be comprehensive and include active exercise, motor, sensory, and cognitive retraining, often combined with other therapeutic interventions, which range from botulinum toxin injection to electrical stimulation. Furthermore, since assessment of success in rehabilitation therapies is often subjective, more efforts should be devoted to adopt qualitative indicators of success, both in the daily practice and even more so in clinical trial design.

In the definition of the rehabilitative approach, several issues must be considered and adapted to the individual situation. Identification and avoidance of triggers or, on the contrary, the positive use of suppression modalities (i.e. a contact stimulus, such as placing a hand on the ipsilateral or contralateral side of the face or neck in a patient with spasmodic torticollis) represents useful means to improve dystonia.

Some dystonic movements may last seconds or minutes, but others may last hours or weeks. These latter can lead to permanent contractures, cause bone deformity, or can significantly impair function. Appropriate use of upper and lower extremity splints and orthotics to support, guide, reduce, or stabilize movements can help prevent orthopedic deformities.

Physical therapy techniques (e.g., massage), slow stretching, and physical modalities (e.g., ultrasonography, biofeedback) may

be helpful in persons with focal or regional dystonias. Patients with generalized dystonia often benefit from gait and mobility training and instruction in the use of assistive devices.

Various psychiatric therapies and modalities have been used with limited success for the treatment of dystonia symptoms. These include relaxation training, sensory stimulation, biofeedback, transcutaneous electrical nerve stimulation, and percutaneous dorsal column stimulation.

Occupational therapy is similarly important for training of activities of daily living and for the adoption of proper postures in patients with impaired mobility. Adaptive equipment should be provided to enhance function.

Speech therapists can offer training and communication aids to patients with oromandibular or laryngeal dystonia.

## C9

### Rehabilitation of postural instability

*Elisa Pelosin*

Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa

Postural instability represent an important and widespread problem in most of the movement disorders and related conditions. Although Parkinson disease, Corticobasal Degeneration, Generalized Dystonia, Huntington's Disease, Multiple System Atrophy, Progressive Supranuclear Palsy and some of drug-induced movement disorders have a different pathophysiology, certainly share some motor symptoms such as postural instability and gait problems.

Reduced balance is known to be an important risk factor for falls in this population and is often associated with poor mobility, disability, and reduced quality of life in these patients.

Balance requires maintenance of the body's center of mass within the limits of the base of support while sitting or standing, and control of the center of mass while moving to a new base of support during walking or running. Balance is often assessed with tasks designed to make controlling the center of mass over the base of support difficult. However, many daily activities, such as walking or standing up from a chair, are also balance-related, as they require control of the center of mass while moving to a new base of support. Therefore, balance can be measured indirectly by tests of the individual's ability to perform balance-related activities, particularly in individuals with impaired mobility.

Most people with movement disorders will ultimately develop reduced balance, which worsens with disease progression. Reduced balance is associated with falls, poor mobility, disability, and reduced quality of life in most of these movement disorders. Furthermore, it is well known, that postural instability and some related problems respond only partially to the standard medication treatment in this group of patients.

In addition, it has been recently pointed out that cognitive impairments represent an independent contributing factor to increase the risk of falls in a variety of neurological patients population among which a lot of movement disorders.

For all these reasons, in the last years a pressing need to explore interventions that may significantly improve balance and so that preventing falls is growing rapidly.

In clinical practice, different modalities of treatment have been developed and found to be helpful in improving balance in these patients such as: stretching, progressive/aerobic exercise training, relaxation and muscle activation, strength and balance training, unweighted or weighted treadmill, proprioceptive training and augmented feedback. In addition, new techniques has been successfully used on balance recovery, taking advantage of the basis of some martial arts. Tai-Chi and Qigong training have shown a

significant improvement in balance, especially in Parkinson Disease. All these approaches were found to have a positive effect on postural instability as well as a moderate effect on gait velocity, and step/stride length. However, the effect of exercise and motor training on balance-related activities and then on prevention of falls is still unclear. Indeed it has been demonstrated that all these interventions are not sufficient to improve mobility and prevent falls in severely affected patients. In addition, it is important to underline that most of researches have been developed and tested in Parkinson patients, while data on the efficacy of physical therapy in the other movement disorders are still poor and conflicting. Moreover, across all of these studies, the interventions were clinically heterogeneous with regards to the type of exercise, to the frequency and duration of exercise being undertaken (between 6 and 36 hours spread over 4–12 weeks) and to the target group (some studies used a group intervention while other used an individual approach).

Altogether these results suggest that physical-therapists should consider including highly challenging balance training in exercise programs for people with postural instability and balance problems. Although many forms of exercise and motor training improve the performance of balance-related activities in this population, exercise that specifically involves movement of the center of mass, narrowing of the base of support, and minimizing upper limb support may produce the best results. Moreover, the growing possibility to combined physical therapy training with new technologies (wearable audio-biofeedback, virtual reality, game console) is paving the way to the development of innovative rehabilitation protocols, focused on balance and falls prevention. Recently, Mirelman and co-workers have demonstrated interesting results in PD patients and Mild Cognitive Impairment using both audio-biofeedback and virtual reality combined with treadmill training. Even if these preliminary results are encouraging, it is important to underline that the longer-term effects of exercise and motor training in patients with movement disorders remain unclear. For that reason, the possibility to test and verify these new approaches also in movement disorders other than PD patients is required.

Certainly, the progressive nature of all these disorders suggests that balance training would be required to be ongoing. Providing highly challenging balance training in a sustainable way for this population is problematic, as it is difficult to achieve the required level of challenge while maintaining safety in group or semi-supervised home-based programs. For these reasons, future research working toward the development of effective programs that are sustainable for the long term would be an important step in solving this problem.

### References:

- [1] Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *MovDisord*. 2008 Apr 15;23(5):631–40. Review.
- [2] Allen NE, Sherrington C, Paul SS, Canning CG. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. *MovDisord*. 2011 Aug 1;26(9):1605–15. doi: 10.1002/mds.23790. Epub 2011 Jun 14.
- [3] Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, Maddalozzo G, Batya SS. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med*. 2012 Feb 9;366(6):511–9.
- [4] Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A Biol Sci Med Sci*. 2011 Feb;66(2):234–40.

## COURSE “Complex therapies fo Parkinson’s disease”

### C10

#### Infusional therapies in Parkinson’s disease

*Letterio Morgante<sup>1</sup>, Maurizio Zibetti<sup>2</sup>*

<sup>1</sup>Dipartimento di Neuroscienze, Scienze Psichiatriche ed Anestesiologiche, Università di Messina, Messina

<sup>2</sup>Dipartimento di Neuroscienze, Azienda Ospedaliera Città della Salute e della Scienza, Torino

Progression of striatal denervation and short half-life (60–90 min) of oral levodopa cause severe motor complications in Parkinson’s disease (PD) patients with advanced disease, such as unpredictable fluctuations, delayed ON, dose failures and dyskinesia. Deep Brain Stimulation (DBS) is recommended in PD to manage such complications; however, a subset of patients is not eligible for surgery because of comorbid cerebrovascular disease, brain atrophy, presence of major depression or mild cognitive decline, older age. In such cases infusion therapies may be used to promote a continuous dopaminergic administration and improve those motor complications secondary to troublesome gastric emptying and intestinal absorption problems.

Apomorphine (APO) is a powerful D1 and D2 agonist characterized by an efficacy equivalent to oral levodopa, but with a significantly faster onset and shorter duration of effect. APO is administered as continuous subcutaneous infusion (APO-INF) by means of a portable mini-pump, usually activated during the waking day. The aim is to reduce oral medication as much as possible to avoid pulsatile therapy. Eligible patients for APO-INF are those with severe motor fluctuation and/or dyskinesia in spite of optimized medical therapy causing severe disability and poor quality of life. Moreover, good compliance of the patient and the caregiver is required in order to manage daily infusion. Exclusion criteria are: clinically significant orthostatic hypotension, current drug-induced psychosis not controlled by atypical antipsychotics, dementia, severe cardiac arrhythmias, severe liver or renal insufficiency, respiratory or cardiovascular disease.

After 3 days of domperidone p.o. (60 mg/day), the start of APO-INF in a naïve patient can be done according to two modalities: 1) all antiparkinson drugs, including levodopa, have to be discontinued 12 hours before starting APO-INF. Add-on of levodopa can be done successively according to patient’s needs; 2) antiparkinson drugs, excluding levodopa, have to be discontinued 12 hours before starting APO-INF. The process of tailing down levodopa will be done slowly over the months, until reaching the minimum efficacious dose. This second modality of APO-INF was demonstrated to be more efficacious in controlling levodopa induced dyskinesia.

At the starting day, apomorphine is infused at a dosage of 1 mg/hour and flow rate will be gradually increased of 1 mg with time intervals of 1 hour, until reaching a good clinical effect without significant side effects. Mean APO-INF dosages are 4–8 mg/hour during the waking day, with discontinuation at sleep time.

Clinical studies (level II and III trials) have demonstrated that APO-INF is efficacious in controlling severe motor fluctuations in PD with an amplitude of the response comparable to Levodopa and a reduction of “off” periods (from -40% to -87% according to the studies) and of levodopa daily dose. Dyskinesia are reported to be both decreased or unchanged; the only three studies directly comparing APO-INF and subthalamic deep brain stimulation (STN-DBS) demonstrated that surgery decreases dyskinesia at a higher extent compared to infusion therapy.

The most common side effect of APO-INF is the formation of local skin nodules, reflecting focal panniculitis, in most of the patients. Sometimes these nodules can get infected, requiring

antibiotics treatment or excision and rarely causing APO-INF discontinuation. Abdominal wall nodules can be minimized by regularly rotating injection sites, respecting scrupulous aseptic technique of needle insertion, using of very thin needles, massaging the injection site after removing the needle; moreover, low frequency ultrasound treatments have been found to be of benefit in reducing nodule formation as well not using higher concentration than 5 mg/ml apomorphine. Haemolytic anaemia is a rare complication which can be monitored by performing blood test every six months (full blood count, reticulocyte count and Coombs test). Short follow-up studies showed that psychosis and cognitive decline do not worsen in appropriately selected patients treated with APO-INF. There have not been reports of higher frequency of impulse control disorders in PD patients treated with APO-INF, although prospective studies are lacking; retrospective analysis of published cases have demonstrated that APO-INF is more frequently associated to punding and compulsive use of levodopa.

In conclusion, APO-INF is an efficacious treatment in PD patients with motor complications causing severe disability and poor quality of life. This treatment can be reserved in patients not fulfilling selection criteria for DBS, either due to brain atrophy/vascular comorbidity or co-occurrence of mild cognitive dysfunction and severe depression.

Intraduodenal delivery of levodopa/carbidopa gel (Duodopa) is an effective therapeutic option for the treatment of advanced PD complicated by motor fluctuations and dyskinesias. The direct intestinal infusion is generally maintained for 12–14 hours daily and has been shown to provide a more stable plasma levodopa concentration, allowing a better control of motor fluctuations and dyskinesias.

Duodopa is indicated for the treatment of advanced idiopathic PD patients with a sustained response to levodopa, with severe motor fluctuations and dyskinesia that are not adequately controlled by all combinations of oral medications available. The procedure is feasible also in patients over 70 years of age, in good general conditions and without a significant cognitive impairment. On the other hand, Duodopa is not recommended in patients with atypical parkinsonian syndromes, not responsive to dopaminergic treatment. The presence of a caregiver is very helpful for the correct use of the infusion device. Duodopa represents a further treatment option that is being added to various other consolidated treatments of the advanced phase (traditional oral poly-therapy, APO-INF, DBS). The most relevant negative aspects of Duodopa are the high cost of this therapy and the frequent technical problems with the infusion system (dislocation, kinking or obstruction of the intestinal tube). Furthermore, some cases of subacute axonal neuropathy during Duodopa treatment have been reported, possibly in relation to vitamin B6 deficiency.

#### References:

- [1] Antonini A and Tolosa E: Apomorphine and levodopa infusion therapies for advanced Parkinson’s disease: selection criteria and patient management. *Expert Rev Neurother* 2009;9:859–67
- [2] Morgante L, Basile G, Epifanio A, Spina E, Antonini A, Stocchi F et al: Continuous apomorphine infusion (CAI) and neuropsychiatric disorders in patients with advanced Parkinson’s disease: a follow-up of two years. *Arch Gerontol Geriatr Suppl* 2004;291–6
- [3] Gallagher DA, O’Sullivan SS, Evans AH, Lees AJ, and Schrag A: Pathological gambling in Parkinson’s disease: risk factors and differences from dopamine dysregulation. An analysis of published case series. *Mov Disord* 2007;22:1757–63
- [4] Fernandez HH, Odin P: Levodopa-carbidopa intestinal gel for treatment of advanced Parkinson’s disease. *Curr Med Res Opin* 2011;27:907–919.

**C11****DBS and stimulation**Leonardo Lopiano

Dipartimento di Neuroscienze, Università di Torino, Torino

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or Globus pallidus internus (Gpi) is an effective therapeutic option for the treatment of advanced Parkinson's disease (PD); in fact, many short-term studies have showed that continuous high frequency stimulation (130 Hz) of the target significantly improves PD cardinal symptoms and motor complications. More recently, large randomized controlled trials have demonstrated that after 6 to 12 months, STN-DBS is more effective than best medical therapy, while studies with 5 to 6 years of follow-up have shown that the improvement is maintained over time.

However, a worsening of axial symptoms is often observed with a consequent impairment of activities of daily living (ADL) and a worsening in the quality of life. Recent studies with a follow-up of 8-10 years of continuous high frequency stimulation showed a worsening of the functional state of operated PD patients, despite a persistent positive effect on motor symptoms. The development of L-dopa-unresponsive symptoms, mainly related to the disease progression, significantly influences the long-term outcome of DBS. In addition, cognitive impairment is progressively more relevant during the progression of PD and may contribute to the worse functional state of the patients.

In order to obtain the best outcome of PD-stimulated patients is fundamental a correct selection of patients and a correct choice of the target; moreover, the modulation of the frequency of stimulation as well as alternative modality of stimulation or new targets are under evaluation.

**References:**

- [1] Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol.* 2011 Dec; 68 (12):1550-6
- [2] Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, Artusi CA, Arduino N, Marchisio A, Lanotte M, Rizzone M, Lopiano L. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord.* 2011 Nov; 26 (13):2327-34
- [3] Vitek JL. Long-term benefit from deep brain stimulation of the subthalamic nucleus: is it for everyone? *Alzheimers Res Ther.* 2012 May 9; 4 (3):13
- [4] Vingerhoets FJ, Tagliati M. Treating PD axial signs with DBS: is two better than one? *Neurology.* 2012 Apr 3; 78 (14):1036-7

**C12****Practical Session**Fabrizio Stocchi<sup>1</sup>, Maurizio Zibetti<sup>2</sup><sup>1</sup>IRCCS San Raffaele Pisana Roma, Roma<sup>2</sup>Dipartimento di Neuroscienze, Azienda Ospedaliera Città della Salute e della Scienza, Torino

During this session we will provide practical information on the use of the various techniques employed in the treatment of the advanced phase of Parkinson's Disease. Participants will be able to familiarise with the different devices in use (continuous subcutaneous apomorphine pump, intrajejunal levodopa infusion pump, setting of different deep brain stimulation parameters) with videos of clinical cases and eventually with the presence of patients.

**COURSE "Medico-legal aspects in clinical practice of patients with movement disorders"****C13****Adverse reaction due to anti-parkinsonian treatment**Mario G. Rizzone

Dipartimento di Neuroscienze, Università di Torino, Torino

The treatment of Parkinson's disease (PD) is still symptomatic and based on the use of drugs belonging to a few pharmacological classes: levodopa, dopamine-agonists, iMAO-B, iCOMT, amantadine and anti-cholinergics.

All of these drugs, alone or in combination, can determine adverse reactions in PD patients.

Generally, an adverse drug reaction is defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.

Adverse drug reactions can be classified in different types; the principals are type A and type B reactions.

Type A reactions are dose-related, generally predictable, expected and usually linked to the pharmacological properties of the drug. They are usually not severe or deadly, but often their prevalence is high. Type B reactions are not dose-related; they are rare, unpredictable, unexpected but often serious, and they frequently require the drug withdrawal.

In the last decades the attention of the scientific community focused on potentially severe adverse reactions due to use of antiparkinsonian drugs: from the pleuro-pulmonary, pericardiac or retroperitoneal fibrosis due to ergot dopamine-agonists, to the 'sleep attacks' referred to the use of dopamine-agonists, to the most recent problem of the link between dopaminergic drugs and impulse-control disorders.

Those observations continue to raise both clinical and medico-legal relevant issues, requiring a multidisciplinary approach to the problem.

**Reference:**

- [1] Edwards, I.R., Aronson J.K., 2000. Adverse drug reactions: definitions, diagnosis and management. *Lancet.* 356, 1255-1259.
- [2] Antonini, A., Cilia, R., 2009. Behavioural adverse effects of dopaminergic treatments in Parkinson's disease: incidence, neurobiological basis, management and prevention. *Drug safety: an international journal of medical toxicology and drug experience.* 32, 475-563.
- [3] Bhatt, M.H. et al., 1991. Pleuropulmonary disease associated with dopamine agonist therapy. *Ann Neurol.* 30, 613-6.
- [4] Frucht, S. et al., 1999. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology.* 52, 1908-1918.

**C14****Side effects of the treatment of Parkinson's disease**Carlo Colosimo

Department of Neurology and Psychiatry, Sapienza University of Rome, Rome

Two categories of side-effects related to dopaminergic medications used in Parkinson's disease have particular relevance from the medico-legal point of view:

1 – Patients with Parkinson's disease may have excessive daytime somnolence and the so-called sleep attacks at the wheel while taking dopaminergic drugs (it is believed that all dopamine agonists can induce sleep attacks, and also levodopa).

2 – They may also show the so-called impulse control disorders (ICDs); these are common phenomena in Parkinson's disease, with a frequency of 13.6%. These abnormal behaviors are associated with impaired functioning and with depressive, anxiety and obsessive symptoms, novelty seeking and impulsivity. They are mainly associated with the use of the non-ergot dopamine agonists and may frequently lead patients to financial and legal problems.

#### References:

- [1] Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999 Jun 10; 52 (9): 1908-10.
- [2] Frucht SJ, Greene PE, Fahn S. Sleep episodes in Parkinson's disease: a wake-up call. *Mov Disord* 2000 Jul; 15 (4): 601-3.
- [3] Park A, Stacy M. Dopamine-induced nonmotor symptoms of Parkinson's disease. *Parkinsons Dis* 2011; 2011: 485063. Epub 2011 Apr 11.
- [4] Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, Weintraub D, Wunderlich GR, Stacy M. Impulse control disorders in Parkinson disease: a multicenter case-control study. *Ann Neurol* 2011 Jun; 69(6): 986-96

#### C15

##### Medico-legal aspects of Parkinson's Disease

Stefano Ferracuti

UOC Psichiatria, Azienda Ospedaliera Sant'Andrea, Sapienza Università di Roma, Roma

Besides the motor symptomatology, Parkinson disease patients typically display variable cognitive deficits, that may even configure a clear disexecutive symptomatology or a dementia. The possible and often frequent occurrence of psychiatric syndromes, usually with depressive manifestation, or, less frequently, with psychotic symptoms, may create dilemmas about the competency of these patients. The major problems in civil law regarding Parkinson disease patients will be discussed.

Iatrogenic manifestation may stem from dopaminergic drugs, such as stalking and gambling, behaviors that may have with possible forensic psychiatric implications. Finally the medical liability of such cases will be discussed under the current Italian legislation.

##### COURSE "Body-mind therapies"

#### C16

##### Rational for conventional therapies in PD: from epigenetic to neuronal plasticity

Francesca Mancini

Parkinson's Disease and Movement Disorders Center, San Pio X Clinic, Milano

Parkinson's Disease (PD) is a chronic disease characterized by the progressive degeneration of substantia nigra pars compacta neurons associated to the loss of striatal dopamine. This alteration is correlated also to an increase in glutamatergic corticostriatal drive, contributing to motor symptoms that are not responding to dopaminergic treatments.

Neural degeneration is due to the combination of different events: cellular oxidative stress, glutamatergic toxic action, apoptosis and intracellular proteins accumulation.

Although pharmacological therapies allow a fair control of motor symptoms, both in early and advanced phases, several treatment issues, such as the management of non motor symptoms, or the control of motor symptoms which may be either resistant to dopaminergic treatment or caused by the treatment itself, are still open.

In the last years, several studies have shown the beneficial effects of exercise in PD, but it's not clear yet whether its mechanism of action is compensatory or neuroprotective, and how it stimulates neuro-plasticity.

The phenomenon named "activity-dependent neuroplasticity" is defined as the modification within the Central Nervous System (CNS) in response to physical activity and that promotes a skill acquisition process. This phenomenon is demonstrated in patients with acute lesions of CNS, when exercise is able to activate the genetic modulation and consequently neural re-adaptation with re-learning. Less clear is the role of this mechanism in chronic neurodegenerative diseases, like PD.

Anyway, the genetic modulation stimulated by exercise is based on epigenetic mechanisms.

Epigenetic is the branch of biology that studies the causal interactions between genes and their product, or the cellular phenotype. Epigenetic mechanisms play a main role in acute regulation of genes expression as reply to environmental stimuli and experience. They refer, in the medium term, to functionally relevant modifications of the genome that do not involve a change in the nucleotide sequence. In particular, environmental stimuli or experiences, through epigenetic signals, act by means of DNA methylation and histone modification. These modifications of genetic expression promote, for example, the activation and secretion of growth factors (Brain Derived Neurotrophic Factors).

Several animal studies have demonstrated that motor training triggers lasting neuronal changes throughout the brain such as glial cell proliferation, changes in neurotransmitter levels, changes in the expression of endogenous neurotrophic factors which are associated with a protective/preventing effect to onset of extrapyramidal symptoms.

Other studies have demonstrated that exercise is able to activate compensatory strategies increasing dopamine release from dorsolateral striatum and reducing the dopamine transporter (DAT), which is the main clearance mechanism of dopamine from extracellular space. DAT inhibition allows a greater availability of dopamine, in terms of diffusion and permanence time.

To confirm these data, many studies highlight exercise efficacy on extrapyramidal motor and non motor symptoms in humans too, with positive effects on motor global function and disability.

Nowadays, exercise is recommended by the main scientific societies because higher level of exercise may reduce the risk of PD (class IV evidence), may improve parkinsonian motor impairment and disability (class II and III), may improve gait and reduce episodes of freezing (class III and IV). In particular, four specific treatment recommendations reached level II of evidence: cueing strategies to improve gait, cognitive movement strategies to improve transfers, exercise to improve balance and training of joint mobility and muscle power to improve physical capacity.

The selection of a particular physical activity has to take into account some specific issues that are needed to influence neuroplasticity. These issues are intensity, specificity, difficulty and complexity.

Exercise intensity is proportional to its ability of increase synaptic plasticity (neuronal activity); exercise has to be specific for the targeted symptoms (posture, equilibrium, etc); higher is the complexity of the activity, better is the structural adaptation;

physical activity should be progressively more difficult to carry out, with a learning curve. Moreover, if the physical activity is pleasant and rewarding, it is able to increase dopamine levels, promote learning and favor compliance. This last property is important because dopaminergic neurons are reactive to activity and inactivity (use it or lose it) and removal of activity can decrease or reverse the beneficial effects of exercise.

Thus, many are the evidences that show how exercise has to be considered a fundamental treatment, to recommend not only in the complicated phase of the disease, but also in the early stage.

Several activities are now available for patients, with a proven efficacy in PD.

Therefore, it is possible to individualize the type of exercise in relation to patient's preferences and stage of disease.

Some programs of conventional physiotherapy can present the desirable features but it is rarely available in a continuous manner and it is often perceived as not rewarding.

Alternatively, several other activities are proposed, collectively named "non conventional" or "psycho-motor" or "body-mind" therapies. These are complex interventions integrating physical, psychosocial, emotional, spiritual, and behavioral elements and promoting the mind-body interaction.

Mind-body therapies focus on the relationships among the brain, mind, body, and behavior, and their effect on health and disease. Mind-body therapies are often implemented by patients because of the playful aspects and the possibility to play a more active role. These therapies are often carried out in groups, favoring socialization. Moreover, they are organized in order to modulate their intensity, they are performed with an increasing complexity during the activity learning and can be selected on the basis of the specific symptoms that need to be targeted, as well as patients' tastes and characteristics.

#### References:

- [1] Petzinger GM, Fisher BE, Van Leeuwen JE, Vukovic M, Akopian G, Meshul CK, Holschneider DP, Nacca A, Walsh JP, Jakowec MW. Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Mov Disord.* 2010;25 Suppl 1:S141-5.
- [2] Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord.* 2008 Apr 15;23(5):631-40. Review.
- [3] Hirsch MA, Farley BG. Exercise and neuroplasticity in persons living with Parkinson's disease. *Eur J Phys Rehabil Med.* 2009 Jun;45(2):215-29.
- [4] Ang ET, Tai YK, Lo SQ, Seet R, Soong TW. Neurodegenerative diseases: exercising toward neurogenesis and neuroregeneration. *Front Aging Neurosci.* 2010 Jul 21;2. pii: 25.

#### C17

### Occupational and alternative therapies in the management of Parkinson's disease: review of literature

Nicola Modugno

Istituto Neuromed, Pozzilli (IS)

Occupational or alternative therapies are unconventional approaches that clinicians use to improve motor and non motor symptoms control when conventional medical and rehabilitative therapies produce only a partial recovery. The general impression is that as the disease progresses, a parkinsonian patient needs to be not only treated and rehabilitated but also assisted, because too often he is socially isolated, has a bad quality of life and lack of self confidence. When this is the case, PD patients worsen motor and

non motor control and alternative therapies might help. The aim of this approaches is to preserve as longer motor and non motor skills, recreate self confidence and improve relations and the quality of life. It is not possible, at the moment, to provide recommendations based on evidence even if different studies demonstrated that physical activity, training and artistic activities can improve motor and non motor symptoms, unexpectedly.

Several activities such as physical activities, tai chi, yoga, music, dance and tango and acupuncture have been tested in PD patients. Each study has demonstrated variable clinical improvements after a period of activity but all studies have a limited power for methodological reasons. It can be however suggested that physical activity, balance and proprioceptive training, music therapy, tango and tai chi are useful to ameliorate the physical and mental status of the patients and eventually motor and non motor symptoms. Improvements can be small and limited in time but also quite significant and for longer time. Generally, when the training is interrupted the improvements decay with time. Some studies have also tested acupuncture, biofeedback, osteopathy, Trager Therapy but a significant effect has not been demonstrated. Speech therapy can improve significantly voice disorders but it is still unclear which is the best method. In conclusion, also supported from recent Scottish Guidelines (SIGN), it can be suggested that multidisciplinary alternative activities are a good practice for PD patients. It is still not possible to provide recommendations based on evidence and further controlled studies need to be performed.

#### References:

- [1] Suchowersky O, Gronseth G, Perlmutter J, Reich S, Zesiewicz T, Weiner WJ. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006 Apr 11;66(7):976-82.
- [2] Diagnosis and pharmacological management of Parkinson's disease. A national clinical guideline "Scottish Intercollegiate Guidelines Network" 2011
- [3] Dixon L, Duncan DC, Johnsn P, Kirkby L, O'Connell H, Taylor H, Deane K. Occupational therapy for patients with Parkinson's disease. *Cochrane Database of Systematic Reviews* 2007, Issue 3.
- [4] The professional guide to Parkinson's Disease. Parkinson's Disease Society 2011
- [5] Diagnosis and pharmacological management of Parkinson's Disease. A national clinical guideline. Scottish intercollegiate guidelines network. 2010

#### C18

### Motor activity promotion, musicotherapy and social theatre as alternative therapies for Parkinson's disease

Ernesto Gastaldo<sup>1</sup>, Francesca Mancini<sup>2</sup>, Nicola Modugno<sup>3</sup>

<sup>1</sup>Unità Operativa Complessa di Neurologia, Azienda ULSS 12 Veneziana, Ospedale dell'Angelo, Mestre (Venezia)

<sup>2</sup>Parkinson's Disease and Movement Disorders Center, San Pio X Clinic, Milano<sup>3</sup>Istituto Neuromed, Pozzilli (IS)

Physiotherapy in PD should play a significant role in the maintenance of the physical state of patients and improve the motor and non motor symptoms. At the moment there is lacking of recommendations about which is best approach and, even if it is not possible to give recommendations, there is a general impression that alternative therapies and more olistic approaches might help significantly patients in improving the control of their symptoms.

Alternative therapies are different activities such as music, dance, theater and physical activities that have the aim to help patients in enjoying, developing new skills and projects.

In the first part brief extracts of “health promotion motor activity” sessions videos with ipokinetic movement disorders patients will be showed. Motor activity promotion is an adapted to pathology proposal, based on music and dance: through complex movement motor and cognitive skills are trained with a consequent improvement of motor and cognitive fitness and mood. The aim therefore is not to reduce the neurologic disability (as in the sanitary approach) but to train and to expand people’s potentials and health. Such activity should be paired to the sanitary approach (pharmacological and physical therapy), by inducing pleasure in movement and by stimulating people’s activity.

The typical session (in these videos managed by a dancer, Giulia Brugnoli) is in group, with four defined steps: Warm-up, First step: «cleaning the movement», Second step: «choreography», Cool-down. These activities have been evaluated in numerous studies confirming the subjective improvement referred by the patients, both on motor and quality of life items.

The concept of the importance of complex movements in PD patients are also well explained by videos on activities such as Musicotherapy, Tai Chi, Pilates, that will be showed.

In the second part brief extracts of the activities organized by Parkinzone Onlus ([www.parkinzone.org](http://www.parkinzone.org)) will be showed. Parkinzone Onlus have developed a model to rehabilitate and to assist patients with PD through the active participation to laboratories of social theater alone or integrated with dance and music.

In a recent paper [5] we demonstrated that a patient who participate regularly to these activities can improve significantly non motor symptoms such as anxiety, apathy, anhedonia, social retire and the quality of life, and successively motor symptoms too.

In the extracts learning activities in the laboratories, rehearsals and other activities will be shown.

## References:

- [1] Pacchetti C, Mancini F, Aglieri R, Fundarò C, Martignoni E, Nappi G. Active music therapy in Parkinson’s disease: an integrative method for motor and emotional rehabilitation. *Psychosom Med.* 2000;62:386-93.
- [2] Fazio P, Brugnoli G, Della Coletta E, Quatralo R, Granieri G, Da Ronch C, Gastaldo E, Granieri E. The efficacy of Motor Training with pleasant Music in Parkinson’s Disease. *Neurol Sci* 2005;26,S241
- [3] Gastaldo E, Izzia G, Granieri E, Nagliati C, Brugnoli G, Preda F, De Gennaro R, Da Ronch C, Caniatti L, Casetta I, Tola MR, Granieri. The Efficacy of Emotional and Functional Stimulation on Motor Promotion in Multiple Sclerosis. *Neurol Sci:* 2007;27,126-127
- [4] Granieri G, Fazio P, Simioni V, Allione L, Brugnoli G, Nagliati C, Groppo E, De Gennaro R, Gentile M, Gastaldo E, Casetta I, Granieri E. Accelerometric Gait Analysis Among Parkinson’s Disease after an adapted Motor Activity. *Neurol Sci.* 2010;31, S37.
- [5] Modugno N, Iaconelli S, Fiorilli M, Lena F, Kusch I, Mirabella G. Active theater as a complementary therapy for Parkinson’s disease rehabilitation: a pilot study. *ScientificWorldJournal.* 2010, 10:2301-13.
- [6] COURSE “Management of cognitive and behavioral disturbances in Parkinson’s disease and movement disorders”

## C19

### Cognitive evaluation

Gabriella Santangelo

Department of Psychology, Second University of Naples, Caserta and Neurodegenerative Diseases Center, University of Salerno, Salerno

Parkinson’s Disease (PD) is a neurodegenerative disease characterized by motor symptoms and non motor symptoms (sleep disorders, gastrointestinal disorders, affective and behavioural disturbances, cognitive dysfunctions including selective Cognitive Deficits (CD), [1] Mild Cognitive Impairment (MCI) and frank dementia). The MCI is common in PD patients (mean prevalence, 27%) and it is associated with several demographic (advanced age) and clinical (disease duration and severity) aspects [2,3]. Four clinical subtypes of MCI exist (amnestic vs. nonamnestic, and single- vs. multiple-domain); among these subtypes, non-amnestic, single-domain impairment (i.e., any single nonmemory domain) is the most common subtype. The MCI-PD is a predictive factor for dementia; therefore the evaluation of DC or MCI in PD patients seems to be relevant in order to identify individuals at high risk for developing dementia and who may benefit from preventive strategies.

Recently, the Movement Disorders Society Task Force has proposed and delineated diagnostic criteria useful for identifying of MCI-PD [4]. These criteria utilize a two-level operational schema depending on the comprehensiveness of neuropsychological testing. Level I and II categories differ regarding method of assessment and level of diagnostic certainty. Level I is based on an abbreviated cognitive assessment by means of screening tools (Montreal Cognitive Assessment, Parkinson’s Disease-Cognition Rating Scale, Scales for Outcomes of Parkinson’s Disease-Cognition, Mattis Dementia Rating Scale) or limited neuropsychological battery including less than two tests within each of the five cognitive domains, or assessing less than five cognitive domains. Level I criteria provide less diagnostic certainty than level II. This latter level is based on administration of formal, comprehensive neuropsychological testing that includes at least two tests for each of the following five cognitive domains: attention and working memory as well as executive, language, memory, and visuospatial functions. Impairment should be present on at least two tests, either within a single cognitive domain or across different cognitive domains. The MDS task force recommends the use of two cognitive tests for each of the cognitive domains and proposed examples of tests to assess cognitive domains: Word list learning test with delayed recall and recognition conditions, Prose recall test with a delayed recall condition, Brief Visuospatial Memory Test-Revised (BVMT-R) to assess memory domain; WAIS-IV (or earlier version) Letter Number Sequencing, WAIS-IV Coding (or earlier version) or other substitution task, Trail Making Test, Digit span backward or digit ordering, Stroop color-word test to assess attention and working memory; Wisconsin Card Sorting Test (CST), or modified CST (Nelson’s modification), Tower of London test-Drexel version, or Stockings of Cambridge (CANTAB), Verbal fluency test and 10 points Clock Drawing Test to assess executive functions; WAIS-IV (or earlier version) Similarities, Confrontation naming task to assess language; Benton’s Judgment of Line Orientation, Hooper Visual Organization Test and Clock copying to assess visuospatial functions.

The proposed MDS Task Force PD-MCI criteria provide a uniform method to characterize and diagnose the MCI-PD. These criteria are not validated, but they represent useful guidelines to perform a correct assessment to identify parkinsonian patients at high risk for developing of dementia.

## Reference:

- [1] Barone P, Aarsland D, Burn D, Emre M, Kulisevsky J, Weintraub D. Cognitive impairment in nondemented Parkinson’s disease. *Mov Disord* 2011;26:2483-2495.
- [2] Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, Burn D, Barone P, Pagonabarraga J, Allcock L, Santangelo G, Foltyniec T, Janvin C, Larsen JP, Barker RA, Emre

- M. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology* 2010;75:1062-9.
- [3] Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, Rodriguez-Oroz MC, Tröster AI, Weintraub D. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord* 26:1814-24.
- [4] Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012;27:349-56.

## C20

### Behavioural framework

#### Roberta Biundo

"Fondazione Ospedale San Camillo", Venice Lido (VE)

Among the common non-motor symptoms in Parkinson's disease (PD) impulsive and compulsive behaviour (ICBs), have surged to relevance as they may develop in relationship to dopaminergic drug therapy. It is important to recognize ICBs because they are underreported (more than 10-15% of PD patients may develop ICDs) and because of the considerable distress they cause to patients and caregivers.

Also known as repetitive and reward-seeking behaviours, ICBs include impulse control disorders (ICDs) namely pathological gambling, binge or compulsive eating, pathological hypersexuality and compulsive shopping, punting (non-goal oriented behaviors consistent with prior work or hobby experiences), dopamine dysregulation syndrome (DDS) (compulsive use of dopaminergic treatment with secondary cognitive and behavioural disturbances) and more recently hoarding (failure to discard large numbers of possessions that appear to be useless), kleptomania (failure to resist urges to steal items) and impulsive smoking.

The multicentre North American DOMINION cross-sectional study (3090 patients) is the largest epidemiological study of ICDs in Parkinson's disease although the study was retrospective and diagnosis was based on a telephone interview. The authors reported a 6-month ICDs prevalence of 13.6% (pathological gambling 5.0%, compulsive sexual behaviour 3.5%, compulsive buying 5.7%, and binge eating disorder 4.3%) [2]. In an Italian case control study, the prevalence of ICD in PD was 28% vs. 20% in healthy non-PD controls highlighting the importance of using a structured interview with patient and caregiver in the assessment of these disturbances [6]. Although similar frequencies of ICDs have also been identified in other dopamine agonist (DAA) treated conditions such as restless-leg syndrome or fibromyalgia, the prevalence of ICDs in PD on DAAs is found to be more common than in the general population. ICDs frequencies did not differ between "de novo" PD patients and non-PD controls [3], suggesting that maladaptive behaviours may be the result of an interaction between predisposing factors and dopaminergic medication and that the presence of Parkinson's disease alone can not be considered neither the cause nor a protective factor for ICDs. Among the potential risk factors for the development of ICBs there are the use of levodopa and dopamine agonists (specially when given in combination), gender (male seems to be more predisposed to develop hypersexuality and gambling, women more prone to develop compulsive shopping and binge eating), younger age at PD onset, a pre-PD history of ICBs symptoms, personal or family history of substance abuse, and high impulsivity and novelty-seeking personality traits. Recently, the akinetic-rigid PD phenotype was suggested to be associated with greater impulsivity and

risk taking traits than the tremor-dominant phenotype. Moreover other studies showed that presence of ICDs in PD are associated with depressive, anxiety and obsessive symptoms and impaired activities of daily living and that different ICDs subgroups may be differently associated with personality traits (gambling and compulsive shopping subgroups score higher in novelty seeking compare to binge eating and hypersexuality ones).

Brain regions functionally involved in these aberrant behaviours are the basal ganglia, orbitofrontal cortex, ventrolateral prefrontal cortex, the amygdale and the hippocampus. These regions are known to play a role in reward-based learning, response inhibition and decision-making and several theories in impulsivity and addiction underlined their role in the development of repetitive reward-seeking maladaptive behaviours. The preference of small immediate over delayed rewards of larger value is known to be associated with impulsivity and impaired decision-making and to be a common feature shared by ICDs and substance use disorders.

Functional neuroimaging studies in healthy subjects showed that activities in medial orbitofrontal cortex, amygdale and ventral striatum increase during reward events [4], while increased activities in ventrolateral prefrontal cortex, ACC and ventral striatum is associated with decision making under risk [5]. These findings support the concept of reduced engagement of brain areas involved in the prevention of negative outcomes (VLPFC) (bottom-up regulation) and an increased role of areas mediating goal-directed behaviour via motivational circuits (medial OFC) (top-down regulation). In non-PD population with gambling, substance disorders and binge eating, a reduced activation of the mesocorticolimbic "reward" system has also been reported. Weintraub et al., [13] found reduced ventral striatal activity in PD with ICDs, suggesting that ICDs in all these population share the same common mechanism.

Fronto-striatal circuits based cognitive tests such as planning, attention and set shifting are more commonly impaired in PD [2] and could be associated with ICDs in normal population and in untreated PD [1]. However cognitive studies focusing on frontal lobe function alteration in PD with ICDs are controversial. Santangelo et al., [9] showed executive dysfunction associate to maladaptive behaviour in PD while Siri et al., [10] found no differences in frontal lobe functions between gamblers vs. no gamblers. One possible explanation may be associated to the use of Frontal Assessment Battery (FAB), a brief screening instrument with limited specificity for dorsal or ventral prefrontal function. Using a more comprehensive neuropsychological battery, Biundo et al., [2] showed relatively preserved function in PD-ICDs with the exception for slower performance in the Trail Making Test B-A suggesting difficulties to maintain goal-directed tasks and suppress irrelevant responses. Pathological gamblers seem to have reduced response shifting after losses supporting the hypothesis of impaired sensitivity to negative reinforcers. Other studies showed visuo-spatial working memory impairment in PD "on" medication with ICDs compared to PD controls [11]. Overall, these data suggest the involvement of dorsolateral cortico-striatal network in PD with ICDs as well as the influence of DA hyper/hypoconcentration also on this circuit. In non-PD subjects with ICDs, there is reduced decision-making abilities and executive dysfunction compared to controls [7]. However, further studies are needed to clarify the cognitive profile of PD with or without ICDs.

Patients and caregivers should be warned about the risk of development ICDs at treatment onset and actively questioned on follow up. Patients with family history for ICBs are at greater risk and should be followed more accurately. There are limited options in terms of assessment instruments for ICDs and related disorders in PD. Some of them investigate the whole ICDs spectrum [diagnostic criteria from DSM IV TR, the Minnesota Impulsive

Disorders Interview (MIDI)], others are disorder-specific screening instruments used in PD [the South Oaks Gambling Screen (SOGS), the Buying Questionnaire, a clinician designed hypersexuality questionnaire, a punding questionnaire, and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)]. These questionnaires do not investigate the severity of ICDs but only the presence/absence of maladaptive behaviors. However assessing the severity of these behaviors is important. In this regard the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale (QUIP-RS) has been recently validated and promises to be a useful tool to establish an optimal diagnostic cut-off point as well as to monitor changes over time [12].

## References:

- [1] Antonini A, Siri C, Santangelo G, et al., Impulsivity and compulsivity in drug-naïve patients with Parkinson's disease. *Mov Disord.* 2011 Feb 15;26(3):464-8.
- [2] Biundo R, Formento-Dojot P, Facchini S, et al., Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. *J Neurol Sci.* 2011 Nov 15;310(1-2):64-9.
- [3] Cilia R, Ko JH, Cho SS, et al., Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiol Dis.* 2010 Jul;39(1):98-104. Epub 2010 Mar 22.
- [4] Hampton AN, Adolphs R, Tyszka MJ, et al., Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. *Neuron* 2007 55:545–555
- [5] Hewig J, Straube T, Trippe RH, et al., Decision-making under risk: an fMRI study. *J Cogn Neurosci* 2009 21:1642–1652
- [6] Isaias IU, Siri C, Cilia R, et al., The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Mov Disord.* 2008 Feb 15;23(3):411-5.
- [7] Marazziti D, Catena Dell'osso M, et al., Executive function abnormalities in pathological gamblers. *Clin Pract Epidemiol Ment Health* 2008 4:7
- [8] Rao H, Mamikonyan E, Detre JA, et al., Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov Disord.* 2010 Aug 15;25(11):1660-9.
- [9] Santangelo G, Vitale C, Trojano L, et al., Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. *Mov Disord.* 2009 Apr 30;24(6):899-905
- [10] Siri C, Cilia R, De Gaspari D, et al., Cognitive status of patients with Parkinson's disease and pathological gambling. *J Neurol.* 2010 Feb; 257(2):247-52.
- [11] Voon V, Reynolds B, Brezing C, et al. Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl)* 2010; 207:645–659.
- [12] Weintraub D, Mamikonyan E, Papay K, et al., Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Mov Disord.* 2012 Feb;27(2):242-7.
- [13] Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010; 67:589–595

## C21

### Pharmacologic treatment and clinical cases

Manuela Pilleri

Fondazione Ospedale San Camillo, Venice Lido (Venezia)

The currently available evidence supports the use of cholinesterase inhibitors in patients with Parkinson Disease Dementia (PDD), with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating

scales. The effect of these drugs in Lewy body disease remains unclear.

On the other hand, memantine has been shown to improve global clinical status and behavioural symptoms and QOL in Lewy body dementias, while no effect was noticed in patients with PDD.

Pharmacological treatment with clozapine has proved effective against psychosis in Parkinson's disease, but is associated to the risk of agranulocytosis; quetiapine does not require any special precaution or plasmatic parameters monitoring, thus nowadays it is considered the elective therapy for psychosis in PD; due to safety issues, olanzapine is not currently employed.

Recently, ziprasidone has been shown to be at least as effective as clozapine to ameliorate psychotic symptoms in PD in a 4-week, randomized, single-blind comparison with clozapine; this evidence worth further confirmation, due to the methodological limits of this study.

As regards non pharmacologic approaches, some studies have reported improvements in patient performance using cognitive stimulation programs.

Finally, we should point out the possible positive and negative effects of dopaminergic drugs on cognitive and behavioral features: therapy simplification, instead of add-on of new stimulating or sedative drugs, remains the first choice approach for the treatment of neuropsychiatric complications of PD.

## References:

- [1] Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database Syst Rev.* 2012
- [2] Emre M, Tsolaki M, Bonuccelli U et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, doubleblind, placebo-controlled trial. *Lancet Neurol* 2010; 9: 969 – 77.
- [3] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebocontrolled trials. *JAMA* 2005; 294: 1934 – 43.
- [4] Pinter L, Valldeoriola F, Baillés E, Martí MJ, Muñoz A, Tolosa E. Ziprasidone versus clozapine in the treatment of psychotic symptoms in Parkinson disease: a randomized open clinical trial. *Clin Neuropharmacol.* 2012 Mar-Apr;35(2):61–6.
- [5] Rand D, Eng JJ, Liu-Ambrose T, Tawashy AE. Feasibility of a 6-month exercise and recreation program to improve executive functioning and memory in individuals with chronic stroke. *Neurorehabil. Neural Repair* 2010; 24: 722–29.

## COURSE “Diagnosis and management of hyperkinetic movement disorders”

### C22

#### Movement disorders: suggestions for a clinical diagnosis

Anna Rita Bentivoglio

Istituto di Neurologia, Università Cattolica, Roma

The dystonic movements are jerky, rhythmic, or may be irregular, slow or fast, but they are structured and always show a certain repetitiveness; this clinical feature distinguishes the movement from other dystonic hyperkineses. Furthermore, the dystonic movements have a prevalent direction. When dystonia affects long muscles (trunk, limbs) generally produces a torsional movement along the major axis.

These aspects are not present in choreic movements, which are more irregular and give the impression of flowing from one muscle to the contiguous ones. Furthermore, some choreic movement may

be disguised into a voluntary movement (paracinesia), and this is peculiar of choreic dyskinesias.

The atetotic movement is a distal movement of the limbs.

Myoclonus is fast (shock-like), can be repetitive, intermittent, or rhythmic, but does not produce twisting. Tics are involuntary movements, simple or complex (comprising structured sequences), their phenomenology is very variable: they can be short and quick as myoclonic jerks (clonic tics), or may result in prolonged contractions (“dystonic” tics). The latter may be indistinguishable from dystonic movements, whereby the diagnosis of tics is reinforced when it is noted that: the patient can voluntarily control the movements, movements are also present during sleep, and when rapid tics or other features of Gilles de la Tourette syndrome are evident.

Besides motor tics are, also phonic tics may occur; similarly to motor tics can be simple (guttural sounds, vocalizations) or complex (words, phrases).

#### References:

- [1] A.Kishore & D.B. Calne. Approach to the patient with a movement disorder and overview of movement disorders. Chapter 1. In: *Movement Disorders*, 2nd Edn. R. L. Watts and W. C. Koller (editors). Published by McGraw Hill Medical Publishing, Columbus. ISBN 0-07-137496-5
- [2] Elia AE, Lalli S, Albanese A. Differential diagnosis of dystonia. *Eur J Neurol*. 2010 Jul; 17 Suppl 1:1-8. Review. PubMed PMID: 20590801.
- [3] Ha AD, Fung VS. Huntington’s disease. *Curr Opin Neurol*. 2012 Aug;25(4):491-8. PubMed PMID: 22772878.
- [4] A.R. Bentivoglio, R. Di Giacomo. Malattia di Parkinson ed altri disturbi del Movimento. In: *Trattato di Medicina Interna*. G. Gasbarrini. Ed. Verduci. Vol.2, Sez. XVI, Cap. 200. 2010 ISBN 8-87-6208324-8

## C23

### Instrumental and genetic diagnosis

Peter Pramstaller

Centro di Biomedicina, EURAC Research, Bolzano

Hyperkinetic movements represent a group of disorders very heterogeneous from an etiological, phenotypic and genotypic point of view. Their diagnosis is often complex, being able to occur both in isolation or in combination with each other, and requires, in addition to a proper semeiological classification, a series of diagnostic investigations. They are represented by tremor, dystonia, chorea, myoclonus, and ICT. Since they can be a symptom of systemic and/or nervous system disorders, the initial phase of the diagnostic process often requires the exclusion of secondary causes by mean of both biochemical and instrumental procedures. The differential diagnosis of primary forms is also often complex, both because of the wide phenotypic overlap between the various syndromes, and for the partial etiological knowledge in this field. A key role is represented by molecular biology investigation: many of these movement disorders have a genetic basis, in some cases well characterized (Huntington’s disease, some forms of primary dystonia), in other hypothesized based on the detection of genetic factors susceptibility (some forms of focal dystonia, Tourette’s syndrome). Moreover imaging studies play an important role in the diagnostic workup of hyperkinetic syndromes: functional neuroimaging, structural investigations of nuclear medicine and neurophysiological type can help in the differential diagnosis between various hyperkinetic syndromes, and they also brought more knowledge of the pathophysiological basis of this type disorders.

#### References:

- [1] Mascalchi M, Vella A, Ceravolo R. Movement disorders: role of imaging in diagnosis. *Journal of magnetic resonance imaging* 2012; 35: 239-256.
- [2] Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis and pathogenesis. *Lancet neurology* 2011; 10: 1074-85;
- [3] Walker FO. Huntington’s disease. *Lancet* 2007; 369: 218-228.
- [4] Robottom BJ, Factor SA, Weiner WJ. Movement disorders emergencies Part 2: hyperkinetic disorders. *Arch Neurol*. 2011 Jun;68(6):719-24.

## C24

### Iperkinetic movement disorders: treatment

Paolo Del Dotto

U.O.C. Neurologia, Ospedale Versilia, Az. USL12, Viareggio (Lucca)

The most common hyperkinetic movement disorders are represented by L-dopa induced dyskinesias, choreic syndromes, particularly Huntington’s disease, tardive dyskinesias and dystonias.

L-dopa-induced dyskinesias in advanced Parkinson’s disease are the prevailing hyperkinetic disorders in clinical practice. Early therapy with dopamine agonists is associated with delayed appearance of these complications. Once dyskinesias develop, dopaminergic treatment manipulation can be made (L-dopa dose reduction and dopamine dose increase). Amantadine, an NMDA receptor antagonist, is so far the only approved compound with evidence of providing a sustained antidyskinetic benefit, supporting the hypothesis of glutamate overactivity in the development of L-dopa induced dyskinesias. More continuous delivery of dopaminergic medications, such as through intestinal (Duodopa) or subcutaneous route (apomorphine), has been associated with less dyskinesias. New nondopaminergic agents, particularly glutamate and A<sub>2A</sub> adenosine antagonists, have shown promising antidyskinetic effects in early clinical trials, but long-term safety, tolerability and efficacy studies are still required. In most severe cases deep brain stimulation of subthalamic nucleus usually is able to dramatically abate the severity of dyskinesias.

Choreic movements associated with Huntington’s disease and tardive dyskinesias are treated with classic and atypical neuroleptics. Recently, tetrabenazine, a reversible dopamine depleting agent that is highly selective for the central vesicular monoamine transporter type 2 (VMAT2), has been approved for the treatment of these disorders. Sometimes, amantadine can also be beneficial.

Currently, there are no known treatment that can reverse the course of primary dystonia. However, symptoms may usually be managed with a combination of treatments, such as atypical neuroleptics and botulin toxin. Surgical treatment, particularly deep brain stimulation of the globus pallidus, is another option to consider in more severe cases.

#### References:

- [1] Elahi B, Phielipp N, Chen R. N-methyl-d-aspartate antagonists in levodopa induced dyskinesia: a meta-analysis. *Can J Neurol Sci*. 2012;39:465-72.
- [2] Gottwald MD, Aminoff MJ. Therapies for dopaminergic-induced dyskinesias in Parkinson disease. *Ann Neurol*. 2011;69: 919-27
- [3] Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. *Clin Ther*. 2012; 34:1487-504
- [4] Kartha N. Therapeutic challenges in dystonia. *Neurol Clin*. 2010;28:927-40

## COURSE “Nutrition and neurodegenerative diseases”

### C25

#### Pathophysiology and management of dysphagia in Parkinsonian syndromes

*Enrico Alfonsi, D. Fontana*

Unità Operativa di Neurofisiopatologia del Territorio, Istituto Neurologico Nazionale, IRCCS “Casimiro Mondino”, Pavia

Epidemiologic studies show that dysphagia is present in about 53–54% of patients with Parkinson's Disease (PD). This frequency is also underestimated as neurogenic dysphagia is observed in quite all patients in late phases of the disease. Dysphagia can be showed by clinical examination or as subjective complaints in these patients. Occasional investigations used to explore the deglutition as the fiberoptic endoscopic evaluation of swallowing (FEES), the video-fluoroscopy (VFS), the manometry, or the recent electromyographic/electrokinesiographic investigation of swallowing can reveal abnormalities responsible for dysphagia in PD. In about 15–20% of PD patients without clinical findings of dysphagia radiological (VFS) signs of inhalation have been observed. Dysphagia severity is related to illness duration in PD. In these patients dysphagia appears most frequently at about 10<sup>th</sup>–11<sup>th</sup> years of disease. The onset of dysphagia is clearly different among the parkinsonian syndromes. This aspect could be very useful since dysphagia appears very early, at about 3–4 years from the onset of illness, in parkinsonian syndromes as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Lewy-body disease (LBD). Latency of dysphagia is related to survival in all parkinsonian syndromes. Most of the pathophysiological abnormalities related to the oral phase of swallowing (voluntary phase) can be related to typical symptoms of the parkinsonian syndromes due to dysfunction of sensory-motor integration as bradykinesia, hypokinesia, rigidity, and start hesitation. In the early phase of the disease these alterations are not yet able to cause dysphagia. Early swallowing abnormalities in PD can be corrected, almost in part, by L-Dopa and dopamine agonists. When pathophysiological mechanisms involve automatic/reflexive phases of deglutition (pharyngeal and esophageal phases) this therapy becomes ineffective. In this case logaedic treatments with adequate nutrition, selective treatments as botulinum toxin injected in the upper esophageal sphincter, myotomy of the cricopharyngeal muscle or, most definitively, the percutaneous endoscopic gastrostomy (PEG) could represent effective therapeutic options.

#### References:

- [1] Barer. *J Neurol* 1989;52:236–241.
- [2] Bird et al. *Age Ageing* 1994;23:251–254
- [3] Muller et al. *Arch Neurol* (2001);58:259–264
- [4] Pfeiffer, *Lancet Neurology* (2003), 2: 107–116.
- [5] Baijens and Speyer. *Dysphagia* (2009), 24:91–102
- [6] Alfonsi et al. *Neurology* (2007), 68: 583–590

### C26

#### Malabsorption and movement disorders

*Paolo Stanzione*

IRCCS Santa Lucia Foundation, European Centre for Brain Research CERC, Rome and Clinica Neurologica, Università di Roma “Tor Vergata”, Rome

L-dopa (LD) orally administered, is absorbed by the neutral amino acid transport system at duodenal level.

The gastric environment including: gastric motility, pH, inflammatory disease of gastric mucosa, amount and quality of food present in the gastroduodenal tract, may substantially affect of amino acid as well as L-dopa absorption.

Afterwards the cross of the blood brain barrier may be a second variable influencing the kinetic of L-dopa arrival to the cerebral tissue. The cross is regulated by neutral amino acid transport system as well.

From the clinical point of view reduction, delay, or any other change in the modalities of L-dopa transition through these two barriers is not evident in the initial stage of the disease. Intracellular storage capacity of residual dopaminergic terminals may largely buffer the possible reduction or lack of transition of a single dose of L-dopa from the intestine to the brain tissue. The large storage allow the dopamine to be released when necessary from the intracellular vesicles replete by previous L-dopa administrations. Thus in early stage a prolonged L-dopa treatment may still improve motor status after more than 15 days of withdrawal. Disease progression further reduces surviving dopamine fibres thus reducing or nullifying storage capacity. At this stage all factors able to affect the single dose absorption may affect motor performance during the day/night cycle. At this stage food (mainly protein food) in the gastroduodenal tract, may produce motor effect preventing the absorption of the single dose necessary to maintain an adequate level of L-dopa/dopamine at brain level. This is the classic after lunch lack of effect of L-dopa dose very often observed in advanced PD patients, if an adequate diet is not observed. Apart from food in the gastroduodenal tract, inflammatory conditions of stomach or duodenum, such as those produced by helicobacter pylori infection, may also substantially reduce L-dopa absorption independently from the food impact. Treatments able to eradicate inflammatory conditions, such as those due to helicobacter pylori, have been demonstrated to improve of about 20% the AUC after L-dopa administration. The effect is time locked and proportional to inflammation disappearance.

L-dopa solubility is maximal at 2–3 of pH. Treatment or conditions reducing gastric acidity may negatively affect L-dopa absorption. In particular treatment reducing gastric pH through proton pump inhibitors may double affect L-dopa absorption: through pump inhibition and through pH increase.

Gastroduodenal motility is also essential in order to let L-dopa progress from the stomach to the duodenum where it is absorbed. Intestinal motility is affected by disease itself so that constipation is a very common feature of the disease. Dopaminergic stimulation of intestinal autonomic system further reduce intestinal motility further reducing transition of L-dopa from stomach to duodenum. A correct treatment for constipation may also help to obtain a more constant L-dopa absorption.

#### References:

- [1] Pierantozzi et al. *Neurology* 2006; 66: 1824–1829.
- [2] Lee et al. *Mov Dis* 2008; 23(12): 1696–1700.
- [3] Nutt *JG Mov Dis* 2008; 23 Suppl. 3: S580–S584.
- [4] Travaglini et al. *Ann. Rev. Physiol.* 2006; 68: 279–305.

### C27

#### Nutrition and Dementia

*Alessandra Nicoletti*

Dipartimento G.F. Ingrassia, Sezione di Neuroscienze Università di Catania, Catania

The prevalence of dementia in the Western world is about 1% in individuals aged 60–64 years, but shows an almost exponential increase with age. Alzheimer's disease (AD) is the most frequent neurodegenerative dementia in the elderly, and it is probably due

to a complex interaction between genetic and environmental factors. Epidemiological studies have identified several environmental risk factors potentially associated with the development of AD such as low educational, hypercholesterolaemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, diabetes and malnutrition, while APOE 4 allele thought to account for most of the genetic risk.

Recently there are growing evidences concerning the possible role of dietary factors in the development of AD and the age-related cognitive decline. In particular, several epidemiological studies suggest that the risk of AD may be reduced in people with a high dietary or supplemental intake of antioxidant vitamins such as vitamin E and C or omega-3 fatty acids. Similarly, low serum levels of vitamin B12, vitamin C, folic acid, folate as well as hyperhomocysteinaemia have been associated with an increased risk of AD [1].

Epidemiological evidences concerning the possible role of nutritional factors are also supported by animal studies showing that administration of polyunsaturated fatty acids, uridine monophosphate (UMP) and choline increases the level of phosphatides, specific pre- or post-synaptic proteins and the number of dendritic spines – a requirement for new synapse formation [2-3]. This multi-nutrient approach in animals has also shown to decrease amyloid beta protein (Ab) plaque burden, to improve learning and memory through increased cholinergic neurotransmission and to have a neuroprotective effect in several mouse models of AD. Similarly, in vitro cell-culture studies have shown that both vitamin E and C can inhibit Ab deposition, neuronal cell death and apoptosis [4].

Although several evidences support the association between nutrition and cognitive status, the relevance of nutritional factors in AD has not been extensively studied to date and only few clinical trials using nutritional approaches in AD have been performed reporting conflicting results.

Current treatment options offer often only symptomatic relief, however, there is a growing body of evidence that nutritional intervention may be able to play a key role in the management of the disease. However, randomized clinical trials are needed to test this approach.

#### References:

- [1] Ramesh BN, Rao TS, Prakasam A, Sambamurti K, Rao KS. Neuronutrition and Alzheimer's disease. *J Alzheimers Dis*. 2010;19(4):1123-39.
- [2] Wurtman RJ, Ulus IH, Cansev M, Watkins CJ, Wang L, Marzloff G. Synaptic proteins and phospholipids are increased in gerbil brain by administration of uridine plus docosahexaenoic acid orally. *Brain Res* 2006; 1088: 83–92.
- [3] Sakamoto T, Cansev M, Wurtman RJ. Oral supplementation with docosahexaenoic acid and uridine-5'- monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res* 2007; 1182: 50–59.
- [4] Yatin SM, Varadarajan S, Butterfield DA. Vitamin E prevents Alzheimer's amyloid beta-peptide (1-42)-induced neuronal protein oxidation and reactive oxygen species production. *J Alzheimers Dis* 2000; 2: 123–131.

#### COURSE "Ataxias and spastic paraparesis"

##### C28

#### Hereditary ataxias

Alessandro Filla

Department of Neurological Sciences, Federico II University, Naples

We have recently proposed a pathogenic classification of hereditary ataxias (HA) in five main categories: 1. mitochondrial; 2. metabolic; 3. impaired DNA repair; 4. impaired protein folding and degradation, 5. channelopathies. Other pathogenic mechanisms have been recently recognized. Mitochondrial ataxias can be caused by mutations in nuclear DNA (Friedreich Ataxia; Mitochondrial Recessive Ataxia Syndrome; Infantile Onset Spinocerebellar Ataxia; Autosomal Recessive Cerebellar Ataxia 2) or in mitochondrial DNA (Myoclonus Epilepsy with Ragged Red Fibers; Neuropathy, Ataxia, and Retinitis Pigmentosa). Metabolic ataxias can be intermittent or progressive. They can be caused by hereditary disorders of the urea cycle, aminoacids, pyruvate, vitamin E and lipid metabolism, liposome and peroxysomal disorders. Ataxias associated with impaired DNA repair may be separated in ataxias caused by impairment of single strand break repair (Ataxia with Oculomotor Apraxia; Spinocerebellar Ataxia with Neuropathy 1; xeroderma pigmentosum; Cockayne syndrome) or double strand break repair (ataxia telangiectasia [AT]; AT-like disorder; possibly Ataxia with Oculomotor Apraxia 2). Ataxias associated with abnormal protein folding and degradation include ataxias caused by abnormal chaperones (Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; Marinesco-Sjögren), by mutations in PRNP gene (Gerstmann-Sträussler-Scheinker disease) or by expanded CAG triplet sequence. An expanded CAG encoding for polyglutamine sequence is responsible for SCA1–3, 6–7, 17. This is the most common cause for Autosomal Dominant Spinocerebellar Ataxias. Channelopathies, involving Ca and K channels, may cause episodic ataxias which have dominant transmission and early onset (Episodic Ataxia 1–2). Other possible causes of HA include RNA toxic gain of function (Fragile X-associated Tremor Ataxia Syndrome); endonuclease pathway (Polyneuropathy, Hypoacusia, Ataxia, Retinitis Pigmentosa, Cataract); opioid pathway (SCA23); structural proteins and vesicular trafficking (SCA5; Autosomal Recessive Cerebellar Ataxia 1; Salih ataxia); transglutaminases (SCA35); tau phosphorylation (SCA11).

#### References:

- [1] Arnheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med* 2012;366:636-46.
- [2] De Michele G, Coppola G, Coccozza S, Filla A. A pathogenetic classification of hereditary ataxias: is the time ripe? *J Neurol*. 2004;251:913-22.
- [3] Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *Lancet Neurol*. 2010;9:885-94.
- [4] Pandolfo M, Pastore A. The pathogenesis of Friedreich ataxia and the structure and function of frataxin. *J Neurol*. 2009;256 S1:9-17.
- [5] Klockgether T, Paulson H. Milestones in ataxia. *Mov Disord*. 2011;26:1134-41.

##### C29

#### Imaging of ataxias

Mario Mascalchi

Departement of Clinical Physiopathology University of Florence, Florence

Imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI) and spectroscopy (MRS), single photon emission computed tomography (SPECT), and positron emission tomography (PET) have been widely applied to the investigation of patients with acute or chronic ataxias. Fundamentally, CT has a role in the emergency evaluation of the patient with acute ataxia to ascertain brainstem or cerebellar hemorrhage and

to exclude a mass lesion in the posterior cranial fossa. Conventional MRI is the most frequently performed imaging investigation in patients with ataxia. It can support the diagnosis of acute cerebellitis and Wernicke encephalopathy by revealing T2 signal changes with a typical distribution. In patients with inherited or sporadic chronic ataxia it reveals three fundamental patterns of atrophy of the brainstem, cerebellum, and spinal cord which match the gross neuropathological descriptions. These are represented by olivopontocerebellar atrophy (OPCA), cortical cerebellar atrophy (CCA), and spinal atrophy (SA). A substantial correspondence exists among these patterns of atrophy shown by MRI and the etiological classification of inherited or acquired chronic ataxias. This, along with demonstration of T2 signal changes characteristic of some diseases, makes conventional MRI potentially useful for the diagnostic work-up of the single patient, especially in the case of a sporadic disease. MRS and non-conventional MR techniques including diffusion MR and functional MR have been used in patients with acute or chronic ataxia, but their exact role in the evaluation of the single patient is not yet established. They are currently investigated as potential tools to monitor progression of neurodegeneration in chronic ataxia and to serve as “surrogate markers” in clinical trials. Several radiotracers have been utilized in combination with SPECT and PET in patients with ataxia. Perfusion SPECT can reveal cerebellar blood flow abnormalities early in the course of cerebellitis. It has also been utilized to investigate perfusion of the brain in several inherited or sporadic chronic ataxic diseases, contributing to improved understanding of the pathophysiology of these conditions. Recently, perfusion SPECT has been tested as a “surrogate marker” to verify the effects of newly developed therapies in patients with a variety of chronic ataxias. Whole-body FDG-PET is recommended in patients with suspected paraneoplastic cerebellar degeneration to detect the primary malignancy. Brain FDG-PET has provided important information on the pathophysiology of several acquired and inherited conditions. PET and SPECT with radiotracers able to assess the nigrostriatal system or the density of D2 dopamine receptors in the striatum are increasingly used in patients with adult-onset sporadic ataxia for the differential diagnosis between multiple system atrophy in which overt striatal abnormalities are found and idiopathic late-onset cerebellar ataxia in which no abnormality is detected.

#### References:

- [1] Mascalchi M et al. MR spectroscopy of the cerebellum and pons in patients with degenerative ataxia. *Radiology* 2002; 223:371–378.
- [2] Mascalchi M, Vella A. Magnetic resonance and nuclear medicine imaging in ataxias. *Handbook of Clinical Neurology* 2012;103:85–110
- [3] Ginestroni A, et al. Neurodegeneration in Friedreich's ataxia is associated with a mixed activation pattern of the brain. A fMRI study. *Hum Brain Mapping* 2011 Jun 14. doi: 10.1002/hbm.21319. [Epub ahead of print]

#### C30

##### Hereditary Spastic Paraplegias

C. Fiorillo, E. F. Inguaggiato, Filippo M. Santorelli

IRCCS Fondazione Stella Maris, Dept. Child Neurology, University of Pisa, Pisa

Hereditary spastic paraplegias (HSP) are a heterogeneous group of neurological disorders. Insidiously progressive spastic weakness of the lower extremities is the common criterion in all

forms described. Clinically, HSP is differentiated into pure (uncomplicated) and complex (complicated) forms. Whilst pure HSP is predominantly characterized by signs and symptoms of pyramidal tract dysfunction, additional neurological and non-neurological symptoms occur in complicated forms. Autosomal dominant, autosomal recessive, and X-linked pattern of inheritance have been described and at least 50 subtypes, termed SPG1–50, have been genetically defined. Although in autosomal dominant HSP families 50–60% of etiologies can be established by genetic testing, genotype predictions based on the phenotype are limited with a high degree of intrafamilial variability and reduced penetrance. Autosomal recessive forms appear to be more heterogeneous and single forms fairly stereotyped in clinical terms.

We offer an overview on clinical, neurophysiologic, and neuroradiologic characteristics of the more common HSP subtypes. For quick reference, we also propose a laboratory strategy to help clinicians in prioritizing genetic testing.

##### COURSE “Functional assessment and program objectives in rehabilitation physiotherapy: what problems to which patients with Parkinson's disease?”

#### C31

##### Parkinson disease is not a motor disturbance only

Giovanni Fabbrini

Dipartimento di Neurologia e Psichiatria, Sapienza, Università di Roma, Roma

Parkinson's disease is characterized by rest tremor, bradykinesia, rigidity and postural instability. Recently it has become clear that non motor symptoms are also very frequent in parkinsonian patients. Some of these symptoms such as hyposmia, depression, constipation and REM behavior disorders may antedate the appearance of the typical motor signs. Non motor symptoms more frequently complicate the advanced phases of the disease. The most important non motor symptoms are: sleep disturbances (excessive daytime somnolence, sleep attacks, insomnia, parasomnias), neuropsychiatric disturbances (anxiety, depression, hallucinations, psychosis, impulse control disorder), cognitive disturbances (changes in executive functions, dementia), vegetative disturbances (urinary disturbances, constipation, sexual dysfunction, orthostatic hypotension) and sensory disturbances (particularly pain). Some non motor disturbances are related to the dopaminergic deficit (for example, motor disturbances during sleep), some are adverse events of the treatment (for example impulse control disorders) and others are the consequence of the degeneration of other neurotransmitter systems (for example, depression, dementia). A better knowledge of non motor symptoms is important for a complete assessment of patients with Parkinson's disease.

#### References:

- [1] Chaudhuri KR, Healy D.G, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol* 2006; 5:235–45
- [2] Adler CH. Non Motor Complication in Parkinson's disease. *Mov. Disord.* 2005; Suppl 11; S23–S29.
- [3] Schrag A. Psychiatric aspects of Parkinson's disease. *J Neurol* 2004 251: 795–804.
- [4] Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain* 2000;123:733–745

## C32

**The multidimensional assessment of rehabilitation for the clinical complexity of Parkinson's disease: new perspectives?***Simone Cecchetto*

Azienda ULSS 5 Ovest Vicentino, Arzignano (Vicenza) and Corso di Laurea in Fisioterapia, Università di Verona, Verona

The rehabilitation of patients with Parkinson's disease (PD) presents various aspects and levels of complexity. The physiotherapy process, as important part of the rehabilitative process, also reflected inside this complexity.

According to Systems theory, the patient is interpretable as a complex adaptive system. The various methods and schools of physiotherapy have developed over the years different models of interpretation, that is partial and simplified representations of reality, through which they interpreted from different points of view of the complexity of patient-oriented and consequently the rehabilitation treatment. It is felt the need to overcome the fragmentation of knowledge in rehabilitation, by building a conceptual framework and models of clinical reasoning to enable the sharing of language and experience between professionals, both within the physical therapy profession, both with other disciplines. The International Classification of Functioning Disability and Health (ICF) proposed by the WHO can contribute concretely to respond to this need. It propose a systematization of the body Structures and Functions and the actions and the interactions that a person can do, assessed in a standard environment (Activities), such as the rehabilitation gym, or in the context of the patient's life (Participation).

It is interesting the distinction between "Capacity", as indicator of the component Activities, and "Performance", as indicator of the component Participation. Capacity describes functioning of the person in a standard setting, without barriers or facilities; the capacity is an intrinsic characteristic of the person and it express what a person can do, regardless of the environment. The Performance describes functioning of the person in involvement in a life situation (home, work, etc.); the performance expresses what the person can actually do in their life contexts and depends on the impact that environmental factors have on the functioning [2].

In this context, it is possible to define the physical therapist (PT) aims primarily to an improvement in capacity by reducing the functional impairments resulting from the PD; however, since the ultimate goal is to maximize the Social Participation of a person, the PT should carefully consider, in collaboration with other multidisciplinary team members, as environmental factors affect the levels of performance, in order to plan appropriate interventions on these elements.

The adoption of the perspective proposed by the ICF suggests that the PT "widens the look" beyond the simple motor aspects, usually regarded as the only field of functional impairments of patients with MP of physiotherapist's interest, but also to cognitive, emotional and environmental factors. In particular, attention to environmental factors could be useful whenever barriers in the environment are not explicitly reported or it may not achieve a reasonable level of performance [3]. This allows to highlight aspects not considered such as the relationship between MP and ability to work, not usually regarded by the common scale for assessing disability in MP [3].

This assessment is a multidimensional process that does not exhaust its importance in early sessions but it's present in all phases of physical therapy process. They can be divided into: *physiotherapy evaluation*, which aims to quantify and describe,

through various strategies, patient's functional impairments, activity limitations and participation restriction; *physiotherapy diagnosis*, aimed to suggest and describe the causal relations between elements of interest detected in the patient, in order to plan properly sequencing of therapeutic interventions; *physiotherapy prognosis* and planning of the goals, with associated outcome's indicators, which are based, as well as on the physiotherapy diagnosis and prognosis, also on patient expectations and on structural, temporal and cultural available resources; selection and implementation of *interventions* of functional rehabilitation, compensation, education and secondary/tertiary prevention, based on evidence; *monitoring and verifying* the achievement of goals through the outcome indicators reevaluation at defined intervals.

Multidimensional assessment of each element may acquire different meanings: central role is taken by the identification, in that patient, of the critical aspects that can be modified through a physiotherapy intervention. Next to them, other elements will be interpreted as predictors of functional recovery or as factors influencing physiotherapy intervention. Other elements will be interpreted as risk factors for deterioration of critical aspects interesting in physiotherapy and their assessment will be needed to plan interventions for secondary prevention. Still others, finally, as the expectations of the patient and their family members and related psycho-emotional impairments, should be considered when formulating the objectives of the physiotherapy program [4].

For example, a large systematic review [1] found that depressive symptoms and abilities in performing activities of daily life, have a high correlation with the quality of life, while weak correlations were found with aspects usually considered crucial such as postural instability, gait abnormalities, dyskinesia, bradykinesia, tremor, cognitive impairments. These weak correlations seem to support the need for an individualized multidimensional evaluation aims to identify, or at least to suppose, the causal relations that exist between the restrictions of the participation, levels of activity in a standard environment, environmental factors and functional impairments (motor and non motor) that the MP has led in that particular patient.

Based on ICF, on scientific contributions of the different physiotherapy schools and techniques, and new findings in the literature, particularly on issues of cognitive problems of PD and the impact of MP on the levels of social participation, we can define an interpretative framework of the complexity of the patient, aiming to systematize the complexity of physiotherapy, to lead the physiotherapist in evaluation, planning and implementing phases of the rehabilitative process and to facilitate possible future research in different areas so far unexplored.

**References:**

- [1] Den Oudsten BL, Van Heck GL, De Vries J. (2007) Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord.* 2007 Aug 15;22(11):1528-37.
- [2] Leonardi M, Meucci P, Ajovalasit D, Albanesi F, Cerniauskaite M, Invernizzi V, et al. (2009). *ICF in neurology: functioning and disability in patients with migraine, myasthenia gravis and Parkinson's disease.* *Disabil Rehabil.* 2009;31 Suppl 1:S88-99.
- [3] Raggi A, Leonardi M, Ajovalasit D, Carella F, Soliveri P, Albanese A, Romito L. (2011) *Disability and profiles of functioning of patients with Parkinson's disease described with ICF classification.* *Int J Rehabil Res.* 2011 Jun;34(2):141-50.
- [4] Van der Eijk M, Faber MJ, Al Shamma S, Munneke M, Bloem BR. (2011) *Moving towards patient-centered healthcare for patients with Parkinson's disease.* *Parkinsonism Relat Disord.* 2011 Jun;17(5):360-4. Epub 2011 Mar 10.

## C33

**Physical therapy assessment: from medical history to clinical tests in order to define functional profile of patient***Lorella Pellegrini*

Corso di Laurea in Fisioterapia, Università di Trieste, Trieste

Evaluation process for physical therapy in Parkinson's disease (PD) is very important, in order to assess its severity and patient's health problems, which can be correlated to and lead to considerable disability. Designing treatment programs could be rather complex, because of considerable variation across individuals with PD in their movement disorders, as well as variations of motor performance over time.

Indeed M.E. Morris [1] believes that assessment becomes mandatory in order to understand the extent to which physical therapy can influence patient's motor behavior, while designing a rehabilitation program, tailored to changing needs of patients and their caregivers, because of disease progression. In her model for physical therapy of people with PD, in addition to establish the importance of stadiation (HY), she emphasizes the necessity to consider and be able to recognize specific symptoms: rigidity, bradykinesia, tremor, balance disorders and postural control, dyskinesia, freezing episodes.

Dutch Guidelines for physical therapy in patients with Parkinson's disease (2004) provide useful indications to assess physical impairments such as physical ability, transfers, body posture, reaching and grasping, balance and gait. Anyway, taking medical history is considered an essential starting point, in order to better understand this pathology, related to very individual symptoms. Patients' interview is also the first step to define quality of care according to the model of patient-centered healthcare, even if, despite individual effort of professional caregivers, it is far to be implemented in clinical practice.

Especially in PD this model is important to attend disease complexity and not only motor, but cognitive and emotional worsening of patients.

In the Netherlands, M. Van der Eijk [4] showed that data, from focus group patients and caregivers interviews, underline their necessity to be emotionally supported from healthcare professionals and desire to be actively involved in choices concerning their treatment.

In the same study, another relevant finding was the perceived lack of multidisciplinary collaboration between healthcare providers and especially insufficient expertise of physical therapists in assessment and treatment of patients, as showed in other studies. Cultural and psychosocial limitations for care providers (low level of knowledge of disease and technical skills) and for patients (low level of information about opportunity to apply for rehabilitation and prejudices on exercise efficacy) represent a barrier for improvement of assessment and taking charge of subjects and implementation of guidelines.

Through a questionnaire aimed to develop quality indicators for physiotherapy, submitted to expert and general physiotherapists, M.J. Nijkrake et al [2,3] showed a great difference between groups, both for use of PD specific outcome measures and for specific rehabilitation interventions (cueing or cognitive movement strategies).

Therefore medical history is of great importance to set patients' treatment expectations and outcomes and could be a good help to develop quality indicators for a tailored rehabilitation program, sometimes difficult to design, because of pathology complexity and of different symptoms appearance across patients. Moreover, shared outcomes, defined in the very early phase of rehabilitation program, let patients be able to constantly verify their changes.

Indeed, in physical therapy, it is increasingly necessary to consider subjective outcome measures too. In 2009, the authors of a study proposed a different Patient-Specific-Instrument version in Parkinson's disease (PSI-PD), recommended by Dutch guidelines. It consisted of three different sections, where first, patients must select most relevant limitations based on a predefined list, as well as one self-report item. Then patients rank their selected items in order of importance and rate the severity of the ranked items on a Numeric Rating Scale from 0 to 10. The study showed that PSI-PD is a valid and reliable instrument, able to detect limitations in daily living activities and to be very helpful in designing proper physical therapy intervention in Parkinson's disease patients.

Objective outcome measures, always reliable and valid instruments to evaluate rehabilitation intervention, sometimes are not specific for Parkinson's disease patients. Therefore it could be necessary to use some clinical tests aside, able to underline some peculiar disease aspects. For example, in assessing Freezing of Gait (FOG) we can use a standard gait trajectory, with possible circumstances that may provoke FOG, like walking while crossing a door or another narrow space, full turning 360°, or walking while performing a dual task.

In order to design a rehabilitation program, physical therapist must be able to detect even other non motor symptoms of the disease. We need to take into account cognitive impairments and analyse patient's behavior during functional tasks, to identify specific treatments.

Because of promising evidences about use of Action observation and Motor Imagery during exercise, we should consider patients' ability of Motor imagery performance, especially during the first stage of disease, when they still have effective chances of motor learning. Some questionnaires, based on visual-analogue scales, could represent reliable tool to assess ability in Parkinson's patients.

Moreover it is essential to assess changes on movements in response to medication, concurrent pathologies, secondary adaptive changes in musculo-skeletal and cardiovascular system, environment and quality of life.

Therefore evaluation of these patients results in a quite long process, often impossible to be fully concluded in the same session. It is definitely necessary for physiotherapists to consider opinions and requests of patients and their caregivers as fundamental assessment steps, in order to improve quality and efficacy of physical therapy intervention.

**References:**

- [1] M. E. Morris. Movement Disorders in People With Parkinson-Disease: A Model for Physical Therapy. *Phys Ther.* 2000; 80:578-597.
- [2] M.J. Nijkrake et al. *Quality indicators for physiotherapy in Parkinson's disease.* *Eur J Phys Rehabil Med* 2009; 45:239-45
- [3] M.J. Nijkrake et al. Evaluation of a Patient-Specific Index as an outcome measure for physiotherapy in Parkinson's disease. *Eur J Phys Rehabil Med* 2009;45:507-12
- [4] M. van der Eijk et al. Moving towards patient-centered healthcare for patients with Parkinson's disease. *Parkinsonism Relat Disord* 2011;17:360-364

## C34

**Assessment tools in Parkinson's Disease: most used clinical scales in rehabilitation practice***Marco Baccini*

Motion Analysis Laboratory, Azienda Sanitaria di Firenze, Firenze

In 1967 Hoehn and Yahr [1] developed the simplest clinical scale to assess Parkinson's disease (PD) severity, based upon on the

distinction of five stages of the disease from unilateral involvement with no or minimal disability (stage 1) to confinement to wheelchair or bed (stage 5). In a modified form, it is still the most commonly used discriminative scale to depict the course of the disease and to group patients samples for comparisons. Though reliable and valid, however, this scale has poor sensitivity to changes, therefore it is inadequate to be used as an evaluative scale to assess the effectiveness of interventions. Over the years a number of clinical rating scales have been developed for this aim, mainly focusing on the core signs of rigidity, tremor, bradykinesia and postural instability [2]. To tackle the variability between clinical scales, a standardized scale was developed in 1987 [3] by a committee in order to produce a unified measurement tool. This instrument, named Unified Parkinson's Disease Rating Scale (UPDRS), is a composite of different pre-existing tools and comprises four sections (mental status, activity of daily living, motor signs, complications of drug therapy), besides a modified Hoehn-Yahr staging system and a disability scale. The UPDRS is the most frequently used scale in drug trials for PD [4] and together with the most recent version, the MDS-UPDRS (Movement Disorders Society-Unified Parkinson Disease Rating Scale) [5], is currently considered the "gold standard" tools for assessing the severity and the advancement of the disease [6].

However, the potential impact of PD on individuals is very wide and encompasses a number of problems not directly addressed by clinical scales, e.g. fear of falling or lack of social support. Moreover, there is increasing support concerning the importance of assessing outcomes from the patient's perspective [7]. For example, both the presence and severity of Freezing of Gait (FOG) episodes are likely more accurately evaluated when reported by patients rather than judged by a rater. Conversely, for disability assessment the opposite may be true, since many external (e.g. caregivers support) or internal (patient's insight) factors may influence patient's judgement [8]. When PD patients were asked to rate their disability, they were found to underestimate it in the early stages of the disease and to overestimate it in the advanced stages [9]. In that case, performance tests (i.e., directly observed, standardized tests of functional ability) may offer information not accurately provided from self-reported ratings [10].

The use of the UPDRS as the only primary outcome measure in trials aimed at verifying the efficacy of physiotherapy for PD might also be questioned for the reason that such interventions, unlike drugs, usually focus on specific functional limitations and have no effect on neurological signs like tremor, rigidity or dyskinesias. Therefore the UPDRS should be conveniently associated to other measurement tools more focussed to functions that are the primary targets of rehabilitation.

Several physical therapy rehabilitation core areas have proven to be efficient in PD. Among these, four areas have reached "level 2" practice recommendations [11]: 1) use of visual or auditory cueing strategies to improve gait, 2) application of cognitive movement strategies for improving transfers, 3) specific balance exercises associated with muscle strengthening to improve postural control, 4) joint mobility and power training associated with task-oriented exercises to improve physical capacity. From these data it is evident that much effort has been directed towards investigating the effectiveness of exercises and training programs aimed at improving lower limb functioning, such as gait and transfers.

When rehabilitation focuses on gait and gait-related activities, the UPDRS should be used together with one or more of the following performance measures: the Short Physical Performance Battery (SPPB) [12], the Timed-Up and Go (TUG) [13], the

Functional Reach (FR) [14], the Berg Balance Scale [15]. All these measures, though originally developed for assessment of older people, have been repeatedly employed in PD. However, the measures differ in terms of tasks and scoring system, therefore the choice must rely upon the specific aim of the intervention. For example, the BBS and the FR focus exclusively on balance, whereas the SPPB comprises three tasks (gait speed, balance and repeated chair stand) that are all commonly affected in PD. A self-reported measure of freezing, the Freezing of Gait Questionnaire (FOGQ) [16], should also be employed when exercises are aimed at attenuating the frequency and the severity of FOG episodes. Recently, the FOGQ was found to be reliable and more sensitive than the corresponding item of the UPDRS for detecting freezing and assessing the effect of treatment [17].

Upper limb functioning is also affected in PD. Though the effectiveness of specific upper limb interventions in patients with PD has not been extensively evaluated, limited evidence exists that PD patients can improve the speed of arm movement through practice [18,19]. When the physiotherapy treatment aims at improving manual dexterity and arm functioning a suitable outcome measure should be selected among performance measures like the Purdue Pegboard Test (PPT) [20] or other tests using similar apparatus. The PPT has been used to compare manual dexterity in PD and healthy controls [21] and was found to be able to detect the effect of medications [22].

Finally, a complete evaluation of outcomes of interventions in PD, as in any chronic disabling disease, should include a measure able to detect the impact on perceived health-related quality of life. Though generic health status measures have been also successfully employed, the current opinion is that generic measures may be not as sensitive as specific measures to detect the impact on health quality of a specific disease [7]. Among the specific instruments for PD, the Parkinson's Disease Questionnaire (PDQ-39) [23], has been extensively validated and at present is considered the most appropriate tool [24].

## References:

- [1] Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–42.
- [2] Martinez-Martin P. Rating scales in Parkinson's disease. In: Jankovic J, Tolosa E, eds, *Parkinson's Disease and Movement Disorders*, 2nd ed. 1993, Williams and Wilkins, Baltimore: 281–92.
- [3] Fahn S, Elton R and members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, Goldstein M, eds, *Recent Developments in Parkinson's Disease*. 1987, Macmillan Healthcare Information, Florham Park: 153–63.
- [4] Mitchell S, Harper D, Lau A, Bhalla R. Patterns of outcome measurement in Parkinson's disease clinical trials. *Neuroepidemiology* 2000;19:100–8.
- [5] Goetz C, Poewe W, Rascol O, Sampaio C, Stebbins GT. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and Recommendations. *Mov Disord* 2003, 18:738–50.
- [6] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R e coll. Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23(15):2129–70.
- [7] Fitzpatrick R. Evaluating the outcome of rehabilitation interventions. In Playford D, Thompson AJ (eds). *Neurological*

- Rehabilitation of Parkinson's Disease. 2003, Martin Dunitz, London and New York, NY.
- [8] Shulman L, Pretzer-Aboff I, Anderson K. et al. Subjective patient-report versus objective performance-based measurement of activities of daily living in Parkinson's disease. *Mov Disord* 2006;21:794–799.
  - [9] Tanji H, Gruber-Baldini AL, Anderson KE, Pretzer-Aboff I, Reich SG, Fishman PS, Weiner WJ, Shulman LM. A comparative study of physical performance measures in Parkinson's disease. *Mov Disord* 2008;23(13):1897–905.
  - [10] Andresen E, Rothenberg B, Zimmer JG. Assessing the health status of older adults. 1997, Springer Publishing Company, New York, NY.
  - [11] Keus SH, Bloem BR, Hendriks EJ, Bredero-Cohen AB, Munneke M; Practice Recommendations Development Group. Evidence-based analysis of physical therapy in Parkinson's disease with recommendations for practice and research. *Mov Disord* 2007;22(4):451–460.
  - [12] Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol Med Sci* 1994;49:85–94.
  - [13] Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–148.
  - [14] Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol Med Sci* 1990;45:M192–M197.
  - [15] Berg KO, Wood Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. *Can J Public Health* 1992;83:S7–S11.
  - [16] Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with parkinsonism. *Parkinsonism Relat Disord* 2000;6:165–170.
  - [17] Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe WH, Stocchi F, Tolosa E. Validation of the freezing of gait questionnaire in patients with Parkinson's disease. *Mov Disord* 2009;24(5):655–61.
  - [18] Behrman AL, Cauraugh JH, Light KE. Practice as an intervention to improve speeded motor performance and motor learning in Parkinson's disease. *J Neurol Sci* 2000;174(2):127–36.
  - [19] Farley BG, Koshland GF. Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson's disease. *Exp Brain Res* 2005;167(3):462–7.
  - [20] Instructions and normative data for Model 32020 Purdue Pegboard. 1999, Lafayette (IN): Lafayette Instrument Co.
  - [21] Proud EL, Morris ME. Skilled hand dexterity in Parkinson's disease: effects of adding a concurrent task. *Arch Phys Med Rehabil* 2010;91(5):794–9.
  - [22] Tan EK, Ratnagopal P, Han SY, Wong MC. Piribedil and bromocriptine in Parkinson's disease: a single-blind crossover study. *Acta Neurol Scand* 2003;107:202–6.
  - [23] Giladi N, Shabtai H, Simon ES, Biran S, Tal J, Korczyn AD. Construction of freezing of gait questionnaire for patients with parkinsonism. *Parkinsonism Relat Disord* 2000;6:165–170.
  - [24] Marinus J, Ramaker C, van Hilten J, Stiggelbout A. Health-related quality of life in Parkinson's disease: a systematic review of disease-specific instruments. *J Neurol Neurosurg Psychiatry* 2002;72: 241–8.

## C35

### From assessment to physiotherapy treatment planning in Parkinson's Disease

Susanna Mezzarobba

Corso di Laurea in Fisioterapia, Università degli Studi di Trieste, Trieste

Despite considerable progress in biomedicine, Parkinson's Disease (PD) is a chronic disease that involves progressive disability. Drug therapy has changed the natural history of patients and ensures the same life expectancy of the general population. However, the absence of a causal treatment and the presence of dopamine-resistant symptoms (freezing, postural instability and non-motor symptoms, like cognitive dysfunction), justify the use of non-pharmacological therapeutic approach, in different stages of disease, to ensure recovery and functional independence. In fact, even with best medical therapy, patients are faced with progressive activity limitations and participation restrictions in the domestic and social life.

To date, a growing number of scientific evidence has pointed out, also on experimental models, the potential benefits of physical therapy intervention in the MP. However indications about the best model of treatment (i.e. type of exercises) and the dosing timing (when to start and how long to continue) are still lacking. Therefore it is necessary to question on the mechanisms underlying the basis of the exercise efficacy. First we need to define correct rehabilitative hypothesis through an up to date knowledge of altered motor control process at the basis of the symptoms and mechanisms of re-learning new skills. Applying physiological concepts to rehabilitation becomes essential prerequisite of effective intervention.

*Which should be the exercise characteristics in Parkinson's Disease?* In 2000 Morris described a theoretical framework supporting the use of physical therapy in PD. The model was based on the pathophysiology of movement disorders in basal ganglia disease, on scientific evidence and on personal observations of physical therapy interventions in PD. Converging data from the scientific literature suggest that the patient with PD is able to realize the movement with the focus of attention to the task (use of task "goal directed" vs. habitual movements). The use of external stimuli (cues visual, auditory, tactile) and the anticipated preparation of successive movements also with cognitive facilitation strategies (Motor Imagery, Action observation) would bypass the insufficient production of internal stimuli from basal ganglia. Use of task-specific strategies has a double meaning: compensatory movement strategies (to bypass the defective basal ganglia) and learning strategies to improve performance through practice. Their efficacy and use are still related to the presence of cognitive impairment and then designed in different ways in relation to different stages of disease.

Another key issue for planning the rehabilitation treatment for patients with PD is the answer to the following question: *patients with Parkinson's disease can re-learn motor skills through exercise?* Studies in experimental models of PD suggest possible existence of regenerative mechanisms mediated by exercise and learning. Increasing evidence underlines the efficacy of motor rehabilitation in MP, also if the acquisition of new skills requires more exercise. However, the short duration of benefit raises doubts about the integrity of the learning mechanisms in patients with PD. From meta-analysis of Nieuwboer on "behavioral studies", while emerging a certain maintenance of acquisition capacity of new skills in these patients, their learning process is characterized by a

reduced efficacy (greater slowness, increase in the neural network, increased dependence on the environment). Therefore it gets important consequences in physiotherapy program. Patients may benefit from new treatments with functional relevant goals, more ecological and with a reinforcement effect due to sensory information, with frequent references helping retention.

However if learning new skills remains the first goal of rehabilitation, we must not forget the management of secondary adaptive changes that affect the musculoskeletal system after the onset of a process of “*learning non use*”. Reduced physical activity being present however in early stages, requires constant prevention of complications. Finally, a third rehabilitation objective is an education program aiming to develop patients' ability to recognize and manage their altered movement and their necessity to maintain a constant physical activity. Thus, the physical therapist needs to shift his role from being a “coach” to a role of “consultant” as the patients takes on the responsibility of his motor activity.

*Planning physical therapy treatment.* A tailored rehabilitative program in subjects with MP is a tricky challenge. Disease shows a multifaceted progressive course, whose severity and clinical manifestation vary across individuals a lot and especially over time. However, the rehabilitation program is primarily based on some general principles

- Rehabilitation process should be tailored to patients (according to stage, disease course, clinical condition, effects of drug therapy, cognitive impairment, co-morbidity) based on their needs and of their caregiver.
- In planning rehabilitation objectives, active participation of patients and their family is strictly required.
- Changes in motor performance, ADL (Activities Daily Living) and QoL (quality of life) should be measured after treatment through specific outcome measures.
- Rehabilitation must have the continuity of a long term care despite different context conditions and intensity of treatment.

It is essential to answer with different rehabilitation programs, according to quality process indicators, to such a complexity of problems, as proposed by the Dutch Guidelines for Physical Therapy in patients with Parkinson's disease (2004) and several authors (Keus 2007). In the model proposed, three phases in the course of the disease were identified, early (HY 1 to 2.5), middle (HY 2–4) and late (HY 5) in which the six “core” areas of physiotherapy intervention (transfers, balance, walking, posture, reaching and manipulation) have to be declined.

Many authors identify the early stage (HY 1 to 2.5) as a key moment for the rehabilitative treatment (as a secondary preventive care) due to more effective learning opportunities and maintenance of correct motor patterns. Cognitive strategies such as Motor Imagery and Action observation could find a more effective use in the maintenance of complex functions such as walking and postural control. Prevention of inactivity and improvement of physical capacity should be guaranteed already at this stage. Even a sport, without fatigue, stress and competition, can provide good integrity of the musculoskeletal and cardiovascular system. Increasing evidence of the literature emphasizes activities efficacy, such as dance (tango) and tai chi, in maintaining motor function. In this early phase the educational objective is to inform the patient and his caregiver about the disease and how to manage future complications for a better patient's self control over the disease process.

In the middle phase (HY2–4) physiotherapy treatment is always planned aiming to facilitate learning and therefore the maintenance of proper motor performance through compensatory movement strategy to bypass altered fronto striatal control. Different rehabilitation approaches are proposed in literature.

Cueing (e.g auditory to improve gait cadence also in dual task condition, visual to change stride length) and treadmill training with or without cues, are current best practices. Motor Imagery and Action observation are a new challenge in physical therapy, also in this phase. Aim of cues and cognitive strategies is to maintain gestures “goal directed” even at home reducing multitasking, especially in more advanced stages. Prevention of falls is proposed as an indicator of adequate therapeutic process in this phase. Using a diary of falls is an important tool.

Aim of treatment at this stage is to ensure the best musculoskeletal condition as a prerequisite for using alternative strategies as reported in the literature.

Caregivers should always learn use of cues, for encouraging patient's active cooperation. Use of aids need to be supervised. Their efficacy may be compromised by their own use, because of a dual task condition. The target of the last phase (HY5) is rehabilitation “nursing” at home and at hospital. It is a key tool in order to maintain the best patient's active collaboration in changing pattern of movement in activities of daily living.

Clinical experience in stroke indicates that training effects highly depend on the intensity of physical therapy, both in terms of frequency and duration of treatment. However, in Parkinson's disease we are not able to provide indicators about best treatment frequency and duration yet, despite many studies. The proposed new models of “chronic-term care”, whose merits are supported by evidence for other chronic neurological disorders, could be an interesting research field.

#### References:

- [1] Morris ME. Movement disorders in people with Parkinson disease: a model for physical therapy. *Phys Ther.* 2000 Jun; 80 (6):578-97
- [2] KNF Guidelines for physical therapy in patient with Parkinson Disease, Supplement to the Dutch Journal of Physiotherapy 2004 Vol. 114, 3 Disponibile su URL: [www.parkinson-limpe.it](http://www.parkinson-limpe.it)
- [3] Meg E. Morris, Clarissa L. Martin, Margaret L. Schenkman Striding Out With Parkinson Disease: Evidence-Based Physical Therapy for Gait Disorders *Phys Ther* 2010 Vol. 90 No.2:280-08
- [4] Samyra H.J. Keus, PT, MSc, Bastiaan R. Bloem, MD, PhD, Erik J.M. Hendriks, PT, PhD, Alexandra B. Bredero-Cohen, and Marten Munneke, PT, PhD, Evidence-Based Analysis of Physical Therapy in Parkinson's Disease with Recommendations for Practice and Research *Movement Disorders* Vol. 22, No. 4, 2007, pp. 451–460

#### Oral, Poster and Video Session

##### SC1

#### Virtual simulator of deep brain stimulation in Parkinson's disease

E. Pedrolì<sup>3</sup>, C. Vigna<sup>3</sup>, L. Romito<sup>6</sup>, P. Cipresso<sup>3,4</sup>, A. Albanese<sup>6</sup>, A. Mauro<sup>1</sup>, G. Riva<sup>3,5</sup>, A. Franzini<sup>2</sup>, Giovanni Albani<sup>1</sup>

<sup>1</sup>Department of Neurosciences IRCCS Istituto Auxologico Italiano, Piancavallo (VB)

<sup>2</sup>Department of Neurosurgery, Neurological Institute “Carlo Besta”, Milano

<sup>3</sup>Applied Technology for Neuro-Psychology Lab, IRCCS Istituto Auxologico Italiano, Milan

<sup>4</sup>IULM University, Milan

<sup>5</sup>Department of Psychology, Catholic University of Milan, Milan

<sup>6</sup>Department of Neurology “Carlo Besta”, Milan

During Deep Brain Stimulation (DBS) procedure, it is mandatory that the recognition of the target to neurostimulate it is identified by the best degree of patient collaboration, and thus is performed

while the patient is awake. This procedure may need long time and it result very stressfull for the patient that is awake, fasting and 24 hours off-medication. On the other side, it is needed the best degree of collaboration to reach the best postsurgery outcome. For this reason, we decide to try to reduce the intraoperative stress, by preparing the patient to the surgery, by a virtual immersion on each single step of the procedure. In this video we report a case of a person with Parkinson's disease (PD), who performed the Virtual Deep brain stimulation (VDBS), which reproduces in 3-D all the real stages of the intervention by the exact view of the patient. Sounds, voices and times of the operating room are lived in an immersive session, by simulating the operating bed position. We videoregistered the surgery scenario by a double prospective: by an external moving camera and by a microvideocamera mounted on glasses of the patient himself.

The simulating session includes the same stress conditions of the real one, so that the patient will perform it in the early morning, after an overnight fasting without assuming breakfast, and a drug withdrawal of 12 hours. During the simulation some clinical parameters are noted down, such as blood pressure, heart frequency, glucose blood level, skin temperature, oxygen saturation that are continuously updated in a dedicated display. This, by mean of a biofeedback approach, may affect the control of the stress of the virtual surgery scene.

We believed that this tool will significantly reduce the intraoperative stress of the patient, improving his collaboration and thus the outcome of the intervention.

#### References:

- [1] Anthony E. Lang, M.D., and Andres M. Lozano, M.D. Parkinson's Disease. *N Engl J Med* 1998; 339:1130-1143 October 15, 1998.
- [2] Appleby BS, Duggan PS, Regenberg A, Rabins PV (2007). "Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: A meta-analysis of ten years' experience". *Movement Disorders* 22:1722–1728.
- [3] Ferrolì P, Tringali G, Acerbi F, Aquino D, Franzini A, Broggi G. Brain surgery in a stereoscopic virtual reality environment: a single institution's experience with 100 cases. *Neurosurgery*. 2010 Sep; 67.

## SC2

### Speech audiometry is impaired in Parkinson's Disease

C. Vitale<sup>1,2</sup>, M. Cavaliere<sup>7</sup>, V. Marcelli<sup>3</sup>, T. Abate<sup>7</sup>, Roberto Allocca<sup>3</sup>, G. Santangelo<sup>2,4</sup>, R. Erro<sup>5</sup>, M. Amboni<sup>1,2</sup>, M.T. Pellicchia<sup>5</sup>, A. Cozzolino<sup>5,6</sup>, K. Longo<sup>2,5</sup>, M. Picillo<sup>5</sup>, M. Moccia<sup>5</sup>, V. Agosti<sup>1,2</sup>, E. Marciano<sup>3</sup>, G. Sorrentino<sup>1,2</sup>, P. Barone<sup>2,6</sup>

<sup>1</sup>University of Naples "Parthenope", Naples

<sup>2</sup>IDC, Hermitage Capodimonte, Naples

<sup>3</sup>Audiology and Vestibology Unit, Department of Neuroscience, University of Naples "Federico II", Naples

<sup>4</sup>Department of Psychology, Second University of Naples, Caserta

<sup>5</sup>Department of Neurological Sciences, University of Naples "Federico II", Naples

<sup>6</sup>Neurodegenerative Diseases Center, University of Salerno, Salerno

<sup>7</sup>Department of Otolaryngology, University of Naples "Federico II", Naples

**Background and Objectives:** Pure tone audiometry testing (PTA) have been evaluated in patients with Parkinson's disease (PD) with conflicting results. We have recently demonstrated age-dependent peripheral, unilateral or bilateral hearing loss in PD patients by means of PTA. PTA provides only a partial picture of the patient's auditory status and gives no information about patient's ability to

hear and understand speech. To find out hearing ability and speech discrimination of PD patients, we expanded audiologic evaluation by means of Speech Audiometry (SA). Speech Test are currently used in clinical practice in order to: 1) check the validity of pure tone audiometry; 2) determine speech discrimination; 3) establish rehabilitation needs; 4) determine the site of lesion of the hearing impairment (central vs peripheral).

**Patients and Methods:** 40 consecutive patients with clinical diagnosis of PD were screened. Severity of motor symptoms and staging were measured with the Unified Parkinson's Disease Rating Scale (section III) and the Hoehn and Yahr scale. Audiometric evaluation consisted of a comprehensive audiologic case history and questionnaire, visual otoscopic examination, acoustic immittance measures (tympanogram and acoustic reflexes), pure tone and speech audiometry. Healthy age- and sex-matched subjects were selected as control group.

SA is a technique where standardized samples of language are presented through a calibrated system in order to measure some aspects of hearing abilities. The speech material may be presented monaurally or binaurally, live voice or by using a recording. There are lists of words that have been devised for this purpose (Monosyllabic words, Disyllabic words, Paired words, Sentences with key words). A performance intensity (PI) function (i.e. the discrimination score achieved at a number of different intensity levels [dB]) is plotted on a graph. If the speech discrimination reaches a maximum point and then gets worse as the intensity is increased this shows *rollover* phenomenon and points to central more than peripheral site of hearing dysfunction.

SA of both patients and controls were compared with their own PTA according to Fletcher's equation ( $PTA + 20 = SRT$  100%;  $SRT =$  Speech Reception Threshold is defined as the intensity [dB] at which simple speech material, usually can be detected 50% of the time).

**Results:** 32/40 patients were enrolled (18 M e 14 F; average age 68 ys), 8 were excluded because of middle ear disease. PTA confirmed our previous finding of age-dependent high-frequency hearing loss in PD patients as compared with both normative values and healthy age- and sex-matched controls ( $p = 0.005$  and  $p < 0.001$ , respectively).

**Conclusion:** Our results confirmed an age-dependent, sensorineural hearing loss in PD patients as compared with healthy subjects. Moreover, SA showed impaired speech discrimination in PD patients as compared with control group. Increased tonal-vocal dissociation together with a weak rollover phenomenon suggest a peripheral more than central origin of hearing impairment in PD patients. The finding that  $\alpha$ -synuclein is located predominately in the cholinergic efferent neuronal system within the inner ear (basal inner hair cell) raises the possibility that its dysfunction might interfere with cochlear transduction mechanisms thus promoting speech discrimination impairment in PD patients.

## SC3

### Impulse control disorders in patients with Parkinson's disease: outcome after three years of continuous subthalamic electrical stimulation

Paolo Amami<sup>1</sup>, I. Dekker<sup>2</sup>, S. Piacentini<sup>1</sup>, F. Ferré<sup>1</sup>, L. Romito<sup>1</sup>, E.M.J. Foncke<sup>2</sup>, A. Albanese<sup>1,3</sup>

<sup>1</sup>Fondazione Istituto Neurologico Carlo Besta, Milano

<sup>2</sup>Neurology VU University Medical Centre, Amsterdam, Netherlands

<sup>3</sup>Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma

**Introduction:** Impulse Control Disorders (ICDs) are behavioural complications of PD triggered by dopaminergic medication. STN

DBS is an effective treatment for advanced PD which allows great reduction of dopaminergic medication. To date the data regarding the relationship between ICDs and STN DBS are unclear as both resolutions and de novo-onsets were reported after implant.

**Aim:** We aimed to observe the outcome of ICDs in a group of PD patients after three years of continuous STN stimulation.

**Methods:** We followed a group of 37 PD patients in whom detailed assessment of ICDs was carried out at baseline and after three years of STN stimulation. The difference between baseline and follow-up prevalence of ICDs was calculated. At follow-up patients with ICDs and patients without ICDs were compared based on demographical and clinical features. Further, among the patients with ICDs at baseline we compared those who resolved ICDs and those who did not.

**Results:** After three years of STN stimulation motor improvement (60%) and dopaminergic medication reduction (50%) was observed. At baseline 40% of patients had ICDs. At follow-up the prevalence decreased to a non-significant 32%. The 16% of patients resolved their symptoms and the 8% of patients reported a de novo onset after implant. PD patients with ICDs at follow-up took an higher baseline dopamine agonist dose compared to patients without ICDs after implant. Such difference was confirmed comparing patients who resolved their behavioural symptoms with those who did not. We found an association between a history of hypomania and the occurrence of ICDs.

**Conclusion:** In keeping with previous findings we observed both resolutions and new-onsets of ICDs after implant. The dopamine agonist dose before the surgery and a history of hypomania seem to be predictors of the ICDs outcome. We recommend the routine pre-operative neuropsychiatric assessment and we emphasize the importance of post-operative neuropsychiatric monitoring.

#### SC4

##### **Proposal for multidisciplinary rehabilitation treatment in patients with Parkinson's disease: evidence of effectiveness and tolerability**

S. Recchia, L. Melotti, *Francesca Andretto*, F. Panico, M. Bendinelli, M. Sacchetti, S. Menini, B. Falomi, C. Baroni, P. Brunelli, M.G. Bempensanti, C. Fava, E. Ceriani, C. Rossi, P. Antonello, M. Bonomi, M. Ligabò, S. Tomelleri, S. Carlucci, B. Montagnana

Centro Polifunzionale Don Calabria CMS "Claudio Santi", Verona

**Introduction:** The recent literature emphasizes the importance of a multidisciplinary approach in the rehabilitation treatment of Parkinson's disease (PD)[1,2]. In 2011, our centre recruited 98 patients with PD for the rehabilitation treatment. We proposed a rehabilitation approach that provides for the application of at least two types of individual/group treatment for each patient and a evaluation at the beginning and end of treatment.

**Objective:** The aim was to evaluate the efficacy and tolerability of a multidisciplinary rehabilitation approach in patients with PD.

**Methods:** 98 patients were examined before and after the treatment by a physician. The following scales were assessed: UPDRS I-IV, BBS, FAC, WHS, Tinetti, TUG. A total of 80 patients (mean age  $72 \pm 8$  y) took part in the multidisciplinary rehabilitation program; 18 patients were unable to participate. The rehabilitation treatments were: individual and/or group physiotherapy (phy-t) and hydrokinesiotherapy (hyd-t) therapy, music-therapy, individual and/or group speech therapy, massages, cognitive stimulation group. Two treatments could take place on the same day. In particular, for the group approach it was necessary to separate patients in homogeneous

groups with respect to the severity of PD, in this manner, for each group were assigned exercises compatible with the motor resources of patients (5 groups; duration: 10 months). The main program was: 5 months of phy-t alternating hyd-t (biweekly) and 5 months of music-therapy (once a week).

**Results:** The data did not show significant changes of the clinical features, in particular we observed the absence of worsening of typical signs and symptoms such as rigidity, bradykinesia, balance etc.

**Conclusions:** Most patients has been able to adhere and complete the program. We observed that, in a program that provides more hours of treatment in a day, the "on fase" is crucial to the success of the session, otherwise the patient may experience difficulty in endurance and performance.

#### References:

- [1] van der Marck MA et al., Multidisciplinary care for patients with Parkinson's disease, (2009) Parkinsonism Related Disorders, 19-23.
- [2] Carne W. et al, Efficacy of multidisciplinary treatment program on long-term outcomes of individuals with Parkinson's disease, (2005); Journal of Rehabilitation Research & Development, 779-86.

#### SC5

##### **Non motor symptoms and Wearing-Off in Italian Parkinson's disease patients: results from the DEEP study**

*Angelo Antonini*<sup>1</sup>, G. Abbruzzese<sup>2</sup>, F. Stocchi<sup>3</sup>, M. Attar<sup>4</sup>, D. Colombo<sup>4</sup>, P. Barone<sup>5</sup> on behalf of DEEP study group

<sup>1</sup>IRCCS San Camillo, Venezia

<sup>2</sup>Università degli Studi di Genova, Genova

<sup>3</sup>IRCCS San Raffaele Pisana, Roma

<sup>4</sup>Novartis Farma Italia S.p.A.

<sup>5</sup>School of Medicine, University of Salerno, Salerno

**Introduction:** Non-motor symptoms (NMS), including psychotic symptoms, fatigue and sweating, afflict up to 98% of patients with Parkinson's Disease (PD). In contrast to motor fluctuations, NMS related to wearing off (WO) are poorly researched.

**Objective:** In an Italian sample of PD patients, to report occurrence of NMS in relation to the presence of WO.

**Methods:** We performed an observational cross-sectional study, involving 37 movement disorders clinics across Italy, recruiting 634 consecutive ambulatory non-demented PD patients, who had been under dopaminergic agents for at least one year. Clinicians administered the NMS scale (NMSS), composed by 9 NMS domains and a total score ranging 0-108 (no-severe NMS). WO was assessed both by the neurologist as well as by the patients using the self-administered Italian validated version of the 19-items WO Questionnaire (WOQ-19), 10 items of which regard non-motor symptoms; WO was defined for scores > 2.

**Results:** NMSS was filled in by 568 patients. WO was diagnosed by neurologists and by self-assessed WOQ-19 > 2 in 57% and 67% of patients, respectively (p 5 years NMS score was significantly higher in patients with WO. The score in PD with > 10 year disease was 47.4 (35.5) in subjects with vs. 39.4 (27.9) in those without WO. There was a significant difference in the pattern of NMS severity between patients with and without WO based on neurologist or patient evaluation. WO was associated with worse sleep/fatigue, pain, urinary function and excessive sweating if the WO was evaluated by the neurologist. Based on patients self-rating the symptoms reported to be worse in association with WO were fatigue and mood.

**Conclusions:** NMS are more severe in patients affected by WO. Fatigue is the symptom best associated with WO irrespective of the assessment while mood changes may be perceived as expression of WO mainly by patients. These results may help predict NMS that are most likely to improve as consequence of therapeutic strategies aimed at controlling WO.

## SC6

### Peripheral neuropathy in a Parkinson's disease patient treated with levodopa/carbidopa intestinal gel infusion: report of one case occurring after four months of treatment

Carlo Alberto Artusi, A. Merola, M. Zibetti, M.G. Rizzone, M. Troiano, D. Cocito, L. Lopiano

Dipartimento di Neuroscienze, Università di Torino, Torino

**Background:** Anecdotal cases of subacute peripheral neuropathies (PN) have been reported during treatment with levodopa/carbidopa intestinal gel (LCIG) infusion.

**Clinical case:** Here we describe a 69 year-old Parkinson's disease (PD) patient who developed a subacute PN four months after the start of Duodopa infusion. The subject was affected by PD for 13 years at the time of surgical selection and he was taking a levodopa equivalent daily-dose of 1440 mg/day. An accurate clinical and electrophysiological assessment was performed before the placement of Duodopa enteral tube, excluding signs of PN. Duodopa infusion was then started with good clinical results on the main PD cardinal symptoms, until the patient developed a subacute sensory-motor PN four months later. The electrophysiological assessment revealed prolonged distal motor latencies, motor nerve conduction blocks in both peroneal and ulnar nerves and reduced sensory and motor nerve conduction velocities in the range of demyelination. No alterations were found in homocysteine and vitamine B12 plasmatic levels or in the cellular and protein cerebrospinal fluid levels.

Duodopa treatment was interrupted and the patient switched back to oral dopaminergic therapy with a supplementation of Vit B1, Vit B12 and folate. A partial recovery of symptoms was observed after one month, although only a slight improvement was observed at the electrophysiological evaluation performed two months later.

**Conclusion:** Several hypotheses have been proposed to explain the pathogenesis of LCIG-related PN, including a vitamin adsorption deficiency or immune-mediated reactions. However, the underlying mechanisms still remain unclear and further prospective clinical studies are therefore required.

## SC7

### The ability to perceive the temporal outcome of a writing action is impaired in focal hand dystonia

Laura Avanzino<sup>1</sup>, D. Martino<sup>2</sup>, I. Martino<sup>2</sup>, E. Pelosin<sup>3</sup>, M. Bove<sup>1</sup>, G. Defazio<sup>2</sup>, G. Abbruzzese<sup>3</sup>

<sup>1</sup>Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa

<sup>2</sup>Department of Neurological and Psychiatric Sciences, University of Bari, Bari

<sup>3</sup>Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa

**Introduction:** Patients with focal hand dystonia present cognitive abnormalities of motor control such as impairment in

the temporal discrimination between tactile stimuli and in pure motor imagery tasks, such as mental rotation of corporeal and inanimate objects. However, only limited information is available on the ability of patients with dystonia to process the time-dependent features (speed and duration) of movement in real time. This topic is quite relevant, since the processing of time-dependent features of movement has a crucial role in predicting whether the outcome of a complex motor sequence, such as handwriting or playing a musical passage, will be consistent with its ultimate goal, or results instead in an execution error. In this study we evaluated the ability to perceive the temporal outcome of different movements in a group of patients with focal hand dystonia.

**Methods:** Subjects (14 patients and 17 healthy subjects, age and gender matched) were asked to predict the end of visually perceived movements, either of a body segment (handwriting, that is the action that specifically engages the human body segment specifically affected by dystonia) or of an inanimate object (a moving circle reaching a spatial target). Further, we also included a non-movement-related task of temporal reproduction into the paradigm as control task. All tasks have been programmed using a dedicated software (E-Prime 2.0).

**Results:** Results showed that the accuracy of the performance on biological motion temporal processing was lower in patients with focal hand dystonia than in controls, whereas no difference was detected on inanimate object motion temporal processing and on temporal reproduction.

**Conclusion:** Our findings could be explained by an alteration of the writing movement representation at a central level and nicely fit in the idea that dystonia is not a pure motor problem, but involves sensory and cognitive aspects related to movement processing and planning.

## SC8

### Myoclonus with rash and hyperalgesia during fever treated with ceftriaxone: cephalosporin-induced neurotoxicity?

M. Mannino, V. Terruso, V. La Bua, A.M. Gasparro, Tanina Pia Avarello

U.O di Neurologia, Azienda Ospedaliera Ospedali Riuniti "Villa Sofia – Cervello", Palermo

We describe the clinical case of a young man (24 years) with history of fever treated from the 5th day with ceftriaxone 1 g im. After a few minutes administration of antibiotic therapy, he developed rash, itchiness, altered mental state, myoclonus, asterix, ataxia and diffuse hyperalgesia. Ceftriaxone was discontinued.

First clinical evaluation revealed blood monocytosis, mild alterations of coagulation tests, mild lymphadenopathy and splenomegaly. Renal function was normal. Mono test for diagnosis of mononucleosis was negative.

Cerebrospinal fluid analysis was normal. No neurotropic virus was detected. Brain MRI showed hyperintensity in T2/FLAIR sequences of claustrum and external capsule bilaterally; there was not enhancement after the intravenous administration of a gadolinium-based contrast material. Spine MRI was normal. EEG showed slow semiperiodic activity. After administration of gabapentin neurological symptoms and EEG activity progressively improved.

Patient was also treated with steroid. One month later brain MRI follow up was normal and patient complained exclusively very mild hyperalgesia. Our patient was a young healthy man who developed hyperalgesia and myoclonus after the appearance of fever. The incipient clinical picture, with fever preceding the onset of movement disorders, and detection of monocytosis, alterations

of coagulation tests, mild lymphadenopathy and splenomegaly, could suggest an infective aetiology, but cerebrospinal fluid analysis was normal and we failed to find any infective agent. Patient received a brief treatment with ceftriaxone. It is known as cephalosporins may cause neurotoxicity syndrome with myoclonus, altered mental state, asterix, EEG alterations and sometimes coagulation deficit. Our patient also complained rash and itchiness, symptoms close related to reactions drug adverse. Further, the favourable answer to treatment with gabapentin could confirm this hypothesis. However, patient was also treated with steroid and, in our knowledge, at present there were not report of MRI alterations of basal ganglia related to cephalosporins toxicity.

## SC9

### Acute challenge tests with levodopa and/or apomorphine in the diagnosis of Parkinson disease: a reevaluation

*Filippo Baldacci*<sup>1</sup>, *P. Del Dotto*<sup>2</sup>, *M. Ulivi*<sup>1</sup>, *C. Logi*<sup>2</sup>, *C. Berti*<sup>2</sup>, *M. Giuntini*<sup>2</sup>, *A. Vergallo*<sup>1</sup>, *C. Lucetti*<sup>2</sup>, *U. Bonuccelli*<sup>1</sup>

<sup>1</sup>Department of Neuroscience, University of Pisa, Pisa

<sup>2</sup>Neurology Department, Versilia Hospital, AUSL Viareggio, Viareggio

**Introduction:** A positive levodopa responsiveness is one of the required criteria for a definite Parkinson's disease (PD) diagnosis. Acute levodopa or apomorphine drug challenges have been proposed to quickly diagnose PD or parkinsonisms. However, due to the relatively few and heterogenous studies with a follow-up usually less than one year, the usefulness of an acute dopaminergic challenge test for the diagnostic workout of PD is still matter of debate.

Aim of our study was to evaluate sensibility, specificity and predictive value of acute dopaminergic tests to identify PD patients in a clinic setting population followed up for a long period of time.

**Materials and methods:** 226 consecutive patients (M/F: 136/90; age: 58 + /- 10yy) with denovo parkinsonian syndrome were evaluated at baseline with acute L-dopa or apomorphine tests or both. The patients were subsequently followed-up for at least 5 years for a final reliable diagnosis. The UPDRS motor component and the tapping test were used to evaluate the acute dopaminergic response. Apomorphine s.c. was administered at the dose of 50 µg/kg with clinical evaluations every 10 minutes for 2 hours. Acute levodopa test was performed at the dose of 250 mg p.o. with clinical evaluations every 20 minutes for 4 hours.

**Results:** 159 acute levodopa tests and 131 apomorphine tests were performed; 64 patients underwent both tests. After an at least 5 year follow-up an established diagnosis of PD was made in 141 patients. The sensitivity for the diagnosis of PD was: apomorphine 0.94, levodopa 0.91, and both 0.92. The specificity values were: apomorphine 0.79, levodopa 0.76, and both 0.94. The positive predictive value was: apomorphine 0.95, levodopa 0.90, both 0.97. The predictive negative value was: apomorphine 0.76, levodopa 0.68, both 0.79. No statistical significant differences were found between groups (patients tested with apomorphine, levodopa, and both). Side-effects were significant more present in the apomorphine group.

**Conclusion:** Acute challenge tests either with levodopa or apomorphine help in the diagnosis of PD with equivalent sensitivity and specificity. The acute levodopa administration resulted in less side-effects. Therefore, in the clinical practice it may be preferred.

## SC10

### Is levodopa toxic to the peripheral nerve in Parkinson's disease? Evidence from a large multicentre study

*R. Ceravolo*<sup>1#</sup>, *G. Cossu*<sup>2#</sup>, *Monica Bandettini di Poggio*<sup>3</sup>, *L. Santoro*<sup>4</sup>, *P. Barone*<sup>5</sup>, *M. Zibetti*<sup>6</sup>, *D. Frosini*<sup>1</sup>, *V. Nicoletti*<sup>1</sup>, *F. Manganelli*<sup>4</sup>, *M. Picillo*<sup>5</sup>, *A. Merola*<sup>6</sup>, *L. Lopiano*<sup>6</sup>, *A. Paribello*<sup>2</sup>, *D. Manca*<sup>2</sup>, *M. Melis*<sup>2</sup>, *R. Marchese*<sup>3</sup>, *P. Borelli*<sup>7</sup>, *A. Mereu*<sup>8</sup>, *P. Contu*<sup>8</sup>, *G. Abbruzzese*<sup>3#</sup>, *U. Bonuccelli*<sup>1</sup>. #

#Authors contributed equally

<sup>1</sup>Neurology Unit, Department of Neuroscience, University of Pisa, Pisa

<sup>2</sup>Neurology Unit Azienda Ospedaliera Brotzu Cagliari, Cagliari

<sup>3</sup>Neurology Clinic University of Genova, Genova

<sup>4</sup>Neurology Unit, University of Napoli, Napoli

<sup>5</sup>Neurology Unit University of Salerno, Salerno

<sup>6</sup>Neurology Unit University of Torino, Torino

<sup>7</sup>Neurology Unit Versilia Hospital, Lido di Camaiore

<sup>8</sup>Department of Public Health University, Clinical and Molecular Medicine, University of Cagliari, Cagliari

**Introduction:** Recent reports suggested that Parkinson's disease (PD) patients may present clinical and/or neurophysiological features of polyneuropathy. However, a definitive conclusion could not be reached on the role of levodopa (LD) as a risk factor for neuropathy.

**Methods:** A multicentre study of a large sample of PD patients (n = 330) and age-matched controls (n = 137) was performed, stratifying the PD population according to duration of LD exposure: 144 patients had LD exposure longer than 3 years (LELD), 103 patients had LD exposure shorter than 3 years (SELD), and 83 patients no exposure to LD (NOLD). Nerve function was evaluated by the reduced total neuropathy score. Right sural sensory antidromic and peroneal motor nerve conduction was measured by a neurophysiologist blinded to the subject's condition.

**Results:** 19.40% LELED patients, 6.80% SELD, 4.82% NOLD, and 8.76% controls were diagnosed with neuropathy (axonal, predominantly sensitive). Multivariate logistic analysis indicated that the risk of neuropathy was not influenced by disease duration (p = 0.91; OR = 1.01), UPDRS III (p = 0.20; OR = 1.02), gender (p = 0.25; OR = 1.64). The risk of neuropathy increased by about 8% for each year of age (p < 0.001; OR = 1.08; CI 1.037–1.128).

**Conclusion:** Our results demonstrate that both the duration of exposure to LD and its daily dose, along with age, are the main risk factors for the development of neuropathy. Periodical homocysteine and vitamin B12 screening, and clinical-neurophysiological monitoring for neuropathy may be advisable in PD patients receiving LD treatment.

## SC11

### Stuttering speech disorder is correlated to freezing of gait in Parkinson's disease

*Marianna Barbuto*<sup>1</sup>, *L. Ricciardi*<sup>1</sup>, *C. Sorbera*<sup>1</sup>, *A. Graziosi*<sup>2</sup>, *P. Girlanda*<sup>1</sup>, *M. Ebreo*<sup>2</sup>, *L. Morgante*<sup>1</sup>, *F. Morgante*<sup>1</sup>

<sup>1</sup>Department of Neuroscience, University of Messina, Messina

<sup>2</sup>Division of Neurorehabilitation, Fondazione Don Gnocchi, Sant'Angelo dei Lombardi (AV)

**Introduction:** Parkinson's disease (PD) patients exhibit over disease course a complex impairment of speech, ranging from a hypokinetic to a hyperkinetic dysfluent type (also labeled as stuttering).

**Objective:** Aim of the present study is to define the phenomenology of speech disorder in PD in different disease stages and to

clarify which clinical variables are correlated to stuttering dysarthria.

**Methods:** Forty-five consecutive patients with Parkinson's disease according UK Parkinson's Disease Society.

Brain Bank criteria were recruited. Demographical and clinical features were collected and the following clinical evaluations were performed: UPDRS, Hoehn-Yahr (HY) staging, New Freezing of Gait Questionnaire (NFQQ), PDQ-8. Neuropsychological assessment of executive functions was carried out. Speech was evaluated in its motor and procedural component respectively with the Italian version of the Dysarthria Profile (DP) and the screening battery for aphasia (SBA). DP is a scale composed of 7 sub-sections assessing the following features of speech. Intelligibility/rate/prosody section of DP is composed of sub-scores investigating presence of stuttering. Patients were categorized according to the stability of their drug response (stable responders = 22; complicated PD = 23).

**Results:** articulation (DP part V), intelligibility, rate and prosody (DP part VI) were significantly lower in patients with HY > 2 compared to HY < 2 ( $p < 0.001$ ), independently by co-occurrence of motor complications. Sub-section prosody of DP correlated with NFGQ score ( $p < 0.0001$ ); indeed, more severe FOG was associated to worst prosody/rate and intelligibility of speech. This correlation was not influenced by disease duration. None of the sub-scores of SBA was more impaired in PD patients according to disease stage, duration and occurrence of motor complication, excepted for phonemic and categorical fluency (decreased in more advanced disease stages).

**Conclusions:** our data suggest that stuttering speech disorder in PD is a marker of disease progression and is strongly correlated with presence of FOG, possibly sharing common pathophysiological mechanisms.

## SC12

### Treatment-responsive and non-responsive freezing of gait in Parkinson's disease and relationship with Wearing Off: results from the DEEP study

M. Amboni<sup>1</sup>, Paolo Barone<sup>2</sup>, F. Stocchi<sup>3</sup>, G. Abbruzzese<sup>4</sup>, M. Attar<sup>5</sup>, D. Colombo<sup>5</sup>, A. Antonini<sup>6</sup> on behalf of DEEP study group.

<sup>1</sup>IDC Hermitage-Capodimonte, Napoli

<sup>2</sup>School of Medicine, University of Salerno, Salerno

<sup>3</sup>IRCCS San Raffaele Pisana, Roma

<sup>4</sup>Università degli Studi di Genova, Genova

<sup>5</sup>Novartis Farma Italia S.p.A., Origgio (VA)

<sup>6</sup>IRCCS Ospedale San Camillo, Venezia

**Introduction:** Freezing of gait (FOG) is a paroxysmal event during which patients feel their feet glued to the ground. FOG is frequent in patients with advanced Parkinson's disease (PD), and has been found in up to 26% of early stage PD patients. Little is known about the actual prevalence of FOG in the outpatient setting, given the clinical variability and its unpredictable nature.

**Objective:** To estimate the prevalence of FOG, and its relation to the presence of Wearing-Off (WO) symptoms in PD.

**Methods:** We performed an observational cross-sectional study, involving 37 movement disorders clinics across Italy, recruiting 634 consecutive ambulatory non-demented PD patients, who had been under dopaminergic agents for at least one year. The clinicians administered the FOG Questionnaire and asked the patient whether FOG was treatment-responsive (FOGOFF), non-responsive (FOGONOFF), drug-induced (FOGON), and never present (NOFOG). WO symptoms were identified by the validated Italian version of the Wearing-Off Questionnaire (WOQ-19); WO

was defined for scores  $\geq 2$ . Furthermore patients were assessed with UPDRS, Non-Motors Symptoms Scale (NMSS) and Parkinson Disease Questionnaire (PDQ-8).

**Results:** 599 patients were evaluated for FOG: NOFOG patients were 46%, FOGOFF and FOGONOFF patients were 33% and 20%, respectively. Six patients had FOGON. WOQ-19  $\geq 2$  was found in 49% of NOFOG patients, in 71% and 93% of FOGONOFF and FOGOFF patients, respectively. Mean (SD) UPDRS part I score was 1.7 (1.7) in NOFOG patients vs 2.9 (2.1) and 2.4 (2.0) in FOGONOFF and FOGOFF, respectively (ANOVA's  $p < 0.0001$ ). Different UPDRS part II, III and total scores were found between NOFOG and FOG patients (ANOVA's  $p < 0.0001$ ). Presence of FOG correlated with disease duration, H&Y stage, NMSS and PDQ-8 score.

**Conclusions:** As compared to FOGOFF, FOGONOFF was associated with higher UPDRS part I scores. FOG significantly correlated with WO, non-motor symptoms, and worse quality of life.

## SC13

### The Hybrid Bike Project: an innovative exercise for Parkinson's Disease patients

G. Grazi<sup>1</sup>, Eva Bernardi<sup>1</sup>, S. Uliari<sup>1</sup>, G. Mazzoni<sup>1</sup>, E. Groppo<sup>2</sup>, E. Cesnik<sup>2</sup>, I. Casetta<sup>2</sup>, G. Granieri<sup>2</sup>, M. Manca<sup>3</sup>, E. Granieri<sup>2</sup>

<sup>1</sup>Centro Studi Biomedici applicati allo Sport Università di Ferrara, Ferrara

<sup>2</sup>Sezione di Clinica Neurologica, Dipartimento di Discipline Medico-Chirurgiche della Comunicazione e del Comportamento, Università di Ferrara, Ferrara

<sup>3</sup>Laboratorio Analisi del Cammino, UO di Medicina Riabilitativa, Azienda Ospedaliera Universitaria di Ferrara, Ferrara

**Introduction:** Many studies have shown the beneficial effects of physical activity on brain health and function. However, the association between physical activity and chronic neurodegenerative diseases is less well established, particularly for the better "dose" of exercise prescription. It has been recently documented that an active and assisted tandem cycling (Forced Exercise) can provide significant improvements in motor and central nervous system function in patients with Parkinson's Disease (PD).

**Aim:** To compare the effects of an innovative Active-Assisted cycling exercise (AAE) and of a usual Voluntary Exercise (VE) on clinical and functional parameters in PD patients.

**Methods:** 24 patients with mild-to-moderate PD will be randomly assigned to an 8-wks exercise intervention of AAE or VE training: three 1-h sessions weekly (10 min: warm-up, 40 min: main exercise and 10 min: cool-down). Patients in VE group will train on a traditional electromagnetically braked cycle ergometer at a pedalling cadence of  $\sim 60$  rpm. The AAE subjects will train at 30% to 40% higher pedalling rate on an electric motor-driven bicycle (Hybrid, Carrera-Podium, Italy), clamped to an electromagnetic roller (Realaxiom CT, Elite, Italy), simulating real outdoor cycling. Both groups will exercise at similar aerobic intensities. Cardiorespiratory fitness, Unified Parkinson's Disease Rating Scale, body acceleration, dynamic gait index, and Quality of Life (QoL 36) questionnaire, will be assessed before and after training. In order to evaluate the long-term effects of AAE, clinical testing will be performed four and eight weeks after cessation.

**Expected Results and Conclusion:** Cycle exercise at higher pedaling cadence would improve training effects on motor and central nervous system function. These data could help in the definition of the optimal exercise prescription for neurologic patients. From a practical point of view, AAE is an easy, safe, relatively low-cost and could be used by specialized center and for home program.

## SC14

**GPI DEEP brain stimulation 8 years after STN DBS: cases report**

*Ilaria Bertaina*<sup>1,2</sup>, *A. Fasano*<sup>3</sup>, *B. Minafra*<sup>1,2</sup>, *N.G. Pozzi*<sup>1,2</sup>, *D. Servello*<sup>4</sup>, *R. Zangaglia*<sup>1,2</sup>, *C. Pacchetti*<sup>1,2</sup>

<sup>1</sup>Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>2</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>3</sup>Department of Neurology Catholic University, Rome

<sup>4</sup>Functional Neurosurgical Unit, IRCCS "Galeazzi", Milano

The main targets for deep brain stimulation (DBS) in advanced Parkinson's disease (PD) are the subthalamic nucleus and the globus pallidus interna. Anyway the most source of information about the efficacy of this procedure came from STN DBS and there are limited data to resolve the debate on the comparison between GPi and STN DBS. The long-term follow-up of STN DBS patients shows that the improvement of motor complications are maintained, while freezing, postural instability, falling, cognitive and speech difficulties are the major source of disability. Nevertheless the information emerging from latter studies, some patients manifest a motor disease progression need increasing of dopaminergic therapy after many years of STN DBS. We describe three PD patients who underwent STN DBS with good clinical outcome and in whom GPi DBS has been done as "rescue therapy" after 8 years, in order to manage the disease progression. This procedure was performed after various and unsuccessful adjustments of dopaminergic therapies and STN DBS parameters. Two years after GPi surgery, the patients' motor condition did not present any considerable change in terms of total score of the motor section of the UPDRS. However, GPi DBS led to a substantial improvement of motor function due to the reduction of dystonia and dyskinesias, especially in two of our patients. In these patients, painful dystonias disappeared and motor fluctuations markedly improved. In our cases GPi-DBS, performed 8 years after STN DBS, could still improve persistent dyskinesias and dystonia leading to a global clinical improvement with no need to increase the dopaminergic therapy. Our experience expands the current knowledge on the management of these patients.

## SC15

**Rehabilitation of the cognitive impairment in Parkinson's disease**

*Liana Bestavashvili*, *S. Ippolito*, *M.F. Ioni*, *E. Volpe*, *R. Ricci*, *I. Clemenzi*

Department of Neurological Rehabilitation, San Raffaele Portuense, Rome

Almost all patients with Parkinson's disease (PD) suffer from selective cognitive impairments, including attention deficits, concentration impairment, problem solving, impaired executive function and memory. We have elaborated a cognitive rehabilitation protocol specific for the PD patients.

The aim of this study was to evaluate the improvement of the cognitive impairment in PD and observe if there is any correlation with the drug therapy. We observed 36 patients with mild cognitive impairment who received the cognitive treatment according to our protocol using selected exercises for the impaired cognitive functions peculiar for PD. All patients received 40 individual training sessions of 45 min duration. All of them underwent a neuropsychological testing before and after treatment and evaluation by UPDRS.

The drug therapy of our patients: 19 patients took levodopa (L-DOPA) and rotigotine (4–6 mg), 8 patients L-DOPA and ropinirole

(4–8 mg prolonged release), 5 patients L-DOPA and pramipexole and 4 patients only L-DOPA. The patients mean age was between 65–75 years old with min-max 6–10 years of PD duration. We did not consider patients with severe concomitant diseases, which could limit cognitive performances, as well as patients with a second neurodegenerative disease.

Our evaluation in discharge showed improvements in the following areas: memory, attention, concentration and executive function. We have also noticed that patients with rotigotine and ropinirole therapy had the better outcome in various cognitive areas, 15 patients with rotigotine therapy improved memory, attention and concentration, 2 patients improved attention and short term memory, other 2 patients did not demonstrate any benefit. 6 patients with ropinirole improved memory and attention, other 2 patients improved only short term memory.

Further studies are needed to confirm the preliminary experience and verify the long term effects after the cognitive treatment.

## SC16

**Motor Decision-Making in Parkinson Disease**

*Ambra Bisio*<sup>1</sup>, *B. Berret*<sup>2</sup>, *A. Raffo*<sup>3</sup>, *L. Avanzino*<sup>1</sup>, *M. Bove*<sup>1</sup>, *G. Abbruzzese*<sup>3</sup>, *T. Pozzo*<sup>2,4</sup>

<sup>1</sup>Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa

<sup>2</sup>Department of Robotics, Brain and Cognitive Sciences, Italian Institute of Technology, Genoa

<sup>3</sup>Department of Neurosciences, Ophthalmology & Genetics and Istituto Nazionale di Neuroscienze University of Genoa, Genoa

<sup>4</sup>Institut National de la Santé et de la Recherche Médicale-U1093, Cognition, Action et Plasticité Sensorimotrice, Institut Universitaire de France, UFR STAPS, Université de Bourgogne, Campus Universitaire, Dijon

Human daily life is a chain of decisions that are modulated by a variety of environmental factors and intrinsic contexts. It has been proposed that normal decision-making requires coordinated activity within a wide variety of brain areas and neural networks that includes also the frontostriatal and limbic loops, and basal ganglia (Gleichgerricht et al., 2010). For this reason, Parkinson's disease (PD) has become a popular model for studying decision-making mechanisms. Indeed, significant impairment in making profitable decision were obtained when PD patients performed tasks involving explicit decision-making as the Iowa Gambling Task (Pagonabarraga et al., 2007). Mazzone et al. (2007) tested the unconscious decision-making processes adopted by the motor system during movement planning showing that patients' reluctance to move faster in absence of physical constraints might represent an implicit decision due to a distortion of speed selection mechanisms caused by dopamine deficit. Aiming to more deeply investigate the principles that govern motion planning in PD patients we applied the Manifold Reaching Paradigm (MRP - Berret et al., 2010) on a group of eight PD patients (age =  $68.1 \pm 10.7$ ; UPDRSIII =  $20.2 \pm 10.9$ ) and eight healthy age-matched controls (age =  $69.1 \pm 2.3$ ). In a sitting position, starting from three initial finger's points, participants were asked to perform thirty pointing movements toward a horizontal target wooden bar placed on a table. To leave participants free to choose the more comfortable pointing position no target point was emphasized on the bar. The analysis on movement kinematics showed that, although PD patients performed the pointing movement as fast as the control, motion planning was altered as suggested by the increment of the reaction time, the time to

reach the maximum of velocity, and also the pointing variability especially from right starting position.

Our results suggest that the MRP could represent an innovative technique to test motor decision-making in PD patients.

## SC17

### Neuropsychological profile of Mild Cognitive Impairment in Parkinson's Disease

*Roberta Biundo, M. Pilleri, S. Facchini, L. Weis, P. Formento-Dojot, A. Antonini*

Fondazione Ospedale San Camillo, Venice Lido (Venezia)

**Introduction:** Prevalence of mild cognitive impairment (MCI) in Parkinson's Disease (PD) is variable in different studies, likely due to methodological differences in classification criteria and in neuropsychological tests used for cognitive profiling.

**Objectives:** This study was aimed to determine MCI frequency using a standardized method and to investigate the usefulness of different neuropsychological tests to detect MCI and to characterize different MCI profiles.

**Methods:** A series of consecutive PD patients without dementia were included in the study. All the patients performed an extensive neuropsychological evaluation. Individual test values were converted into z scores using relative normative data. Patients performing 1.5 SDs below the mean score were classified as MCI, according to published criteria (Litvan et., 2012). Two different cognitive MCI profiles were defined: MCI Frontal type (MCI-F) (patients without memory impairment) and MCI Posterior type (MCI-P) (patients with at least one memory task impairment).

**Results:** In our series of 89 PD patients we found 55 PD-CNT (62%) and 34 PD-MCI (38%) (19 MCI-F and 15 MCI-P). PD-MCI showed higher disease duration, lower educational level and higher prevalence of hallucinations compared to PD-CNT. Analysis of cognitive performance showed significant differences in several tasks between the two groups, however only Trail Making test (TMT) A, B and B-A discriminated with good sensitivity and specificity PD-MCI from PD-CNT. MCI-P patients performed significantly worse in verbal fluency and verbal memory tasks and showed higher prevalence of hallucinations compared to MCI-F.

**Conclusions:** Standardized methodology based on z scores is a suitable procedure for definition of cognitive impairment in PD. Among all tests of our extensive neuropsychological battery only TMT discriminated PD-MCI from PD CNT. MCI-P profile is characterized by impairment of specific cognitive tasks.

## SC18

### Where do dyskinesias begin in Parkinson's disease?

*Maria Carmela Bloise, A. Latorre, M. Sarchioto, G. Fabbrini, A. Berardelli*

Dipartimento di Neurologia e Psichiatria, Sapienza Università di Roma, Roma

**Background:** Observations in PD patients chronically treated with L-dopa suggest that levodopa induced dyskinesias (LID) usually manifest in the body site most affected by Parkinsonian symptoms.

**Objective:** To investigate the relationship between the body region in which LID first appeared and the body region where motor symptoms started in Parkinson's disease (PD) patients in which LID were observed for the first time during our clinical observation.

**Methods and patients:** We included patients in which we directly observed the onset of LID. Onset of parkinsonian motor symptoms was evaluated retrospectively. Motor signs and LID

were classified as manifesting unilaterally or bilaterally in the limbs, in the head, neck and trunk.

**Results:** We observed the onset of LID in 58 patients (31 males, mean age  $72.2 \pm 8.2$  years, symptoms duration  $9.4 \pm 5.5$  years). In these patients, motor symptoms started unilaterally in the right limbs in 29 patients (50%); unilaterally in the left limbs in 25 (43,1%) and bilaterally in the limbs in 4 (6,9%). LID started unilaterally in the right limbs in 8 patients (13,8%); unilaterally in the left limbs in 4 patients (6,9%) and bilaterally in the limbs in 7 patients (12,1%). LID started both unilaterally in the limbs and in the cranial-cervical-trunk region in 17 patients (29,3%) and only in the cranial-cervical-trunk region in 22 patients (37,9%).

**Discussion:** Our study shows that there is only a partial relationship between the body region first involved by LID and the body part first affected by motor symptoms. In fact, in 37% of patients, despite the onset of motor symptoms was always referred to the limbs, LID begun in the cranial-cervical-trunk region. The onset of LID and motor symptoms in PD may follow different anatomical patterns. This clinical finding probably reflects "abnormal focussing" and reduced somatotopic specificity in basal ganglia and cortical motor areas.

## SC19

### Rotigotine in motor and non-motor symptoms in Parkinson's disease: a case report

*Stefania Brotini* Neurology Unit, Department of Medicine, Empoli (FI)

**Background:** Advanced Parkinson's Disease (APD) is characterized by decreased response to oral dopaminergic treatment, worsening in motor and non-motor symptoms. Sleep disorders are amongst the most common non-motor symptoms in Parkinson's disease (PD). They occur during the pre-motor stage and throughout all the stages of the disease. Depression affects 30–50% of individuals with Parkinson disease (PD), often preceding the appearance of motor symptoms, and reducing health-related quality of life.

**Case Report:** A 48-year-old woman was admitted to the hospital because of severe bradykinesia, frequent dyskinesia, mood disorder and sleep disturbances. The patient has been followed with PD for 6 years.

Rotigotine therapy was titrated to 16 mg during 24 hours daily in addition to levodopa and COMT-inhibitor. The patient was clinically evaluated at baseline, and then every 3 months to 12 months. She was assessed using UPDRS, Hamilton Scale for Depression, Epworth Sleeping Scale (ESS) and Parkinson's Disease Sleep Scale-2 (PDSS-2). MRI examination was normal and SPECT DaTSCAN demonstrates an asymmetric decrease of the uptake in the putamen of the left. UPDRS-motor score reduced from baseline 43,0 to 5,0. Hamilton scale reduced from 18 to 2. ESS from 16 to 3, and PDSS-2 score falling by an average of 55%.

**Conclusion:** Rotigotine may be an effective treatment in advanced Parkinson's disease, ameliorating sleep disorders, reducing mood disorder and motor symptoms. Rotigotine may play an important role in the quality of life.

## SC20

### A possible corticobasal degeneration syndrome of atypical etiology

*Alexandra Brunetti, N. Modugno, D. Lanni, S. Ruggieri*

IRCCS Neuromed, Pozzilli (Isernia)

We present the case of a 71 years old patient who present a parkinsonian syndrome in the left hemibody predominantly with ideo motor apraxia.

The case would be suggestive of possible cortico basal degeneration. However we observed calcium metabolism abnormalities with deposits in the putamen bilaterally.

We discuss possible differential diagnosis.

## SC21

### Cerebellar intermittent theta burst stimulation modulates cerebellar-cortical-subcortical connectivity in patients with Progressive Supranuclear Palsy (PSP)

*Livia Brusa, V. Ponzo, C. Mastropasqua, S. Picazio, M. Bozzali, A. Stefani, C. Iani, P. Stanzione, G. Koch*

UOC Neurologia Ospedale Sant'Eugenio, Roma  
Fondazione Santa Lucia IRCCS, Roma  
Dipartimento Neuroscienza Università di Roma Tor Vergata, Roma

**Introduction.** Progressive Supranuclear Palsy (PSP) is an atypical degenerative parkinsonism clinically characterized by postural instability, supranuclear gaze palsy and frontal deficits. Recent imaging studies revealed specific cerebellar abnormalities when measuring the volume of the cerebellum, superior cerebellar peduncles (SCPs) and midbrain, that were all significantly reduced in PSP. On the basis of these findings an MRI parkinsonism index obtained by the pons area-midbrain area ratio (P/M) and the MCP width -SCP width ratio was identified to discriminate PSP patients from PD and MSA. Moreover, a transcranial magnetic stimulation (TMS) study by Yuichiro [1] recently demonstrated a subclinical cerebellar involvement in PSP compatible with the severe degeneration of dentate nucleus, showing an impairment of functional connectivity between the cerebellar hemisphere and the contralateral motor cortex (cerebellar-brain inhibition, CBI).

**Objective:** in the current study we applied intermittent theta burst stimulation (iTBS), a novel form of repetitive transcranial magnetic stimulation (TMS), over the lateral cerebellum in a population of PSP patients, in order to investigate the functioning of the cerebello-thalamo-cortical circuits in these patients.

**Methods:** Two iTBS trains, one in each cerebellar hemisphere, were applied during two weeks daily from monday to friday. Before and after the iTBS session, we used standard TMS methods to explore the functional connectivity between the cerebellar hemisphere and the contralateral motor cortex (CBI), and to measure the excitability of the contralateral primary motor cortex assessing intracortical inhibition (SICI) and intracortical facilitation (ICF). Moreover we also performed resting state functional magnetic resonance (fMRI) to investigate changes in other remote interconnected areas. Finally PSP patients included in our study were submitted to a clinical evaluation by administering the clinical rating scale [3] for PSP before and after the cerebellar iTBS.

**Results:** Cerebellar iTBS increased the deficient functional connectivity as assessed by CBI. No effects was seen for SICI and ICF measurements. Resting-state fMRI revealed an increased signal in the head of the caudate nucleus bilaterally. Finally all patients reported a significant improvement of dysarthria as stated by the item 12 of the scale; two out of ten obtained a significant improvement of gait (item 26).

**Conclusion:** These results provide further functional evidence for the abnormal anatomical changes observed in cerebellar structures in PSP patients. Increasing the excitability of the cerebellar hemispheres by means of iTBS resulted in an improvement of the functional connectivity between the cerebellar hemisphere, the caudate nucleus and the cortex, that was paralleled by some mild clinical improvement.

## References:

- [1] Yuichiro S, Masashi H, Ritsuko H et al Cerebellar dysfunction in progressive Supranuclear Palsy: a transcranial magnetic Stimulation Study. *Movement Disorders* 25, 14, 2010:2413-2419.
- [2] Litvan I, Agid Y, Calne D et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy: report of the NINDS-SPSP international Workshop. *Neurology* 1996;47: 1-9.
- [3] Golbe L, PA Ohman-Strickland. A clinical rating Scale for Progressive Supranuclear Palsy. *Brain* 2007; 130: 1552-1565

## SC22

### Adverse drug reaction to dopamine agonists (DA) or appearance of a typical sign of Parkinson's Disease induced by DA

*Francesco Maria Cacciatore, M. De Simone, D. Patrocino, V. Sallustio, L. Serlenga*

ASL Lecce, Lecce

ASL Bari, Bari

**Introduction:** Hypokinetic dysarthria (HD) is a common manifestation of Parkinson's Disease (PD) and has reported to be present in all stages of the disease with an increasing prevalence in the more advanced stages; to date it has been also reported as a complication appeared after STN DBS, but never as a drug-induced.

**Patient and methods:** We present a 79 years old man with PD who, on our initial consultation, had a mild hypokinetic – rigid extrapyramidal syndrome, after three years of illness. He was on L-DOPA and IMAO-B treatment; six months later, due to a worsening of bradykinesia, we added a dopamine agonist (DA) – Rotigotine patch 2 mg once daily; after two days he sudden developed a Speech dysfunction diagnosed by Motor Speech Profile (MPS) as an hypokinetic dysarthria (HD). It improved moderately, but not disappeared completely, after interruption of patch application; meanwhile a cranial mdc-MRI revealed only multiple areas of vascular gliosis in fronto-parietal lobe bilaterally but none of these seems to be related to the speech dysfunction; after twenty days we introduced a different DA Pramipexolo ER cpr 0,26 → 0,52 → 1,05 mg once daily; on the third day the HD worsened quickly and severely; again, after interruption of the last therapy, speech dysfunction improved spontaneously until to disappear completely after two months of Lee Silverman Voice Treatment (LSVT).

**Conclusions:** Hypokinetic dysarthria is a typical sign of advanced stages of PD. Transient and reversible HD is also reported as a collateral effect in patients treated with STN DBS consequently at a stimulation of posterior subthalamic area. Our case suggests that the speech dysfunction (transient and reversible) could be also an unknown adverse drug reaction to DA to date never reported in the Pharmacovigilance database.

## SC23

### Mechanical stimulation of the feet improves motor function and freezing of gait in Parkinson's disease: follow up to 96 hours

*Margherita Canesi<sup>1</sup>, F. Moroni<sup>3</sup>, E. Reali<sup>1</sup>, A. Porta<sup>2</sup>, F. Barbic<sup>4</sup>, G. Cerri<sup>4</sup>, M.L. Rusconi<sup>3</sup>, R. Furlan<sup>4</sup>, G. Pezzoli<sup>1</sup>*

<sup>1</sup>Centro Parkinson e Disordini del Movimento, Istituti Clinici di Perfezionamento, CTO, Milano

<sup>2</sup>Dipartimento di Scienze Biomediche per la Salute, Istituto Ortopedico Galeazzi, Università di Milano, Milano

<sup>3</sup>Department of Human Science, University of Bergamo, Bergamo

<sup>4</sup>Unità Sincopi e Disturbi della Postura, Clinica Medica - Istituto Clinico Humanitas, Rozzano (MI), Università di Milano; Neuroscience Research Association, Milano

**Background:** Foot mechanical stimulation (FMS) has recently shown his efficacy in improving gait and autonomic control of heart up to 24 hours in Parkinson's disease patients (PD). Nevertheless no data were collected about neurological evaluation by means UPDRS immediately after FMS and up to 48 hours of FMS.

The pathogenetics mechanism of FMS is already not known but alterations in sensorimotor central integration and/or peripheral sensory function might play a role in movement disorders in PD.

**Aims:** We tested the hypothesis that motor functions can improve immediately after and up to 96 hours the FMS respectively.

**Methods:** Consecutive outpatients fulfilling UK Brain Banking criteria for idiopathic PD and attending the Parkinson Institute (Istituti Clinici di Perfezionamento, Milan, Italy) were enrolled in this study.

Inclusion criteria included age from 35 to 85 years, modified Hoehn & Yahr staging (HY) between 1 and 3, and MMSE score > 24. All patients were taking stable doses of dopamine replacement therapy since at least one month. Clinical workout included the complete UPDRS and the HY stage, assessed after 90 minutes levodopa dose; the Visual Analogue Scale (VAS) was used to evaluate well-being. Every subject underwent mechanical pressure (0.8 kg/mm<sup>2</sup>) at the big toe tip and at the big toe metatarsal joint (true FMS) on both feet. Sham FMS was performed in a different area of both sole (heel). An experienced therapist performed this procedure. PD pts and the neurologist expert in movement disorders were blinded to FMS throughout the study period. PD patients were randomized into two groups true and sham FMS groups (FMS-t and FMS-s respectively). Three visits were performed: before FMS (FMS-T0), three hours after FMS (FMS-T1) and after 96 hours FMS (FMS-T2).

**Results:** The two groups with true and sham stimulation did not differ in demographic, motor and therapy features at baseline (T = 0) (see Table 1). Significant data we obtain in the FMS-t group immediately after (three hours after FMS, T1) and after 96 hours of FMS (T2) in UPDRS part III (motor score) and in item 14 (FOG) and VAS when compared to baseline data. Activity of Daily Living measured by means of UPDRS part II significant improved at T2. No significant differences we collected in UPDRS-I and UPDRS-IV after 96 hours of FMS (T2).

**Conclusions:** Immediately after and after 96 hours of FMS PD patients showed significant changes in motor score measured by means of UPDRS-III, in activity of daily living measured by means of UPDRS part II, in FOG (item 14) and in wellness measured by means of VAS. FMS may improved motor function and FOG in a relative long-term period.

## SC24

### Different clinical phenotypes, neuroimaging, SPECT-DAT-SCAN and levodopa response in four patients with mutation and parkinsonism

*Antonino Cannas, P. Solla, G. Borghero, G. Floris, E. Costantino, G. Orofino, R. Puddu, M.G. Marrosu, F. Marrosu*

Centro per i Disturbi del Movimento, Dipartimento di Scienze Cardiovascolari e Neurologiche, Sezione Neurologia, Università di Cagliari, Cagliari

**Background:** The nosology of primary neurodegenerative diseases suggests diagnostic categories based on clinical symptoms and their progression. However, in recent years, new discoveries in genetics are revolutionizing the traditional nosology, documenting how different clinical phenotypes may be correlated with the same mutation.

**Objective:** We describe the different clinical phenotypes of four patients with parkinsonism and the c.1144G > A (p.A382T)

missense mutation of TARDBP gene. An interesting variability was also observed regard to SPECT-DAT-SCAN, neuroimaging, neuropsychological performances and levodopa response.

**Case reports:** Patient 1 showed resting tremor, muscular rigidity with hypomimia and important pyramidal dysarthria and dysphagia, DAT-SCAN negative, and absent levodopa response.

Patient 2 showed a clear asymmetric parkinsonism CBD-mimic with alien-like arm and hand in the right side, poor levodopa response, mild bulbar signs (dysarthria and dysphagia), severe postural instability, and DAT-SCAN positive. The patient's brother was previously diagnosed with ALS.

Patient 3 presented with symmetric parkinsonism PSP-mimic, severe rigidity and postural instability with frequent falls, impaired upward and downward gaze, mild bulbar signs, moderate dementia. Two sisters have a similar clinical picture.

Patient 4 presented with symmetric parkinsonism with resting tremor, diffuse muscular rigidity, hypomimia, postural instability, evident bulbar signs and progressive cognitive impairment, mimicking FTD. In the same family, three of five children have a similar clinical picture.

**Conclusions:** These findings suggest that phenotypical clinical, DAT-SCAN, neuroimaging, neuropsychological state, levodopa response are widely variable in patients with parkinsonism and the A382T TARDBP missense mutation. These forms of parkinsonism have an atypical presentation and an uncertain nosology, although the crucial core of the disease and the involvement of the basal ganglia are frequently clinically dominant.

## SC25

### Distinguish between early Parkinson disease patients and normal controls: postural and gait instrumental evaluation with portable accelerometer

*Francesco Cavallieri<sup>1</sup>, L. Codeluppi<sup>1</sup>, V. Fioravanti<sup>1</sup>, S. Mellone<sup>2</sup>, L. Palmerini<sup>2</sup>, L. Chiari<sup>2</sup>, S. Contardi<sup>1</sup>, P. Nichelli<sup>1</sup>, F. Valzania<sup>1</sup>*

<sup>1</sup>Department of Neuroscience, University of Modena and Reggio Emilia, Nuovo Ospedale Sant'Agostino Estense, Baggiovara (Modena)

<sup>2</sup>Biomedical Engineering Group, DEIS, University of Bologna, Bologna

**Introduction:** Timed Up-and-Go (TUG) test is a widely used clinical test to assess mobility and fall risk in Parkinson Disease (PD). Recently they have been proposed instrumental versions of the test, using inertial sensors to evaluate various features of movements during the test.

**Objective:** To verify if instrumental measures recorded with a non-invasive single accelerometer could help in the early diagnosis of PD and to evaluate postural and gate impairment in PD.

**Material and methods:** Twenty early-mild PD patients (62 ± 7 years old, eight women) and twenty age-matched control subjects were tested. The PD subjects were tested in OFF-medication status. A single accelerometer was worn with a belt at the level of L5 during the test. Each subject performed three classical TUG sessions followed by three additional TUG sessions performed with a Dual-task (DT) condition (loud voice consecutive calculation task). Acceleration signals from the antero-posterior (AP), medio-lateral (ML) and vertical (V) direction were considered for the analysis.

**Results:** Several postural instrumental measures were found statistically significant between groups. Combining two of those measures (namely: vertical harmonic ratio and antero-posterior normalized jerk) it was found a statistically significant difference between PD patient and normal control.

**Conclusion:** The applicance of two postural parameters recorded during the test with the accelerometer was found significant in recognize early PD from normal subjects. One of

those measures was found sensitive to variations in gait and posture clinical scores. This data suggest that using a simple portable accelerometer may help in distinguish early PD from normal subjects, and may be useful even in follow-up phase, helping in evaluate the evolution of the gait and postural impairment in PD or response to therapy.

## SC26

### Hemiparkinsonism and olfactory groove meningioma: an unusual association

Matteo Ciocca<sup>1</sup>, F. Cogliamian<sup>3</sup>, G. Ardolino<sup>3</sup>, M. Locatelli<sup>4</sup>, G. Carrabba<sup>4</sup>, B. Zarino<sup>4</sup>, P. Risso<sup>5</sup>, A. Priori<sup>2</sup>

<sup>1</sup>Dipartimento di Scienze Neurologiche, Università degli Studi di Milano, Milano

<sup>2</sup>Centro Clinico per la Neurostimolazione, le Neurotecnologie ed i Disturbi del Movimento, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano

<sup>3</sup>U.O. di Neurofisiopatologia, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano

<sup>4</sup>U.O. di Neurochirurgia, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano

<sup>5</sup>Università degli Studi di Milano – Bicocca, Milano

Brain tumors are uncommon etiologies of parkinsonism. The clinical manifestations of tumoral parkinsonism may sometimes resemble those of idiopathic origin. Increased awareness of this rare entity is important for an earlier prompt diagnosis and treatment. We report on a 43-year-old man presenting with loss of dexterity and rigidity in the right limb starting two months prior to admission. Neurological examinations showed left anosmia, slight rest tremor of the right hand, rigidity on the right side and a reduced right arm swing. An initial diagnosis of essential tremor was made in another institution. We made a clinical diagnosis of right hemiparkinsonism suggesting a complete diagnostic work up. Routine hematological and biochemical examination was normal. We performed a MRI scan that demonstrated a huge high-density mass in the left frontal lobe originating from olfactory groove, with a marked surrounding edema causing compression of the basal ganglia, especially of the head of the caudate. Before surgery, neurophysiological tests were performed, showing a dysexecutive syndrome with mild apathy, poor working memory for verbal and spatial information, mild verbal short and long term memory and visuo-spatial long term memory impairment, ideomotor apraxia, perseveration and irritability. The patient was successfully operated and his symptoms resolved partially, with a slight persisting rest tremor. This case points to the significance of structural neuroimaging in the evaluation of parkinsonism even in cases that fulfill all the necessary clinical criteria for idiopathic PD.

## SC27

### Upper limbs postural tremor as onset of facio-scapulo-humeral dystrophy

Giovanni Cirillo<sup>1</sup>, A. Tessitore<sup>1</sup>, R. De Micco<sup>1</sup>, A. Giordano<sup>1,3</sup>, S. Allocca<sup>2</sup>, G. Tedeschi<sup>1</sup>

<sup>1</sup>Dipartimento di Scienze Neurologiche, Seconda Università degli Studi di Napoli, Napoli

<sup>2</sup>Casa di Cura Neurologica e Neuropsichiatrica Villa Elisa, Casamarciano, Napoli

<sup>3</sup>Istituto di Diagnosi e Cura, Hermitage, Capodimonte, Napoli

*Clinical case:* a 38-year-old man presented with a twenty-year history of upper limbs postural tremor. He had been treated for

essential tremor for a year (propranolol 80 mg/die) with poor clinical benefits. He has familiar history of tremor: his grandfather was affected by upper limbs tremor since youth; his mother (60 y.o.) and his daughter (6 y.o.) are affected by upper limbs tremor.

His neurological examination revealed myopathic face, mild waddling gait; atrophy of right pectoralis major muscle, bilateral winging scapula (dx > sn); hypotrophy of anterolateral muscles of legs; tetra-hypotonia and tetra-hyporeflexia; upper limbs postural, hypostenic tremor. Creatine kinase levels were normal. ECG and echocardiography were normal. Electromyography showed a myopathic pattern in upper and lower limb muscles. Muscular biopsy is consistent with muscular dystrophy. Family and clinical history, neurological examination and instrumental findings prone to hypothesize a diagnosis of autosomal dominant primitive myopathy. A deletion of FRG1 gene (4q35) was found.

*Diagnosis:* upper limbs postural tremor in patient affected by facio-scapulo-humeral dystrophy.

## SC28

### Levodopa-induced neutropenia in Parkinson's disease: a case report

Christian Cordano<sup>1</sup>, A. Schenone<sup>1</sup>, G. Abbruzzese<sup>1</sup>, R. Marchese<sup>1</sup>, L. Schembri<sup>2</sup>, F. Marino<sup>2</sup>, B. Parodi<sup>1</sup>, A. Uccelli<sup>1</sup>, M. Cosentino<sup>2</sup>

<sup>1</sup>Department of Neuroscience, Ophthalmology and Genetics, University of Genoa, Genoa

<sup>2</sup>Center for Research in Medical Pharmacology, University of Insubria, Varese

*Background:* After more than 40 years of clinical use, levodopa (LD) remains the gold standard regarding symptomatic efficacy in the drug treatment of Parkinson's disease (PD). Compared with other available dopaminergic therapies, dopamine replacement with LD is associated with the greatest improvement in motor function, as assessed by reduced scores in the Unified Parkinson's Disease Rating Scale [UPDRS]). In addition, responsiveness to LD (required to exceed 25%–30% reduction in the motor part of the UPDRS) is a diagnostic criterion for PD. In clinical practice, LD slows the progression of disability as assessed by the Hoehn and Yahr staging system, and is associated with a reduction in mortality. Importantly, LD is one of the best tolerated drugs to treat PD, particularly in the elderly population. However, accumulated evidence shows that the therapeutic efficacy of LDOPA is gradually lost over time, and abnormal involuntary movements, dyskinesias, gradually emerge as a prominent side effect of the previously beneficial doses of the drug.

*Case report:* We report the case of a male patient of 82 years of age, without previous history of neurological diseases, who came to our attention in January 2009 for progressive resting tremor, started about 5 years ago. At admission, his neurological examination was positive for right upper limb resting tremor, micrographia, diffuse hypokinesia, decreased physiological synkinesis in left arm and gait difficulties with tendency to festination. DATscan showed bilateral qualitative and quantitative nigrostriatal dopaminergic impairment. At the clinical follow-up in June 2010 he presented with reduced motor autonomies and was thus started on Levodopa–Carbidopa. At the beginning of therapy, the patient showed reduction of hypokinesia and rigidity but also a significant reduction in leukocytes count (2,470xmm<sup>3</sup>), particularly neutrophils (0,710xmm<sup>3</sup>), confirmed by a second control three weeks later. After these findings, Levodopa–Carbidopa therapy was stopped with normalization of blood studies. On April 2011, the patient began treatment with Levodopa–Benserzide to control motor symptoms. For the second time the blood

tests underscored an important neutropenia ( $2,40 \times \text{mm}^3$ ), that forced the suspension of therapy followed by normalization of leukocyte count. To date, the patient is taking dopamine agonists with benefit and no evidence of hematological or other adverse effects. By means of rt-PCR we showed that, in comparison to circulating neutrophils from healthy subjects, cells from our patient underexpressed mRNA for D2-like dopamine receptors (DR) and overexpressed mRNA for D1-like (D5) DR as well as for tyrosine hydroxylase, the first and rate-limiting enzyme in the synthesis of dopamine.

**Discussion and conclusions:** Our case shows an adverse reaction to LD that our knowledge has not been previously reported. Normalization after LD dechallenge as well as relapse after rechallenge with LD in association with a different inhibitor of L-Dopa decarboxylase supports a strong causal relationship between LD and leukopenia. Additional studies are warranted to assess whether DR and/or TH mRNA expression in circulating neutrophils may be a marker of vulnerability to LD-induced leukopenia.

## SC29

### Does diabetes mellitus represent a complication to enteral levodopa/carbidopa infusion in patients with Parkinson's disease?

*Emanuela Costantino, M.M. Masci, P. Solla, R. Pau, M. Vacca, R. Melis, F. Fadda, F. Marrosu, A. Cannas*

Centro per i Disturbi del Movimento, Clinica Neurologica, Università di Cagliari, Cagliari

**Background:** Dysautonomic disorders and axonal sensory-motor polyneuropathy (ASMP) are not uncommon complications in patients affected by type II Diabetes Mellitus (DM). At the same time, dysautonomic symptoms can be present in Parkinson's disease (PD), while an ASMP has been observed, although rarely, in PD patients with enteral levodopa/carbidopa infusion. These considerations raise several issues about possible contraindications to enteral levodopa/carbidopa infusion in PD patients.

**Objective:** To report our experience in a PD patient affected by type 2 DM with dysautonomic symptoms treated with duodenal levodopa infusion.

**Case report:** A 75-year-old man with a 17-year history of PD complicated by severe motor fluctuations, such as wearing off, sudden on-off, gait freezing with falls in off period, and disabling dyskinesias in on period, was being treated with oral dopaminergic therapy without sufficient control of motor complications. He has also been affected by Type 2 DM and related marked (mainly cardiovascular) dysautonomic symptoms since two years. Hoehn and Yahr stage was 4 in off state, while UPDRS-III score was 64 of 108 in off period. No signs of ASMP were noted. Treatment with duodenal levodopa infusion was started with the following parameters: starter dose of 10 ml; continuous infusion: 3.0 ml/h; extra dose 2.0 ml and satisfying control of motor complications. Besides, dysautonomic symptoms were improved by the continuous administration of enteral levodopa/carbidopa.

**Discussion:** Type 2 DM with dysautonomia, but without ASMP, does not represent a contraindication to the enteral levodopa/carbidopa infusion through percutaneous endoscopic gastrostomy in PD patients. In fact, the continuous administration of enteral levodopa/carbidopa might represent a factor of stabilization of dysautonomia. In this regard, from a theoretical point of view, we hypothesize that the concomitant presence of ASMP could be more problematic.

## SC30

### Characterisation and rehabilitation of Pisa Syndrome in Parkinson disease

*Roberto De Icco<sup>1,2</sup>, C. Tassorelli<sup>1,2</sup>, M. Bartolo<sup>6</sup>, M. Bolla<sup>1,2</sup>, I. De Paoli<sup>1,2</sup>, M. Allena<sup>1</sup>, R. Zangaglia<sup>4,5</sup>, C. Pacchetti<sup>4,5</sup>, N.G. Pozzi<sup>4,5</sup>, E. Alfonsi<sup>3</sup>, A. Pichiecchio<sup>7</sup>, G. Nappi<sup>2,5</sup>, G. Sandrini<sup>1,2</sup>*

<sup>1</sup>Unit of Neurorehabilitation, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>2</sup>Department of Public Health, Neurosciences, Experimental and Forensic Medicine, Section of Neurological Sciences, University of Pavia, Pavia

<sup>3</sup>Department of Neurophysiology, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>4</sup>Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>5</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>6</sup>IRCCS INM Neuromed, Pozzilli (Isernia)

<sup>7</sup>Neuroradiology Unit, IRCCS "National Neurological Institute C. Mondino" Foundation, Pavia

**Background and Aims:** Abnormal postures of the trunk represent a typical feature of Parkinson's disease (PD). These include Pisa syndrome (PS), a tonic lateral flexion of the trunk associated with slight rotation along the sagittal plane. In this study we describe the clinical and instrumental features of PS, together with the effect of rehabilitation in a representative group of PD patients.

**Methods:** All patients with trunk deviation underwent EMG and radiological (RX and CAT scan) investigations. Clinical characteristics of patients with PS were compared with a control group of PD without trunk deviation. The rehabilitative program consisted in a 4-week standard approach associated with a specific protocol for core muscles strengthening.

**Results:** PD with PS showed a significantly higher score of disease asymmetry when compared with the control group. In the majority of patients with PS, trunk bending was contralateral to the side of symptom onset. EMG showed an abnormal tonic hyperactivity on the side of the deviation in the paravertebral thoracic muscles and in the abdominal oblique muscles. CT of the lumbar paraspinal muscles showed muscular hypotrophy more marked on the side of the deviation, with a cranio-caudal gradient. Rehabilitation induced an improvement in the range of motion and the posture of all subjects.

**Conclusions:** PS may represent a complication of advanced PD in a subgroup of patients that show a more marked asymmetry of disease and who have a detectable hyperactivity of the dorsal paravertebral muscles on the less affected side. This postural abnormality deserves attention and proper early treatment to prevent comorbidities and pain.

## SC31

### Dopaminergic modulation of the resting-state sensori-motor network in drug-naïve patients with Parkinson's disease

*Rosa De Micco<sup>1</sup>, A. Tessitore<sup>1</sup>, A. Paccone<sup>2</sup>, A. Giordano<sup>1,2</sup>, R. Conforti<sup>1</sup>, G. Pignataro<sup>3</sup>, L. Annunziato<sup>3</sup>, F. Esposito<sup>2,3,4</sup>, G. Tedeschi<sup>1,2</sup>*

<sup>1</sup>Department of Neurological Sciences, Second University of Naples, Naples

<sup>2</sup>Neurological Institute for Diagnosis and Care "Hermitage Capodimonte", Naples

<sup>3</sup>Department of Neuroscience, University of Naples "Federico II", Naples

<sup>4</sup>Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands

**Introduction:** Resting-state functional magnetic resonance imaging (RS-fMRI) allows to investigate the spatiotemporal distribution of the spontaneous coherent fluctuations of blood oxygen level-dependent (BOLD) signals within and between functionally related cortical regions, representing the so-called resting-state networks (RSN). In patients with Parkinson's Disease (PD), functional cortical changes, as assessed by fMRI, are thought to be secondary to a functional deafferentation caused by dopamine neuron degeneration of nigrostriatal system which results in a disruption of basal ganglia–thalamo-cortical loops underlying the classical motor signs and symptoms of PD.

**Objective:** To reveal, through resting-state functional MRI (RS-fMRI), acute changes in the cortical sensori-motor RSN (SMN) connectivity induced by a single dose of levodopa in drug-naïve Parkinson's disease (DNPd) patients.

**Methods:** 10 DNPd patients, were scanned twice in the same morning, immediately before (“drug-off” condition) and 60 minutes after (“drug-on” condition) levodopa administration; control RS-fMRI data were recorded in 18 healthy, age-matched control subjects. RS-fMRI data were collected with a 3Tesla MRI scanner. Independent component analysis (ICA), using Brain Voyager, was performed on all scans to extract SMN maps. A statistical threshold of  $p < 0.05$  corrected for multiple comparisons was used for both within and between groups analyses.

**Results:** Acute levodopa administration increases the connectivity at rest in the SMA of DNPd patients, a region where the same signals were found suppressed in untreated DNPd patients, compared to healthy normal controls; within the SMA, the levodopa effect is maximally selective in the so called “pre-SMA”, a cortical area specialized for motor control.

**Conclusions:** In contrast to previous studies our results did not imply or require the choice of a specific motor task or defining the lay-out of the seeding region(s): therefore pertains to the entire intrinsic distribution of the SMN functional connectivity at rest in DNPd patients.

## SC32

### Effects of dance therapy on balance, gait and neuropsychological performances in patients with Parkinson's disease and postural instability

*Edoardo Rosario De Natale*<sup>1</sup>, *E. Aiello*<sup>2</sup>, *K.S. Paulus*<sup>2</sup>, *G. Sotgiu*<sup>1</sup>, *V. Agnetti*<sup>2</sup>, *E. Tolu*<sup>1</sup>, *F. Deriu*<sup>1</sup>

<sup>1</sup>Dipartimento di Scienze Biomediche, Università degli Studi di Sassari, Sassari

<sup>2</sup>Dipartimento di Scienze Chirurgiche Microchirurgiche e Mediche, Università degli Studi di Sassari, Sassari

<sup>3</sup>Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Sassari, Sassari

**Background:** Postural Instability (PI) is a core feature of Parkinson's Disease (PD) and a major cause of falls and disabilities. Impairment of executive functions has been called as an aggravating factor on motor performances. Dance therapy has been shown effective for improving gait and has been suggested as an alternative rehabilitative method.

**Aims:** To evaluate gait performance, spatial-temporal (S-T) gait parameters and cognitive performances in a cohort of patients with PD and PI modifications in balance after a cycle of dance therapy.

**Methods:** Eight patients with PD and PI (mean age  $66,1 \pm 9,2$  years, mean Hoehn & Yahr  $2,0 \pm 0,75$ ) underwent: comprehensive neurological examination with administration of UPDRS; balance

evaluation through Berg Balance Scale, Gait Dynamic Index, Timed Up-and-Go (TUG), Four-Step-Square Test; neuropsychological evaluation through Frontal Assessment Battery (FAB), Trail Making Tests A&B (TMT-A&B) and Stroop Test. Gait parameters such as cadence, gait velocity, stride length and duration were measured by a portable linear and angular accelerometer (FreeSense, Sensorize, Rome) worn at the belt during the 6-Minutes Walking Test. Such tests were made before, immediately after, and after one month from a cycle of dance therapy (one-hour tango sessions, twice weekly for 9 weeks) supervised by a professional dance instructor.

**Results:** Patients participated enthusiastically in the training. One drop-out was due to difficulties in attending the class. The most notable finding was a remarkable improvement of neuropsychological performances (TMT-A & B both  $p = < 0.0001$  and Stroop  $p = 0.009$ , while FAB  $p = 0.30$ , with comparable Effect Sizes). An amelioration of all motor scores was also found, although only the TUG reached statistical significance ( $p = 0.02$ ). No significant changes on gait S-T parameters were found.

**Conclusions:** Dance therapy seems to be an effective rehabilitative method for PI in PD which, in our sample, improved cognitive performances and on fall risk.

## SC33

### A new approach for the quantitative evaluation of the clock drawing test: preliminary results on subjects with Parkinson's disease

*Maria Francesca De Pandis*<sup>1</sup>, *M. Galli*<sup>2,3</sup>, *S. Vimercati*<sup>2</sup>, *M.V. De Angelis*<sup>1</sup>, *G. Albertini*<sup>3</sup>, *F. Stocchi*<sup>3</sup>

<sup>1</sup>“San Raffaele Cassino” Institute, San Raffaele SPA, Cassino (FR)

<sup>2</sup>Dipartimento di Bioingegneria, Politecnico di Milano, Milano

<sup>3</sup>IRCCS “San Raffaele Pisana”, San Raffaele SPA, Roma

**Introduction:** Writing and drawing are the final output of a complex neurological, psychological, and motor action and can therefore be used to investigate both the movement capabilities and the cognitive functions of the subjects. Simple drawing tests are commonly used for the clinical evaluation of cognitive capabilities, especially in the elderly, in order to assess the presence of dementia and to estimate its extent.

**Aims:** The realization of an experimental set-up for the quantitative and objective description of drawing using optoelectronic systems, which could be used when a quantification of the realization of specific drawing tests is required.

**Methods:** Healthy subjects, subjects with Parkinson's Disease and subjects with Parkinson's Disease and Dementia were evaluated by the Mini Mental Scale Evaluation and by a new approach to the Clock Drawing Test, based on an optoelectronic acquisition. The new protocol hereby described aims to define a parameter related to the movement kinematics in the Clock Drawing test execution.

**Results:** The experimental set-up revealed to be valid introducing new objective measurements beside the subjective Clock Drawing Test. This paper suggests the applicability of this protocol to other fields of motor and cognitive valuation, as well as the introduction of new parameters related to the graphic movement.

**Conclusions:** In this study, an experimental setup was defined for the quantitative and objective assessment of cognitive drawing tests. This setup was firstly applied to a group of healthy subjects (CG), then to a group of subjects with Parkinson's Disease (PD), and to a group of subjects with Parkinson's Disease and dementia (PDD), to assess the validity of the setup in the clinical usage.

## SC34

**Robotic stepping mechanism for gait rehabilitation in Parkinson disease – methods and preliminary data**

*Irene De Paoli*<sup>1,2</sup>, *R. De Icco*<sup>1,2</sup>, *M. Bolla*<sup>1,2</sup>, *M. Allena*<sup>1,2</sup>, *M. Berlangieri*<sup>1,2</sup>, *N. Costa*<sup>1</sup>, *I. Bertaina*<sup>4,5</sup>, *M. Fresia*<sup>3</sup>, *C. Pacchetti*<sup>4,5</sup>, *S. Cristina*<sup>1,2</sup>, *C. Tassorelli*<sup>1,2</sup>, *G. Sandrini*<sup>1,2</sup>

<sup>1</sup>Unit of Neurorehabilitation, National Institute of Neurology Foundation “C. Mondino”, Pavia

<sup>2</sup>Department of Public Health, Neurosciences, Experimental and Forensic Medicine, Section of Neurological Sciences, University of Pavia, Pavia

<sup>3</sup>Department of Neurophysiology, National Institute of Neurology Foundation “C. Mondino”, Pavia

<sup>4</sup>Parkinson’s Disease and Movement Disorders Unit, National Institute of Neurology Foundation “C. Mondino”, Pavia

<sup>5</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation “C. Mondino”, Pavia

**Introduction:** “Erigo” device is made up of a traditional tilt-table with an integrated robotic step system, which is used in the recovery of the standing posture and of the dynamics of walking. Gait impairment is a common cause of disability in Parkinson disease and it is associated with increased disease severity, poor quality of life and increased caregiver’s workload. Falls during walking are a common complication of Parkinson disease. Our aim was to investigate whether and how the use of the “Erigo” may influence gait performance in patients with Parkinson’s disease.

**Materials and methods:** Seven PD patients hospitalised at our Neurological Rehabilitation Unit were recruited and underwent a traditional rehabilitation treatment associated with Erigo robotic treatment. During the rehabilitative sessions with Erigo, the inclination and the frequency of steps were gradually increased. Assistance to the lower limbs movement by Erigo was regulated according to the patient’s ability. All patients were evaluated with gait analysis and outcome scales at the beginning and the end of the hospitalization.

**Results:** We observed a decrease in the number and duration of strides measured in milliseconds, with an increase in walking speed. Outcome scales showed significant clinical improvement at the end of rehabilitative treatment.

**Conclusions:** These preliminary data suggest the potential usefulness of adopting the “Erigo” to improve walking ability in patients with Parkinson disease, in particular in those subjects with significant impairment of gait.

## SC35

**Association between palatal myoclonus, Tako-Tsubo cardiomyopathy and Darier disease: Does a pathogenetic link exist?**

*Eleonora Del Prete*, *D. Frosini*, *V. Nicoletti*, *C. Del Gamba*, *U. Bonuccelli*, *R. Ceravolo*

Dipartimento di Neuroscienze, Università di Pisa, Pisa

**Introduction:** A 70-years old woman with a palatal myoclonus started about 17 months ago arrived to our clinic. The myoclonus produces an ear click that troubles the patient during the all day and does not stop during the night. No hypertrophy of inferior olive was found at MRI exam.

This patient also presents Darier disease, an autosomal dominant skin disorder, caused by mutations of the gene ATP2A2. The ATP2A2 encodes the sarcoplasmic/endoplasmic reticulum

Ca<sup>2+</sup> ATPase (SERCA2) pumps. SERCA 2 belongs to a family of p-type membrane bound ATPase which pump Ca<sup>2+</sup> from the cytoplasm in to reservoirs in the endoplasmic reticulum lumen, using energy from ATP hydrolysis. Moreover she was affected by Tako-Tsubo Cardiomyopathy. A recent study provides evidence that an altered gene expression of the Ca<sup>2+</sup> regulating proteins, as SERCA 2a, contributes to the heart contractile dysfunction in this disease and an increased PNL(phospholamban)/SERCA2a ratio represents a major determinant of contractile dysfunction. Alternative splicing of the ATP2A gene produces three isoforms, SERCA2a, 2b and 2c. The SERCA 2b is expressed ubiquitously and the major isoform is in the skin; SERCA 2a is expressed predominantly in cardiomyocytes, smooth muscle cells and in Purkinje cells. Most of the ATP2A mutation affects the three isoforms of SERCA 2. Symptomatic drug-induced myoclonus have been associated with Ca<sup>2+</sup> channels-blocker such as Diltiazem.

**Result:** The coexistence in the same patient of palatal myoclonus, Tako-Tsubo Cardiomyopathy and Darier disease, three uncommon conditions, brings us to suppose a possible correlation between them, with a possible common ground based on SERCA calcium pump dysfunction.

**Conclusion:** The dysfunction of the dentate-olivary pathway is considered the cause of the palatal myoclonus, and we suggest that, in this patient, this dysfunction is probably related to an abnormal function of SERCA2 pump that are well represented in Purkinje cells.

## SC36

**A case of subacute parkinsonism**

*Claudia Dell’Aquila*, *R. Mastronardi*, *F. Carnicella*, *F. Inversi*, *G. Masi*, *F. Saveriano*, *G. Straffella*, *M. Stuppiello*, *M. De Mari*

U.O. Neurologia Ospedale Civile “Bonomo”, Andria

**Introduction:** Myelinolysis can result from rapid correction of hyponatremia and is generally located central in the pons central pontine myelinolysis (CPM). Extrapontine myelinolysis (EPM) is also described and generally involves basal ganglia. Parkinsonism and dystonia are rarely seen in EPM.

**Case report:** We report the case of a 73 years old lady who was admitted at the Nephrologic Department because of confusional state and somnolence associated with severe hyponatremia occurred during antidepressant treatment with paroxetine. During the following days hyponatremia was rapidly corrected and the mental state of the patient improved. 10 days after admission the patient developed subacute parkinsonism with dysphonia followed by progressive dysarthria and dysphagia.

A first brain MRI showed bilateral symmetrical hyperintensities of caudate nucleus and putamen with sparing of the pons in T2-weighted images. Diagnosis of EPM was posed. Other cause of hyponatremia were excluded suggesting a role of paroxetine in its genesis. Levodopa treatment was started with benefit on parkinsonism.

A second MRI performed 2 weeks later showed typical central pontine hyperintensities together with basal ganglia hyperintensities.

At 2 months follow-up parkinsonism appear to be improved with persistence of prominent axial symptoms, the patient referred no more dysphagia while moderate dysarthria still persist. Sodium levels remained between normal range.

**Conclusion:** EPM could be considered as a cause of subacute parkinsonism in patient with hyponatremia due to its good

prognosis. In patients with otherwise unexplained hyponatremia paroxetine should be considered as a possible cause.

### SC37

#### Rapid eye movement sleep behavior disorder: a risk factor for cognitive impairment in Parkinson's disease?

Raffaella Di Giacopo<sup>1,2</sup>, D. Quaranta<sup>2</sup>, C. Piccininni<sup>2</sup>, F. Bove<sup>2</sup>, A.R. Bentivoglio<sup>2</sup>

<sup>1</sup>Center for Neurocognitive Rehabilitation (CeRiN), Mind/Brain Sciences (CiMeC), Trento University, Trento

<sup>2</sup>Catholic University, Rome

**Background:** Rapid eye movement (REM) sleep behavior disorder (RBD) is strongly associated with synucleinopathies, often heralding and later accompanying motor symptoms of Parkinson's disease (PD) and Lewy Body Dementia (DLB) [1]. Previous neuropsychological assessment revealed in idiopathic RBD patients without dementia the visuo-perceptual and verbal memory dysfunctions similar those observed in patients with PD and DLB [2]; it suggests a common pathophysiological mechanism between these conditions, according to Braak's hypothesis. However, these theory is not confirmed in all PD cases.

Our *objective* is to assess the relationship between the presence of RBD and the cognitive profile of non-demented patients with PD.

**Methods:** 47 patients with PD without dementia were evaluated by a standard neuropsychological battery assessing intelligence, episodic verbal and spatial memory, recall capacity, fluency, executive and visuospatial abilities. 25 patients satisfied clinic and polysomnographic criteria for RBD. Two-sided t tests were performed to compare differences between PD with RBD group and PD without RBD group.

**Results:** No significant differences between groups were found for age, schooling, depression assessment, Hoehn and Year (H&Y) stage (I-II), motor score of Unified Parkinson's Disease Rating Scale, disease duration, levodopa equivalent daily doses. Groups differ significantly in interference condition of the Stroop color word test ( $p = 0,002$ ).

**Conclusions:** Our data confirm a previous study [3] in that PD with RBD patients showed a lower cognitive performance compared to PD without RBD. The cognitive involvement in executive functions is very early, because our patients presented a mild motor phenotype (H&Y:  $1,87 \pm 0,49$ ) compared to literature. In agreement with these data, the RBD phenomenon can be an indicator of a more pervasive neurodegenerative process underlying the Parkinson's disease and can increase the risk of cognitive impairment in patients.

#### References:

- [1] Postuma RB, Gagnon JF, Vendette M, Montplaisir JY. Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. *Brain* 2009;132(Pt 12):3298–307.
- [2] Fantini ML, Farini E, Ortelli P, Zucconi M, Manconi M, Cappa S, Ferini-Strambi L. Longitudinal study of cognitive function in idiopathic REM sleep behavior disorder. *Sleep* 2011;34(5):619–25.
- [3] Vendette M, Gagnon JF, Décarry A, Massicotte-Marquez J, Postuma RB, Doyon J, Panisset M, Montplaisir J. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology* 2007;69(19):1843–849.

### SC38

#### Computer-assisted cognitive remediation for Parkinson's disease

Valeria Dibilio<sup>1</sup>, A. Nicoletti<sup>1</sup>, M. D'Amelio<sup>2</sup>, A. Cerasa<sup>3</sup>, G. Bellavia<sup>2</sup>, L. Di Gesaro<sup>2</sup>, M.C. Gioia<sup>3</sup>, T. Maci<sup>1</sup>, F. Le Pira<sup>1</sup>, S. Realmuto<sup>2</sup>, M. Salsone<sup>4</sup>, C. Sanfilippo<sup>1</sup>, G. Savettieri<sup>2</sup>, A. Quattrone<sup>3,4</sup>, M. Zappia<sup>1</sup>

<sup>1</sup>Dipartimento G.F. Ingrassia, Sezione di Neuroscienze, Università di Catania, Catania

<sup>2</sup>Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università degli Studi di Palermo, Palermo

<sup>3</sup>Consiglio Nazionale delle Ricerche, Unità di Ricerca Neuroimmagini, Catanzaro

<sup>4</sup>Clinica Neurologica, Università degli Studi "Magna Graecia", Catanzaro

**Background:** Cognitive dysfunction, principally involving executive performances, represents a cardinal non-motor symptom of Parkinson's disease which influences patients quality of life. However, few studies have focused on rehabilitation of cognitive performances in PD patients.

**Objective:** This study aimed to assess the compliance and efficacy of a computer-assisted cognitive rehabilitation program on cognitive performances of patients.

**Methods:** Non-demented PD patients were assigned to twelve 1-hours individual sessions (twice per week) of computer-assisted cognitive rehabilitation. Remediation was performed using Reha-Com<sup>®</sup> software. This software has a specific interface consisting of a special keyboard that has been designed to minimize the interferences due to motor and coordination disabilities. The study treatment focused on the rehabilitation of three different attentional processes: selective attention, divided attention and vigilance. All PD patients enrolled in the study were assessed neuropsychologically using a standardized battery, before and at the end of the cognitive rehabilitation program.

**Results:** Eight PD patients (four men; mean age  $66.1 \pm 6.8$ ; mean disease duration  $4.7 \pm 3.0$ ) were enrolled in the study. All patients completed the cognitive assessment battery before and after the rehabilitation program. An improvement in memory and executive functions, particularly attentive performances and working memory, was detected after the cognitive rehabilitation program even if average score differences between assessments were statistically significant only for the Frontal Assessment Battery and Trail Making Test ( $p < 0.05$ ).

**Conclusions:** Cognitive rehabilitation for PD patients has shown to improve performance in subjects with executive functions disorders. Further studies in larger sample and with a longer follow-up are needed to confirm our results.

### SC39

#### Clinical features of onset in monogenic Parkinson's disease

Antonio Emanuele Elia, J. Azzolini, C.F. Bagella, M. Carecchio, C. Barzaghi, B. Garavaglia, A. Albanese

Fondazione Istituto Neurologico, Carlo Besta, Milano

**Introduction:** Genetic causes of Parkinson's disease (PD) account for a significant number of early-onset and familial cases. The most frequently involved genes display both autosomal dominant (PARK1, 8) and recessive (PARK2, 6) patterns of inheritance. Moreover, mutations in the b-Glucocerebrosidase gene (GBA) have been recently found to be associated with PD.

**Objective:** 1) To analyze clinical features at onset in a cohort of Italian patients affected by monogenic PD; 2) to compare onset features in different monogenic forms of PD.

**Methods:** A consecutive series of 962 PD patients was recruited at the Movement Disorder Unit, Besta Institute, Milan (period 2002–2012). Inclusion criteria were: diagnosis of PD (Gelb, 1999), age at onset < 50 years and/or positive family history. Exons and flanking regions of PARK2, PARK6, PARK8 and GBA were analysed by direct sequencing. MLPA was performed for PARK1 and PARK2. Clinical features at onset in mutation positive patients were obtained from by clinical records and interview. Non-parametric statistical analysis was performed.

**Results:** Records of 85 patients who carry mutations in PD genes were reviewed: 2 with PARK1 duplication, 42 with homozygous PARK2, 4 with homozygous PARK6, 12 with heterozygous PARK8 and 25 with heterozygous GBA mutations. Differences in onset features were observed among groups: PARK2 patients showed the earliest age at onset ( $p < 0.01$ ); GBA patients displayed the highest frequency of non-motor onset ( $p < 0.05$ ); onset with dystonia was observed only in PARK2 and PARK6 groups. The highest frequency in lower limb onset was detected in recessive forms ( $p < 0.01$ ). Two patients resulted co-mutated in both PARK2 and GBA, they presented with motor onset but developed prominent non-motor features during follow up.

**Conclusions:** In PD patients with early onset or positive family history lower limb onset is associated with mutations in autosomal recessive genes. Non-motor onset is suggestive for GBA mutations.

#### SC40

##### Theory of mind in essential tremor

G. Santangelo<sup>1,2</sup>, P. Barone<sup>2,3</sup>, L. Trojano<sup>1</sup>, Domenico Errico<sup>1</sup>, I. Improta<sup>1</sup>, V. Agosti<sup>4</sup>, D. Grossi<sup>1</sup>, G. Sorrentino<sup>2,4</sup>, C. Vitale<sup>2,4</sup>

<sup>1</sup>Department of Psychology, Second University of Naples, Caserta

<sup>2</sup>Istituto di Diagnosi e Cura “Hermitage Capodimonte”, Naples

<sup>3</sup>Neurodegenerative Diseases Center, University of Salerno, Salerno

<sup>4</sup>University of Naples “Parthenope”, Naples

**Introduction:** The Theory of Mind (ToM) is the ability to attribute mental states to oneself and others and to understand that others have beliefs, desires and intentions different from one’s own.

**Objectives:** The aim of the present study was to explore the neuropsychological correlates of cognitive and affective ToM in patients affected by Essential Tremor (ET).

**Methods:** Thirty consecutive ET outpatients and 30 healthy age-, sex- and education-matched control subjects underwent tasks assessing short-term memory, verbal learning and executive functions, as well as tasks assessing “cognitive” and “affective” ToM (by means of Advanced ToM Task and Emotion Attribution Task, respectively); questionnaires evaluating behavioral disorders (Frontal Behavioral Inventory, Apathy Evaluation Scale) and quality of life (36-Item Short Form Health Survey, SF-36) were also administered.

**Results:** Although the two groups did not differ on demographic variables, ET patients scored worse on memory tasks, and showed more apathy and worse quality of life than controls. After covarying for mnemonic, behavioral and quality of life scores, ET patients achieved significantly lower scores than controls on task assessing cognitive ToM, whereas no difference was found between the two groups on task assessing affective ToM. In ET, “Cognitive” ToM was significantly associated with frontal tasks, whereas “Affective” ToM was not correlated with cognitive, behavioral and quality of life scales.

**Conclusion:** Our results demonstrate that cognitive aspects of ToM are selectively impaired in ET. Deficits in cognitive subcomponent of ToM might be linked to dysfunction of dorsolateral prefrontal cortex-cerebellum network.

#### SC41

##### Anxiety in newly diagnosed untreated Parkinson’s disease patients: a DAT-Scan study

Roberto Erro<sup>1</sup>, S. Pappatà<sup>2</sup>, M. Amboni<sup>1,3</sup>, K. Longo<sup>1,3</sup>, G. Santangelo<sup>4</sup>, M. Picillo<sup>1</sup>, C. Vitale<sup>3,5</sup>, M. Moccia<sup>1</sup>, M.T. Pellecchia<sup>6</sup>, P. Barone<sup>6</sup>

<sup>1</sup>University Federico II, Naples, Department of Neurological Science, Naples

<sup>2</sup>Institute of Biostructure and Bioimaging, CNR, Naples

<sup>3</sup>IDC Hermitage – Capodimonte, Naples

<sup>4</sup>Neuropsychology Laboratory, Department of Psychology, Second University of Naples, Caserta

<sup>5</sup>University Parthenope, Naples

<sup>6</sup>University of Salerno, Center for Neurodegenerative Diseases – CEMAND, Salerno

**Background:** Anxiety is a common non motor symptom among patients with Parkinson’s disease (PD). Although the etiology of anxiety in PD is likely multifactorial, a dysfunction in the dopaminergic system might be implicated in its pathogenesis. The aim of our study was to investigate a possible dopaminergic mechanism involved in anxiety in newly diagnosed never-medicated PD patients using SPECT and 123I-FP-CIT as dopamine transporter ligand.

**Methods:** Thirty-four newly-diagnosed untreated PD patients with asymmetric motor symptoms were included in the study: the group was constituted by 17 patients with right- and 17 with left-motor onset, matched for age, disease duration and motor disability. They were all evaluated for anxiety and depression and underwent a SPECT with 123I-FP-CIT. Dopamine transporter (DAT) availability values for right and left caudate and putamen were calculated and compared between patients with and without anxiety. Regression analyses were also performed in order to correlate DAT availability with anxiety symptoms severity.

**Results:** Comparison between PD patients with and without anxiety revealed significant differences of DAT availability in all the examined regions except the right putamen. In the group of patients considered as a whole, a significant correlation was found between increased anxiety severity and decreased DAT availability in right caudate.

**Conclusions:** We reported an association between nigrostriatal DAT availability deficits and anxiety symptoms in newly-diagnosed untreated PD patients. Our results suggest that hypofunction of nigrostriatal dopaminergic system may represent a possible mechanism involved in anxiety in PD since the earliest stages of disease and irrespective of any therapy.

#### SC42

##### An uncommon case of pediatric chorea

Marcello Esposito<sup>1</sup>, R. Dubbioso<sup>1</sup>, F. Manganelli<sup>1</sup>, C. Marino<sup>2</sup>, C. Pisciotta<sup>1</sup>, S. Pignatelli<sup>2</sup>, L. Santoro<sup>1</sup>

<sup>1</sup>Department of Neurological Sciences, University Federico II of Naples, Naples

<sup>2</sup>Dipartimento di Assistenza Riabilitativa Territoriale Area Età Evolutiva ASL TA2, Taranto

Here we present the case of a 9 years old boy showing upper limb hyperkinetic involuntary movements. His parents were

unrelated and came from Bulgaria having gypsy origin. The child sustained a birth asphyxia, at 9 months was operated for congenital cataracts and showed a motor and cognitive development delay. The patient was referred to our clinic because of walking difficulties and frequent fall. When he came at our observation the main clinical feature was the occurrence of hyperkinetic involuntary movements affecting especially the upper limbs with brief, random and sometimes shaking movements of the hands resembling choreic disorders; parents reported the onset of this disorder few years ago and there was not definite progression. On physical examination the boy showed mild facial dysmorphism, wild based and slow gait, distal muscle wasting with bilateral pes cavus; deep tendon reflex were absent and the plantar reflex showed an extensor response. Then the child underwent radiological and neurophysiological investigations. Brain MRI scan was normal. Nerve conduction studies showed severe motor and sensory nerve conduction velocity slowing consistent with a primary demyelinating peripheral neuropathy. These features were very suggestive of the “congenital cataracts facial dysmorphism neuropathy (CCFDN)” syndrome often described in Balkan gypsies. The genetic testing for the CCFDN showed a homozygous single nucleotide substitution of the CTDPI gene confirming the diagnosis.

**Conclusions:** This case shows a rare cause hereditary neuropathy in a complex genetic syndrome where chorea appeared one of the main clinical feature. CCFDN syndrome is not used to be included in the list of main causes of paediatric chorea published in scientific literature and we would suggest to consider this genetic disease as a possible further cause of paediatric movement disorders.

#### SC43

##### **Evaluation of neuroprotective effects in PC12 cells of polyphenols expressed by experimental cultivation of sardinian vines**

*Donatella Farina<sup>1</sup>, S. Dedola<sup>1</sup>, M. Pirisinu<sup>1</sup>, Y. Spissu<sup>1</sup>, A. Del Caro<sup>2</sup>, G. Rocchitta<sup>1</sup>, P.A. Serra<sup>1</sup>, R. Migheli<sup>1</sup>*

<sup>1</sup>Dept. of Clinical and Experimental Medicine, Section of Pharmacology, University of Sassari, Sassari

<sup>2</sup>Department of Agricultural and Environmental Sciences Agro-Food Biotechnology, University of Sassari, Sassari

Oxidative stress produced by reactive oxygen species ROS may participate in the cell death of dopamine neurons distinctive of Parkinson's disease (PD). One of the plausible ways to prevent the ROS mediated cellular injuries is to augment or fortify endogenous defense against oxidative stress through dietary or pharmacological intake of antioxidants. Many studies has been focused on red grape polyphenolic components that are able to scavenge ROS and protect cells from oxidative damage.

In the present work, several sardinian vines (bovale, carignano and mazuela), exposed to different light conditions (full wavelength and UV-deprived spectra) have been studied in order to increase red wines nutraceuticals (polyphenols). The potential neuroprotective capacity of red grape skins and seeds-derived polyphenols have been studied on cell death induced by H<sub>2</sub>O<sub>2</sub> in PC12 cells widely used as model for neurobiological and neurochemical studies. At the start of experiments, PC12 were seeded at 1x10<sup>5</sup> cells/ml in 24-well plates and treated 24 h later with red grape skins or seeds-derived polyphenols and H<sub>2</sub>O<sub>2</sub>. After 24 h, cells were processed with MTT reduction assay to evaluate cell viability and with LDH release assay, trypan blue dye exclusion test to evaluate cytotoxicity.

Our results showed that only the polyphenolic fraction derived from seeds was cytoprotective and statistically significant decrease in percentage cell viability was detected following 24 h

exposure of H<sub>2</sub>O<sub>2</sub> (100 μM). However, a significant increase in percentage cell viability (+15-30% vs control) was recorded after pretreatment with the polyphenolic fraction derived from seeds (50 μM – 100 μM).

Although no differences have been found exposing the cultivations to different light conditions, differences in neuroprotection were observed among vines. Our preliminary results support the role of these natural polyphenols in preventive and/or complementary therapies for several human neurodegenerative diseases, such as PD.

#### SC44

##### **T-lymphocyte proteins as biomarkers of Parkinson's disease**

*T. Alberio<sup>1,2</sup>, A.C. Pippione<sup>1,2</sup>, M. Zibetti<sup>3</sup>, S. Olgiati<sup>1</sup>, D. Cecconi<sup>4</sup>, C. Comi<sup>5</sup>, L. Lopiano<sup>3</sup>, Mauro Fasano<sup>1,2</sup>*

<sup>1</sup>Division of Biomedical Sciences, Department of Theoretical and Applied Sciences, University of Insubria, Busto Arsizio

<sup>2</sup>Center of Neuroscience, University of Insubria, Busto Arsizio

<sup>3</sup>Department of Neuroscience, University of Torino, Torino

<sup>4</sup>Proteomics and Mass Spectrometry Laboratory, Department of Biotechnology, University of Verona, Verona

<sup>5</sup>Division of Neurology, Department of Translational Medicine, University of Eastern Piedmont, Novara

The diagnosis of Parkinson's disease (PD) is currently based on the clinical evaluation of extrapyramidal signs, such as tremor, rigidity and bradykinesia, with a considerable error rate. In this study, we used two-dimensional electrophoresis to identify proteome alterations in T-lymphocytes. (T)-Lymphocytes express some features of the dopaminergic system (they express dopamine receptors and transporters, and store catecholamines into vesicles), so in PD patients they could carry some protein alterations peculiar to dopaminergic cells. In particular, patients affected by familial forms of PD (about 20% of all PD cases) may express, also at the peripheral level, alterations that mirror the pathogenic process at the central level. In the discovery phase, we examined 17 control subjects and 15 PD patients. We identified 20 protein spots and assigned their identity. The observed changes were used to build predictive models that were verified by the leave-one-out cross-validation, with sensitivity and specificity approaching 99%. We further built two functions able to stage the subjects in terms of disease duration and Hoehn and Yahr score. We chose to verify the identity of spots corresponding to γ-fibrinogen and transaldolase, two recurrent proteins in six out of 20 spots. By Western blotting, we found that γ-fibrinogen levels are lowered in PD patients, whereas a heavy transaldolase set of isoforms was more abundant. Eventually, we identified a list of seven proteins showing different levels in early-onset with respect to late-onset PD patients.

#### SC45

##### **Differences of distributed sources of cortical EEG rhythms in DLB patients with visual hallucinations respect to non hallucinated DLB and Alzheimer disease**

*Silvia Favaretto<sup>1</sup>, M. Ermani<sup>1</sup>, F. Gnoato<sup>1</sup>, N. Jelcic<sup>1</sup>, N. Bonetto<sup>1</sup>, G. Zarantonello<sup>1</sup>, A. Cagnin<sup>2</sup>*

<sup>1</sup>Dipartimento di Neuroscienze, Clinica Neurologica I, Università di Padova, Padova

<sup>2</sup>IRCSS San Camillo, Venezia

**Background:** Previous neurophysiological studies pointed out different EEG patterns in DLB patients respect to AD, mostly

expressed by a reduction of alfa-wave activity with a prevalence of theta and delta wave activity. EEG abnormalities may represent a valid tool for discriminating between the two types of dementia.

**Aim:** To map distributed sources of cortical EEG rhythms in DLB respect to AD patients and to study the neurophysiological correlates of VH in DLB.

**Methods:** 63 DLB and 25 AD patients were analyzed. Among 63 DLB patients, 32 had VH. Standard EEG was performed and processed with the software sLoreta in order to detect the cortical source of EEG rhythms registered on the scalp. The following standard band frequencies were considered: delta (2–4 Hz), theta (4–8 Hz) and alpha (8–13 Hz). This map was superimposed to the Talairach's map of cortical grey matter to detect the corresponding anatomical source of the band frequency.

**Results:** Upon EEG analysis, comparing DLB vs AD patients, DLB patients showed a source of delta activity in the posterior cingulate (BA 23–30), visual cortex (BA 17–19), and fusiform gyrus (BA 37) (100% of these cortical areas are involved in DLB,  $p < 0.01$ ), and a source of theta activity in the temporal gyri (BA 20–21). A source of theta activity in BA 23–30 and in BA 17–19 was significantly more represented in DLB VH+ respect to VH– (100% of BA 30 is involved in VH+,  $p < 0.05$ ).

**Conclusion:** Diagnosis of DLB is significantly associated with a source of delta wave activity in areas involved in the processing of visual information, and in parahippocampus and fusiform gyrus. The presence of VH in DLB patients is associated with a source of “lesional” band frequencies (delta and theta waves) in the parieto-occipital cortex (involving both primary and associative visual areas), and in the limbic system (occipito-amygdaloid pathway).

#### SC46

##### Putamen and caudate uptake obtained by [123-I] FP-DAT SCAN imaging at different stage of Parkinson disease

*Laura Ferigo*<sup>1</sup>, *S. Rossetto*<sup>2</sup>, *S. Guzzon*<sup>3</sup>, *N. Freddi*<sup>3</sup>, *A. Polo*<sup>1</sup>

<sup>1</sup>UOC Neurologia, ULSS21 Legnago (Verona)

<sup>2</sup>Medicina Nucleare, ULSS21 Legnago (Verona)

<sup>3</sup>UOC Neurologia, ULSS17 Este (Padova)

**Background:** Functional imaging of the dopamine transporter (DAT) defines the integrity of dopaminergic system and provides a marker for pre-synaptic neuronal degeneration. Dopamine loss is seen even in the earliest presentation of true parkinsonism. Abnormal uptake progresses from putamen to caudate and matches contralaterally the clinically more affected side. A normal DAT SCAN in patients with a clinically undefined parkinsonism, does not rule out later confirmed PD.

**Objective:** To investigate SCAN DAT imaging in assisting the differentiation between conditions with and without presynaptic dopaminergic deficit. In patients with clinical diagnosis of PD, to evaluate the effect on DAT results of performing the test at different time of individual history.

**Method:** We study 48 patients. Specific activity of putamen and caudate were obtained by [123-I] FP-DAT SCAN imaging. Image analysis uses quantitative region of interest (ROI) to occipital reference site.

**Results:** Twenty-seven patients underwent DAT SCAN within one year of symptom onset. Specific activity of putamen  $> 2.3$  bilaterally was found in three patients in which PD diagnosis was

clinically rule out. Contralateral putamen and caudate uptake to affected clinical side was significantly lower than the other one (respectively  $p = 7.83564E-05$ ,  $p < 0.0001$ ); fifteen patients underwent DAT scan within 2–5 years of symptom onset. Contralateral putamen and caudate specific activity to affected clinical side was significantly lower than the other one (respectively  $p < 0.0002$ ,  $p < 0.0002$ ,  $p < 0.0002$ ,  $p < 0.0004$ ). There is not any significant difference between values comparing tests at different time.

**Conclusion:** In typical asymmetric parkinsonism, DAT imaging provide quantitative, clinically-related information. Normal values, also later in course of movement disorder, ruled out true parkinsonism. Putamen involvement is clearly worse than caudate one, in each time of testing DAT SCAN.

#### SC47

##### Is the increased blink rate a form of blepharospasm?

*Gina Ferrazzano*<sup>1</sup>, *A. Conte*<sup>1</sup>, *G. Leodori*<sup>1</sup>, *G. Fabbrini*<sup>1</sup>, *G. Defazio*<sup>2</sup>, *A. Berardelli*<sup>1</sup>

<sup>1</sup>Department of Neurology and Psychiatry, Sapienza University of Rome, Rome

<sup>2</sup>Department of Neurosciences and Sensory Organs, School of Motor Sciences, “Aldo Moro” University of Bari, Bari

**Background:** Primary blepharospasm (BSP) is characterized by involuntary spasms in the orbicularis oculi (OO) muscles and an increased blink rate (BR) can be also present in some of these patients.

**Objective:** Whether patients with increased BR but without muscle spasms in OO should also be considered BSP patients is still unclear. Aim of the study was to investigate whether increased BR belongs to the clinical spectrum of BSP.

**Methods:** We enrolled 34 patients (10 patients with increased BR but without typical OO spasms, 10 patients with both increased BR and OO spasms and 14 patients with OO muscle spasms without increased BR) and 18 healthy subjects. Blink reflex recovery cycle and somatosensory temporal discrimination threshold (STDT) were tested in patients and controls.

**Results:** Statistical analysis for blink reflex recovery cycle showed a significant effect of factor ISI ( $F = 88.54$ ,  $p < 0.00001$ ) and a significant interaction of factor group and ISI ( $F = 6.89$ ,  $p < 0.001$ ). Post-hoc analysis showed that BSP patients with involuntary muscle spasm and those with increased BR and spasms had an altered blink reflex recovery cycle, whereas patients who had only increased BR had a normal blink reflex recovery cycle. STDT values were higher in BSP patients than in healthy subjects and the STDT abnormalities did not differ in the three groups of BSP patients. ROC curve analysis performed to investigate diagnostic accuracy of BR, R2 recovery index and STDT in discriminating patients with muscle spasms from those without spasms but increased BR yielded high diagnostic accuracy for R2 recovery index (82.61% sensitivity and 100% specificity with a cut-off value of 64%), whereas it yielded lower diagnostic accuracy for BR (65% sensitivity and 100% specificity with a cut-off value of 33.5%) and STDT (78% sensitivity and 45% specificity with a cut-off value of 147%).

**Conclusions:** Patients with increased BR should be considered a form of BSP as shown by altered STDT but they

differ from typical BSP patients for a normal blink reflex recovery cycle.

#### SC48

##### The interaction between drugs and sexual function in Parkinson's disease

*Roberta Ferrucci*<sup>1</sup>, *V. Raoli*<sup>1</sup>, *G. Ardolino*<sup>1</sup>, *F. Cogiமானian*<sup>1</sup>, *P. Barone*<sup>3</sup>, *L. Bertolasi*<sup>4</sup>, *A. Padovani*<sup>5</sup>, *M. Panzeri*<sup>6</sup>, *L. Ronconi*<sup>6</sup>, *M. Ciocca*<sup>2</sup>, *A. Priori*<sup>1,2</sup>

<sup>1</sup>Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano

<sup>2</sup>Università degli Studi di Milano, Milano

<sup>3</sup>Università degli Studi di Salerno, Salerno

<sup>4</sup>Azienda Ospedaliera Universitaria Integrata Verona, Verona

<sup>5</sup>Università degli Studi di Brescia, Brescia

<sup>6</sup>Università degli Studi di Padova, Padova

**Introduction:** Patients with Parkinson's disease can have impaired sexual function. Although the disease itself likely contribute to sexual dysfunction, antiparkinsonian drugs can also have an effect.

**Objective:** To investigate the interactions between Sexual Function and drug therapy in patients with Parkinson's disease.

**Methods:** 121 patients [(aged 40–80)(male = 70; female = 51)] diagnosed as having idiopathic PD and recruited from four Italian Movement Disorders Clinics. The therapy included the range of drugs commonly used in the treatment of PD: Dopamine Agonist, L-DOPA, Monoamine Oxidase Inhibitor (MAOI-B). To assess sexual function in PD we used the Brief Index of Sexual Functioning (BISF-M for man; BISF-W for woman).

**Results:** Females assuming MAOI-B had increased BISF score than those not assuming MAOI-B. Female patients taking MAOI-B had higher scores for sexual thoughts and desire ( $p = 0.05$ ), arousal ( $p = 0.03$ ) and frequency of sexual activity ( $p = 0.01$ ) than patients not assuming MAOI-B. Males assuming MAOI-B had increased BISF score than those assuming L-DOPA ( $p = 0.05$ ). The assumption of other antiparkinsonian drugs did not modify BISF scores.

**Conclusion:** MAOI-B could positively influence sexual function in patients with Parkinson's disease. Sexual anamnesis is therefore relevant for the choice of the most appropriate drug in patients with PD.

#### SC49

##### A voxel-based morphometry study of disease progression in a cohort of patients with Parkinson's disease

*Valentina Fioravanti*, *F. Benuzzi*, *L. Codeluppi*, *S. Contardi*, *F. Cavallieri*, *P. Nichelli*, *F. Valzania*

Department of Neuroscience, University of Modena and Reggio Emilia, Nuovo Ospedale Sant'Agostino Estense, Modena

**Background:** Using voxel-based morphometry (VBM) we investigate structural brain differences between group of early-mild PD patients at different phase of disease and healthy subjects.

**Objective:** To investigate, using MRI and voxel-based morphometry (VBM), whether specific patterns of gray matter (GM) loss are associated with progression of disease in patients with Parkinson disease (PD).

**Methods:** 20 mild PD subjects (Hoehn&Yahr < 2,5, non-fallers,  $62 \pm 7$  years old, 12 males) in OFF state, compared to 15 healthy

controls. The OFF condition was obtained by a medication washout (a levodopa washout of at least 18 hours and a dopamine agonist washout of at least 36 hours). All patients underwent MRI scan, physical examination (UPDRS scale, H&Y scale) and neuropsychological assessment at baseline and after 2 years of disease. The topographic distribution of brain tissue loss was assessed using VBM as implemented in Statistical Parametric Mapping (SPM8).

**Results:** At baseline patients had reduced brain volume in right putamen and right parietal cortex (angular gyrus and precuneus). After 2 years, the same patients confirmed GM loss in putamen and parietal cortex; moreover, a significantly difference was evidenced in posterior midbrain, referable to the area of peduncolopontine nucleus (PPN) and of the mesencefalic locomotor region (MLR).

**Conclusions:** In this study we demonstrate that parietal cortex and putamen are early affected in PD patients and that these structural brain changes seems to occur gradually during disease progression. Another structure which undergoes atrophy is the part of the inferior-posterior midbrain attributable to the PPN and MLR. The structures that control posture and gait may be involved at an early stage in Parkinson disease, although usually not evident at clinical examination.

#### SC50

##### A comparative study on the efficacy of Lee Silverman Voice Treatment (LSVT<sup>®</sup>) speech therapy on two groups of 14 patients with Progressive Supranuclear Palsy (PSP) and 25 patients with idiopathic Parkinson's disease

*Chiara Fossati*, *D. Castiglioni*, *P. Grassini*, *L. Vacca*, *M. Torti*, *S. Pinnola*, *F.G. Radicati*, *M. Casali*, *F. Stocchi*

IRCCS San Raffaele Pisana, Roma

**Introduction:** The LSVT<sup>®</sup> voice treatment was specifically created and tested to comply with the needs of individuals with Parkinson's disease (PD) and other neurological problems (PSP, MSA). This is an intensive treatment aiming at increasing vocal intensity through the increase of subglottal air pressure for a better cordal vibration. Experimental data from over 15 years' research, financed by the American National Institute of Health (NIH), have produced evidence that a specific speech therapy, LSVT<sup>®</sup>, is effective.

**Purpose:** The main goal of this study is to compare whether the positive impact of LSVT<sup>®</sup>, proven in years of experience with PD individuals, is equally valid with PSP patients.

**Method:** 14 patients with PSP and 25 patients with idiopathic Parkinson's disease were treated with 16 sessions of speech therapy following the LSVT<sup>®</sup> treatment. Initially the two groups of patients had similar voice problems, i.e. low volume and bad articulation of speech.

**Results:** Statistically significant results were found among the data collected during and after treatment in the two groups. Increase in maximum phonation duration and volume of voice in reading were similar in the two groups. Improvement in quality of voice and articulation were more significant in the PD group as compared to the PSP group.

**Conclusion:** These results, along with previous findings, add further support to the generalized therapeutic impact of intensive voice treatment on respiratory and laryngeal functions along with improvement of speech intelligibility in individuals with PD and also, in a certain measure, in individuals with PSP.

## SC51

**Rasagilina and intensive rehabilitation in parkinsonian patients: a randomized controlled study with 12 months follow-up**

*Giuseppe Frazzitta*<sup>1</sup>, *G. Riboldazzi*<sup>2,3</sup>, *G. Bertotti*<sup>1</sup>, *M. Perini*<sup>4</sup>, *N. Boveri*<sup>1</sup>, *D. Uccellini*<sup>5</sup>, *C. Comi*<sup>6</sup>, *R. Rovescala*<sup>1</sup>, *M. Turla*<sup>7</sup>, *G. Pezzoli*<sup>8</sup>, *R. Maestri*<sup>9</sup>

<sup>1</sup>Laboratorio di Diagnostica and Rieducazione Neuromuscolare, Fondazione “S. Maugeri” I.R.C.C.S., Montescano, Pavia, Italy

<sup>2</sup>Centro Parkinson, Fondazione Macchi, Varese, Italy

<sup>3</sup>Dip. di Riabilitazione, “Le Terrazze”, Cunardo, Varese, Italy

<sup>4</sup>Divisione di Neurologia, Gallarate, Varese, Italy

<sup>5</sup>Divisione di Neurologia, Tradate, Varese, Italy

<sup>6</sup>Dipartimento di Neurologia, Università Piemonte Orientale, Novara, Italy

<sup>7</sup>Divisione di Neurologia, Ospedale Vallecamonica, Esine, Brescia, Italy

<sup>8</sup>Centro Parkinson, Istituti Clinici di Perfezionamento, Milano, Italy

<sup>9</sup>Dipartimento di Ingegneria Biomedica, Fondazione “S. Maugeri” I.R.C.C.S., Montescano, Pavia, Italy

**Introduction:** A major focus of PD research is on “disease-modifying” or “neuroprotective” agents to slow PD progression. No drugs has so far given a clear proof of a neuroprotective activity. Increasing evidence suggests that ongoing vigorous exercise may favourably influence disease progression.

**Objective:** To test the efficacy on the disease progression in early stage of disease of the association of rasagiline and intensive rehabilitation treatment.

**Methods:** Thirty-five “de novo” parkinsonian patients were enrolled and randomly assigned to two groups: Group\_1 (20 pts) began therapy with rasagiline and underwent an intensive rehabilitation treatment (IRT); Group\_2 (15 pts) started only rasagiline. Patients were evaluated at the beginning of study and at 6–12-month follow-up. The primary outcome measures were: UPDRS II-III, Berg Balance scale (BBS), 6-Minutes Walking Test (6MWT), Timed up and go test (TUG). The secondary outcome measure was the dosage of Levodopa-equivalent.

**Results:** All patients who underwent IRT showed a significant improvement in all primary outcome measures at the end of treatment. At 12-month follow-up, patients in Group\_1 showed a significant improvement in UPDRS II-III scores, BBS and TUG, while Group\_2 patients showed an improvement in 6MWT and TUG. The 19 pts Group\_1 were still treated only with rasagiline, while in the Group 2 only 3 patients were in monotherapy with rasagiline and 12 patients had to add other drugs (dopamineagonist or levodopa).

**Conclusions:** It is possible to hypothesize that intensive exercise could lead, as seen in the animal models, to an increase in dopamine production and number of D2 receptors in dorso-lateral region of striatum acting in synergy with the rasagilina which also raises the extracellular dopamine concentration in the striatum. Our data suggest that IRT in association with rasagiline can slow the progression in early stage of disease.

## SC52

**Autoimmune syndromes of CNS with subacute onset and movement disorders: proposal of a diagnostic and therapeutic approach**

*Simone Gallerini*, *M. Bartalucci*, *L. Giovanditti*, *C. Scarpini*, *S. Pieri*, *K. Plewnia*, *R. Marconi*

Unit of Neurology, Ospedale della Misericordia, Grosseto

Autoimmune syndromes of CNS are a heterogenous group of diseases in evolution. The onset can be acute or subacute with

rapid progressive disease evolution and the clinical features are extremely variable ranging from cognitive or psychiatric symptoms and seizures to movement disorders. Even if in many cases antineuronal antibodies are not found some of these conditions can benefit from immunomodulatory therapy. We describe seven patients admitted over the last 2 years in the Neurological Unit of Grosseto from Emergency Department with complex movement disorders or neuropsychiatric syndromes and an acute or subacute onset and a rapid evolution: 1) opsoclonus-mioclonus-ataxia; 2) progressive hemiataxia; 3) mioclonus and delirium (two patients); 4) sensitive ataxia and delirium; 5) non convulsive SE; 6) paraneoplastic motoneuron disease. An extensive diagnostic program was done. It included brain and spinal MRI, EEG, neurophysiological studies, CSF examination, chest, abdomen and pelvis CT and PET to reveal associated tumors, detection of antineuronal antibodies. Finally an alternative diagnosis was excluded and an autoimmune basis was considered. The patients were treated with corticosteroids, intravenous immunoglobulin, plasma exchange with improvement in five of them. In our opinion, an autoimmune basis may be considered in patients with such signs and symptoms moreover when the following conditions are associated: 1) History of infection or tumor; 2) Normal brain MRI or presence of signs of an autoimmune disease; 3) Normal CSF examination or presence of signs of inflammation; 4) Detection of antineuronal antibodies; 5) Improvement with immunotherapy.

We believe that in presence of a patient with the above mentioned characteristics an autoimmune basis must be considered and treatment with steroids and intravenous immunoglobulins (IVIG) or plasma exchange should not be delayed.

## SC53

**Comparison of the gait patterns of young Parkinson's disease subjects with healthy elderly subjects**

*Manuela Galli*<sup>2</sup>, *P. Sale*<sup>3</sup>, *S. Vimercati*<sup>2</sup>, *F. Stocchi*<sup>3</sup>, *M. Franceschini*<sup>3</sup>, *S. Mazza*<sup>1</sup>, *M.F. De Pandis*<sup>1</sup>

<sup>1</sup>“San Raffaele Cassino” Institute, Cassino (Frosinone)

<sup>2</sup>Dipartimento di Bioingegneria, Politecnico di Milano, Milano

<sup>3</sup>IRCCS “San Raffaele Pisana”, San Raffaele SPA, Roma

**Background:** The gait of healthy elderly and of subjects with Parkinson's disease (PD) displays some common features, suggesting that PD may be a model of ageing.

**Aim:** The aim of the study was to quantify highlight the differences and similarities between the gait patterns of young PD and healthy elderly, to uncover if PD could be assumed as a model of ageing.

**Design:** An optoelectronic system was used for 3D gait analysis evaluation.

**Population and methods:** We compared the gait parameters of 15 young PD (YPD) with the gait of 32 healthy elderly subjects (ES) and 21 healthy subjects age-matched with the PD subjects.

**Results:** Common features between YPD and ES were majorly found in the parameters that reflect the presence of an unstable, uncertain gait, and of corrective strategies employed to reduce instability. On the other side, typical features were present in the gait patterns of PD subjects.

**Conclusions:** Our study helped identifying some typical characteristics of the onset disease, and to unravel the symptoms of ageing from those of PD by comparing young PD subjects to elderly healthy subjects. This allows a deeper understanding of the mechanisms underlying the gait in ageing and PD.

## SC54

**Training program associated with dual tasking in Parkinson disease patients: Effects on executive functions and gait**

*Michele Gennuso*<sup>1</sup>, *V. Codazzi*<sup>1</sup>, *P. Nicardi*<sup>2</sup>, *S. Ghirardi*<sup>1</sup>, *A. Prella*<sup>1</sup>

<sup>1</sup>Department of Neurology “Ospedale Maggiore di Crema”, Crema

<sup>2</sup>Department of Rehabilitation “Fondazione Benefattori Cremaschi”, Crema

Gait impairments and walking limitations are common among people with Parkinson disease (PD). Gait abnormalities are not pronounced in the early stages of PD; their prevalence and severity increases with disease progression. In the early stages of disease, patients have difficulty in walking, especially during situations of dual tasking. In fact gait is no longer considered an automated motor activity that utilizes minimal higher-level cognitive input. The relationship between gait and specific cognitive faculties, in particular executive function (EF) and dual tasking abilities, has been described in healthy adults and in patients with Parkinson's disease. Impairments in executive capacities are frequently observed in Parkinson patients: they have an increased risk of falls, during walking, if they are doing other tasks. We conducted a study on a training program to improve gait in Parkinson patients undergoing dual tasking in order to evaluate both motor and neuropsychological effects. Fifteen patients (Hoehn and Yahr stage < 2) were evaluated before and after two months of DT training. The training program included 20 sessions of 45 minutes each, during which patients had to walk while performing several distinct cognitive tasks. We evaluated the speed of walking, the frequency of steps and the length of the step during usual walking and during two DT conditions. We also assessed the executive functions through a battery of tests before and after the training period.

At the end of treatment patients showed a motor improvement even under dual tasking. Also neuropsychological evaluations showed an improvement in the majority of studied patients. In conclusion our study demonstrates that in Parkinson patients a training program can produce dual tasking motor effects and also a cognitive performance improvement.

## SC55

**How intracerebral recordings contribute to the neurophysiology of Tourette Syndrome**

*Gaia Giannicola*<sup>1</sup>, *M. Rosa*<sup>1</sup>, *D. Servello*<sup>2</sup>, *S. Marceglia*<sup>1</sup>, *M. Porta*<sup>2</sup>, *A. Priori*<sup>1,3</sup>

<sup>1</sup>Centro Clinico per la Neurostimolazione, le Neurotecnologie ed i Disordini del Movimento, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan

<sup>2</sup>Neurochirurgia Funzionale e Centro Tourette, IRCCS Galeazzi, Milan

<sup>3</sup>Università degli Studi di Milano, Milan

**Introduction:** Deep brain stimulation (DBS) for patients with Tourette Syndrome (TS) is effective in reducing tics and comorbid conditions. Despite intense research, TS pathophysiology is still largely based on models and indirect evidence. Neural activity from DBS target structures can provide direct information about neural dysfunction in TS. The three structures preferentially chosen as targets for DBS in TS are the thalamus, the globus pallidus internus (GPI) and the nucleus accumbens (NA). Local field potentials (LFPs) from ventralis oralis/centromedian-parafascicular (Vo/CM-Pf) nucleus of the thalamus showed oscillations at low frequencies (LF, 2–15 Hz) band (Marceglia et al., 2010) and neural

activity recorded from GPI showed irregular neuronal activity correlated with motor tics (Zhuang et al., 2009).

**Objectives:** To investigate TS neurophysiology studying neural activity recorded through electrodes implanted for DBS in brain structures.

**Methods:** We recorded LFPs in three patients with TS: (1) from Vo/CM-Pf during severe vocal tics three days after DBS surgery, (2) from Vo/CM-Pf at rest 12 months after DBS surgery, and (3) from Vo/CM-Pf and NA at rest in a patient with TS and obsessive compulsive syndrome (OCD).

**Results:** (1) Bilateral LFP recordings from Vo/CM-Pf showed an abnormal frequency modulation from the LF band activity to the high beta band (20–35 Hz) activity only in the dominant hemisphere in the time frame corresponding to tic. (2) The Vo/CM-Pf LFPs recorded twelve months after DBS surgery shows activity within the LF band (2–7 Hz). (3) NA LFPs show strong activity within the beta band (8–20 Hz) whereas in Vo/CM-Pf LFPs beta activity is virtually absent.

**Conclusions:** Although the abnormal frequency modulation observed in the Vo/CM-Pf was not time-locked to the tic, but it is lateralized on the same side of language function, it could be causally related to tic. We also found that Vo/CM-Pf LFPs are stationary over time, suggesting that the Vo/CM-Pf LF activity is a specific rhythm of TS in time. The abnormal NA beta LFP activity observed could be associated with OCD and, in turn, can drive the thalamo-cortical activity ultimately resulting in behavioral dysfunctions. Hence, Vo/CM-Pf and NA DBS in patients with TS could induce its beneficial effects by modulating specific pathological neural rhythms in the cortico-basal ganglia-thalamic network.

## SC56

**Clinical and cognitive correlations of regional gray matter atrophy in patients with progressive supranuclear palsy: a VBM-DARTEL study**

*Alfonso Giordano*<sup>1,2</sup>, *A. Tessitore*<sup>1</sup>, *D. Corbo*<sup>1</sup>, *G. Cirillo*<sup>1</sup>, *R. De Micco*<sup>1</sup>, *A. Russo*<sup>1,2</sup>, *S. Liguori*<sup>1</sup>, *M. Cirillo*<sup>3</sup>, *F. Esposito*<sup>4,5</sup>, *G. Tedeschi*<sup>1</sup>

<sup>1</sup>Department of Neurology, Second University of Naples, Naples

<sup>2</sup>IDC Hermitage Capodimonte, Naples

<sup>3</sup>Department of Radiology, Second University of Naples, Naples

<sup>4</sup>Department of Neuroscience, University of Naples Federico II, Naples

<sup>5</sup>Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands

**Background and Purpose:** Progressive supranuclear palsy (PSP) is the most common neurodegenerative bradykinetic-rigid syndrome after Parkinson's disease (PD). Several volumetric studies have revealed a widespread cortical and subcortical gray matter (GM) atrophy, however the correlations between GM pattern loss and clinical-cognitive features have been poorly investigated.

**Materials and Methods:** By using 3-Tesla magnetic resonance imaging and voxel-based morphometry we compared GM volume in 12 patients with probable PSP, 12 patients with PD and 12 healthy controls. All patients underwent a clinical and neuropsychological evaluation aimed at exploring mainly the executive functions (EF).

**Results:** Patients with PSP, compared to patients with PD showed a reduced GM volume in several cortical and sub-cortical areas including left and right cerebellum, left superior frontal gyrus, middle and inferior occipital gyrus, left globus pallidus and right middle temporal gyrus; moreover patients with PSP performed significantly worse than patients with PD on cognitive tests exhibiting lower scores on Mini Mental Status Examination (MMSE), Frontal Assessment Battery (FAB), Phonological Verbal

Fluency (pVF) and Ten Point Clock Test (TPCT). Interestingly, among different significant correlations between motor and cognitive features and GM loss, we detected a significant positive correlation between FAB and pVF scores with cerebellar atrophy and between pVF score and superior frontal gyrus GM loss; interestingly, we did not detect a correlation between frontal cortex GM loss and FAB score.

**Discussion and conclusions:** Our findings confirm, in patients with PSP, the pattern of GM tissue loss and corroborate the presence of frontal cognitive dysfunction. Correlation analyses suggest that cerebellar atrophy may play a role in the pathogenesis of executive impairment in patients with PSP due to a disruption of its modulation on executive functions. Several studies have confirmed that cerebellum is critical not only for movement coordination but also for cognitive processes; the well-known cerebellar cognitive syndrome refers to impairment of EF in patients with cerebellar damage.

## SC57

### **Adapted motor activity of Parkinson's disease based on emotional involvement: analysis of the effects on walking and on the quality of life**

*Gino Granieri, P. Fazio, G. Brugnoli, E. Groppo, C. Nagliati, V. Simioni, E. Cesnik, V. Govoni, I. Casetta, E. Granieri*

Sezione di Clinica Neurologica, Centro di Promozione di Attività Motoria Adattata in Neurologia, Dipartimento di Discipline Medico-Chirurgiche della Comunicazione e del Comportamento, Università di Ferrara, Ferrara

**Objectives:** To verify the long-term impact of an adapted motor activity based on emotional involvement through pleasant exercises with dance or music, on motor performances and health related quality of life in subjects with Parkinson Disease (PD).

**Material and Methods:** We enrolled 53 outpatients with PD. The mean age was 71.44 (9.27). Patients were stable responders or early fluctuators to levodopa, in Hoehn and Yahr stage 2 or 3, and not affected by severe sensory (auditory or visual) deficits, or cognitive deterioration, or disease affecting movement. The examination protocol included a detailed clinical quality of life questionnaire (QoL SF-36), the third part of the Unified Parkinson's Disease Rating Scale (UPDRS III), the tapping test and the measurement of patient's acceleration with a triaxial accelerometer (applied on the chest and pelvis while patients are walking at a comfortable speed). 53 patients were evaluated two times, among these 43 patients have been reassessed for the third time. The adapted motor activity session based on emotional involvement, with enjoyable exercises as music or dance, was held twice a week for months, each time for 60 minutes and was followed by a 4 months rest period. Patients were assessed at baseline, at the end of the treatment and after the stop-from-activity period.

**Results:** Comparing the values after 4 months of adapted motor activity, the evaluation of the acceleration parameters, with a chest accelerometer, showed an improvement from a mean value of 0.72 (SD 0.22) m/sec to a mean value of 0.77 (SD 0.26) m/sec ( $p < 0.05$ ). On the basis of the pelvic accelerometer we found a mean acceleration of 1.40 (SD 0.37) m/sec and of 1.57 (SD 0.45) m/sec before and after treatment ( $p < 0.01$ ). The mean UPDRS score had significantly improved ( $p < 0.001$ ). The QoL SF-36 score improved in all sections ( $p < 0.01$ ), especially in these subscales: social functioning ( $p < 0.01$ ), physical functioning ( $p < 0.01$ ), vitality ( $p < 0.001$ ), general health ( $p < 0.001$ ) role physical ( $p < 0.05$ ), and with lower score in the section regarding the emotional role ( $p < 0.05$ ). The dominant and non-dominant hand tapping test had

significantly improved ( $p < 0.001$ ). After 4 months of rest of treatment, the values of the tests were down again to those at baseline, only the improvement of QoL SF-36 score continued after the resting period. The acceleration parameters, with the chest and pelvic accelerometer, showed a decrease to a mean values of 0.71 (SD 0.24) m/sec ( $p < 0.005$ ) and 1.45 (SD 0.40) m/sec ( $p < 0.01$ ), similar to those at baseline. Also the mean UPDRS score and the tapping tests had decreased ( $p < 0.05$ ) when compared with those of the end of motor activity.

**Conclusions:** These results suggest that an adapted motor activity, based on emotional involvement through pleasant exercises with music or dance, performed for several months could improve the quality of life perception, also after a long discontinuation. Moreover, after the stop-from-activity period, the motor performances of the patients seem to return to the starting conditions, after the improvement obtained before. A periodical, but repetitive, adapted motor activity in PD and other neurodegenerative diseases could be considered an alternative and concomitant approach to support the social and self-perception of physical performances.

Work supported by the Fondazione Cassa di Risparmio di Cento, Town of Cento and Gruppo Estense Parkinson.

## SC58

### **Analysis of non motor symptoms in patients with progressive supranuclear palsy**

*Paola Grassini, M. Torti, L. Vacca, F.G. Radicati, S. Pinnola, M. Casali, F. Stocchi*

IRCCS San Raffaele Pisana, Roma

**Introduction:** Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder that include supranuclear, initially vertical, gaze dysfunction accompanied by extrapyramidal symptoms, swallowing and language abnormalities and cognitive dysfunction.

**Objective:** The aim of this study was the clinical evaluation of 40 patients with probable PSP diagnosis, with particular regards to the analysis of Non Motor Symptom and the clinical subtypes (PSP-Parkinsonism, Richardson's Syndrome, PAGF – Pure Akinesia with Gait Freezing).

**Materials and Method:** The analysis of frequency and typology of Non Motor Symptoms was evaluated through the use of non motor symptoms scale and questionnaire. The neuropsychological evaluation included MOCA and Hamilton scale for depression (HAM-D). Clinical evaluation of patients was based on PSP-scale.

28 patients with probable PSP were enrolled into the study: 20 with confirmed diagnosis and complete neuropsychological evaluation; 4 patients with probable PSP were not able to conclude all the assessment due to the severe cognitive impairment; in 4 patients the diagnosis was converted to cortico-basal degeneration.

**Results and Conclusion:** The study showed: duration of disease between 2.77 and 3.36 years, equal sex distribution, age at onset between 50-65 years, subdivision of the population observed in 2 subtypes (classic PSP and PSP-P) respected the percentage reported in literature; patients with PAGF have not been observed. The analysis of the MOCA showed deficit of delayed memory, language with particular regards to fluency and visuospatial area. According to Hamilton scale scores all patients showed mild depression. The NMS questionnaire in patients with classical PSP showed prevalence of symptoms such as drooling, dysphagia, constipation and sadness. All patients reported falls, unlike the PSP-P group in which falls were reported only by 55% of patients.

## SC59

**Neurophysiological assesment in two unreported Italian families with autosomal dominant cortical tremor, myoclonus, and epilepsy***Rosa Iodice, A. Coppola, M. Esposito, L. Santoro*

Dipartimento di Scienze Neurologiche, Università Federico II, Napoli

On a clinical basis “autosomal dominant cortical tremor, myoclonus and epilepsy” (ADCME) is mainly characterized by distal action tremor and myoclonus. Neurophysiological findings often show a giant somatosensory evoked potential, enhanced C reflex and a postural high frequency irregular tremor. Here we describe the neurophysiological assessment of few members belonging to two Italian unreported families with ADCME.

**Methods:** 3 members of one family (2F, 1 M) and 2 (2 M) of the other one were studied. All patients were under antiepileptic drugs (AED) and were free from epileptic seizures since several years. They all showed hyperkinetic involuntary movements of the upper limbs against gravity and during voluntary movement. Somatosensory evoked potentials (SEP), C-reflex and a video-multichannel EMG recording were performed.

**Results:** A giant SEP and an enhanced C-reflex were both recorded in two patients. The video-EMG multichannel recording showed cortical jerks mainly against gravity and during movements but there was no definite tremor activity in most of the patients. Only for two patients an irregular postural tremor could be recorded. Spectral analysis of the tremor showed a mean frequency around 8 Hz but there was a high dispersion of the signal.

**Discussion:** Our reports are coherent with neurophysiological features early described in ADCME. The video-EMG multichannel recording showed that these patients present very frequent cortical jerks not producing a regular tremor. This finding and the lack of detection of giant SEP and C reflex in every patient could be ascribed to long term treatment with AED.

## SC60

**Electromyographic and radiological analysis of muscles determining lateral trunk flexion (Pisa Syndrome) in patients with Parkinson's disease***Ina Juergenson<sup>1</sup>, A. Fasano<sup>2,3</sup>, G. Vattemi<sup>1</sup>, G. Squintani<sup>1</sup>, A. Di Matteo<sup>1</sup>, S. Montemezzi<sup>4</sup>, D. Cenzi<sup>4</sup>, A. Fiaschi<sup>1</sup>, P. Barone<sup>5</sup>, T. Bovi<sup>1</sup>, M. Tinazzi<sup>1</sup>*<sup>1</sup>Dipartimento di Scienze Neurologiche, Psicologiche, Morfologiche e Motorie, Università di Verona, Verona<sup>2</sup>Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma<sup>3</sup>Istituto Neuromed, Pozzilli (Isernia)<sup>4</sup>Istituto di Radiologia, Azienda Ospedaliera-Universitaria Integrata di Verona, Verona<sup>5</sup>Dipartimento di Neuroscienze, Università di Salerno, Salerno

**Introduction:** Pisa Syndrome (PS) is clinically defined as a sustained lateral bending of the trunk, worsened by a prolonged sitting position or by walking. Abnormal postures of the trunk (including also camptocormia and anterocollis) are a typical feature of extrapyramidal disorders, especially Parkinson's Disease (PD). In PD, PS can be sometimes observed, both after dopaminergic drugs implementation or spontaneously, but the precise pattern of muscles activation leading to the lateral trunk flexion has not been clearly elucidated.

**Objective of the study:** To investigate the pathophysiological mechanisms leading to PS in patients with PD, by combining an

electromyographic (EMG) assessment of both paraspinal and non-paraspinal muscles with radiological findings obtained by Magnetic Resonance Imaging (MRI) of paraspinal muscles.

**Patients and methods:** We examined thirteen (n = 13) PD patients with a lateral trunk flexion diagnosed as PS. A specifically-designed wall goniometer was used to measure the lateral (and anterior, when present) flexion of the trunk. We performed an enlarged EMG study of paraspinal (lumbar and thoracic) muscles, abdominal muscles (m. obliquus externus) and other muscles potentially involved in trunk stabilization in physiologic condition (m. iliopsoas, m. rectus femoralis). All EMG traces were recorded in laying position, during standing and during voluntary flexion of the trunk. Eventually, all patients underwent a high resolution MRI of the thoracic and lumbar tract, by using T1 (with and without gadolinium), T2, STIR and DWI sequences.

**Results:** Two main muscles activation patterns were observed by EMG. The first group of patients (n = 6) showed a hyperactivity of lumbar paraspinal muscles ipsilateral to the leaning side, combined with a hyperactivity of the ipsilateral (subtype 1) or contralateral (subtype 2) thoracic paraspinal muscles. A hyperactivity of non-paraspinal muscles (ileopsoas and/or rectus femoralis) ipsilateral to the leaning side was observed in 4 of 6 patients. Coexisting lumbar hypertrophy of the ipsilateral paraspinal muscles and hypotrophy of the contralateral lumbar paraspinal muscles could be seen on spinal MRI, accompanied by slight signs of inflammation of the paraspinal muscles of both sides.

The second group of patients (n = 7) showed contralateral thoracic and lumbar paraspinal muscles hyperactivity on EMG. The non-paraspinal muscles (m. iliopsoas, m. rectus femoralis and m. obliquus externus) were hyperactivated ipsilaterally to the trunk leaning side in all patients. Spine MRI revealed hypotrophy of the ipsilateral lumbar paraspinal muscles and widespread signs of inflammation on both sides.

**Discussion:** According to our findings, muscles activation pattern underlying PS is likely to be different among PD patients. In some patients, the most important role is probably played by the dystonic hyperactivity of the lumbar (and thoracic in some cases) paraspinal muscles ipsilateral to the flexion side, whereas the non-paraspinal muscles may have an additive role for the trunk flexion.

In other patients, a primary pathogenetic role might be hypothesized for ipsilateral non-paraspinal muscles, with a compensatory activation of paraspinal contralateral muscles. MRI findings are consistent with EMG data, showing hypertrophy of hyperactivated muscles and hypotrophy of under-utilized muscles.

**Conclusion:** PS is a heterogenous condition from a pathophysiological point of view. The muscles involved in trunk flexion are probably more widespread than suspected initially, involving not only paraspinal muscles, but also abdominal end lower limbs muscles. This could be important for a deeper comprehension of the phenomenon and for a more personalized treatment.

**References:**

- [1] Suzuki T, Matsuzaka H. Drug-induced Pisa syndrome (pleurothotonus): epidemiology and management. *NS Drugs* 2002, 16(3):165–174.
- [2] Yokochi F. Lateral flexion in Parkinson's disease and Pisa syndrome. *J Neurol* 2006, 253(Suppl 7):VII17–VII20.
- [3] Djaldetti R, Mosberg-Galili R, Sroka H et al. Camptocormia (bent spine) in patients with Parkinson's disease-characterization and possible pathogenesis of an unusual phenomenon. *Mov Disord* 1999, 14(3):443–447.
- [4] Umaphathi T, Chaudhry V, Cornblath D, et al. Head drop and camptocormia. *J Neurol Neurosurg Psychiatry* 2001, 73:1–7.
- [5] Ashour R, Jankovic J. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Mov Disord*. 2006, 21:423–431.

[6] Di Matteo A, Fasano A, Squintani G, et al. Lateral trunk flexion in Parkinson's disease: EMG features disclose two different underlying pathophysiological mechanism. *J Neurol*. 2011, 258:740–745.

### SC61

#### Improvement of ICDs and sleep disorders in PD patients treated with rotigotine patch switching from other dopamine-agonists

Stefania Lanfranchi<sup>1</sup>, M. Perini<sup>1</sup>, G. Riboldazzi<sup>2,3</sup>, G. Frazzitta<sup>4</sup>, R. Maestri<sup>4</sup>, G. Veneziano<sup>5</sup>, L. Salvato<sup>2</sup>, D. Zarcione<sup>1</sup>

<sup>1</sup> A.O. "S.A. Abate", Gallarate (Varese)

<sup>2</sup> Istituto Clinico "Le Terrazze", Cunardo (Varese)

<sup>3</sup> Centro Parkinson, Varese

<sup>4</sup> IRCCS S. Maugeri, Montescano (Pavia)

<sup>5</sup> Università degli Studi dell'Insubria, Varese

Parkinson's disease (PD) is characterized by motor and non-motor symptoms including nocturnal akinesia, sleep disorders and impulse control disorders (ICD). These disorders may be directly related to the underlying disease pathology but may also be a consequence of medication use and pharmacological management. Rotigotine is a non ergoline dopamine agonist (DA) applied once a day using a transdermal continuous delivery patch. Several studies demonstrated significant treatment benefit of rotigotine on motor and non-motor symptoms. Objective of this study is to evaluate the benefit on ICD and sleep disorders on PD patients switching from other dopamine agonist to rotigotine. We collected data from 59 subjects with PD treated with DA except from rotigotine in stable management for at least 3 months. Motor functions were assessed using Unified Parkinson's Disease Rating scale (UPDRS) part III. Sleep disorders and ICDs were assessed with Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS) and modified Minnesota Impulse Disorders Inventory (mMIDI). DA was shifted after baseline evaluation and titrated to optimal dose without any other pharmacological modification. Each patients was evaluated after 3 month from baseline. UPDRS Part III score had decreased -1 point from baseline ( $P = 0.0073$ ).

Greater improvement was obtained in PDSS score (-2.9 points;  $p < 0.0001$ ), ESS score (-203 points;  $p < 0.0001$ ) and mMIDI score (-3.3 points;  $p < 0.0001$ ). This represent a significant improvement in sleep disorders and ICD with rotigotine compared with other DA resulting in improved quality of life for PD patients.

### SC62

#### Lateral stepping and rear walking on treadmill for the treatment of freezing of gait and postural instability in Parkinson's disease: randomized controlled trial

Manuela Maieron<sup>1</sup>, S. Mezzarobba<sup>2</sup>, R. Ballestriero<sup>1</sup>, E. Cascio<sup>1</sup>, L. Paviotti<sup>3</sup>, D. Marin<sup>1</sup>, L.M. Bragadin<sup>1</sup>

<sup>1</sup> Istituto Medicina Fisica e Riabilitazione ASS 4 Medio Friuli, Udine

<sup>2</sup> Corso di Laurea in Fisioterapia Università degli Studi di Trieste, Trieste

<sup>3</sup> Corso di Laurea in Fisioterapia Università degli Studi di Udine, Udine

**Introduction:** Treadmill training represent currently the best practices in the treatment of gait disorders in Parkinson disease.

**Objective:** The aim of the study was to compare the results obtained through two different types of treatment: treadmill training with variable walking and classic treatment. The purpose is to reduce freezing and postural instability in patients with Parkinson's disease.

**Material and methods:** We recruited 28 patients (mean age 72; H&Y 2.5–3; MMSE  $\geq 24$ ) and evaluated by clinical tests such as Unified Parkinson's Disease Rating Scale (UPDRS), Berg Balance Scale (BBS), Tinetti, Timed Up and Go Test (TUG), Freezing of Gait Questionnaire (FOGQ), 6 Minute Walk Test (6minWT), 10 meters walk test (10mt.WT), Fall Efficacy Scale (FES), and PDQ39. Finally, some posturographic tests were performed. They were then divided randomly into two groups. Group 1 performed exercises of walking (forward, sideways, backwards, and with no hands) on a treadmill with high difficulties. Group 2 has performed classical rehabilitation. The treatment was performed with one-hour session three times a week for a total of 14 sessions. Assessments were made pre and post treatment and follow-up to one month after treatment.

**Results:** After treatment, the comparison between two groups showed significant results in favor of Group 1 in the following indexes: follow up BBS ( $P = 0.000$ ), 10mt WT (post  $P = 0.001$ , follow up  $P = 0.002$ ), TUG (post  $P = 0.031$ , follow up  $P = 0.001$ ), Tinetti follow up ( $P = 0.048$ ), Six min.WT (post  $P = 0.016$ , follow up  $P = 0.004$ ). In intragroup evaluation the results were significant for Group 1 for all indices investigated comparing post vs pre and at follow-up vs pre.

**Conclusions:** Patients treated with use of variable walking on treadmill training improve significantly gait performance and maintain the results in follow up.

### SC63

#### Impaired deception in essential tremor

Francesca Mameli<sup>1</sup>, E. Scelzo<sup>3</sup>, E. Tomasini<sup>3</sup>, M. Fumagalli<sup>3</sup>, F. Cogliamanian<sup>2</sup>, G. Ardolino<sup>2</sup>, R. Ferrucci<sup>1</sup>, L. Bertolasi<sup>4</sup>, A. Priori<sup>1,3</sup>

<sup>1</sup> Centro Clinico per la Neurostimolazione, le Neurotecnologie ed i Disturbi del Movimento, Fondazione IRCCS Cà Granda–Ospedale Maggiore Policlinico, Milano

<sup>2</sup> U.O. Neurofisiopatologia, Fondazione IRCCS Cà Granda - Ospedale Maggiore Policlinico, Milano

<sup>3</sup> Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milano

<sup>4</sup> Azienda Ospedaliera Universitaria Integrata, Verona

**Introduction:** Neuropsychological research conducted in the past decade has challenged the traditional view of movement disorders as a mono-symptomatic condition characterized by movement dysfunction and increasingly showed that deficits in cognitive and behavioral functioning are consistently present in these patients.

**Objective:** In order to deepen our understanding of cognitive dysfunctions in movement disorders, we aimed to examine those functions that regulate the complex activity of lying in patients with Essential Tremor (ET).

**Methods:** In this study we investigated the lie cognitive processes in 15 ET patients compared to 20 patients with Parkinson's disease (PD) and 17 healthy subjects (HS) using the Guilty Knowledge Task (GKT), a simple, fast and computerized task to test the ability to lie.

**Results:** Results showed that in GKT, ET patients have a significant worse performance in deception when compared to HS, but performed remarkably similar to PD group ( $F(2.49) = 3.38$ ,  $p = 0.042$ ), whereas we found no differences between groups in true responses ( $F(2.49) = 0.73$ ,  $p = 0.488$ ). In addition, reaction times in ET patients were significantly longer than PD and HS, both in true ( $F(2.49) = 10.79$ ;  $p = 0.0001$ ) and lie responses ( $F(2.49) = 5.91$ ;  $p = 0.005$ ).

**Conclusion:** Our finding showed that both ET and PD had difficulty giving deceptive responses relative to HS and showed for

the first time that ET patients may have more cognitive difficulties than PD patients consistent with the hypothesis wherein ET patients require additional cognitive effort to achieve the same level of performance of PD patients. Future studies focused on cognitive and behavioral processes in movement disorders should provide valuable new insights about the clinical nature of such conditions to identify possible areas of intervention in cognitive and behavioral disorders.

#### SC64

### **Percutaneous endoscopic gastrostomy for continuous intestinal delivery of levodopa for the treatment of complicated Parkinson's disease: gastroenterologic issues**

*Francesca Mancini*<sup>1</sup>, *P. Campagnoli*<sup>2</sup>, *D. Calandrella*<sup>1</sup>, *L. Manfredi*<sup>1</sup>, *A. Antonini*<sup>3</sup>, *M. Dal Fante*<sup>2</sup>

<sup>1</sup>Parkinson's Disease and Movement Disorders Center, San Pio X Clinic, Milano

<sup>2</sup>Endoscopy Unit, San Pio X Clinic, Milano

<sup>3</sup>Department for Parkinson Disease, IRCCS San Camillo, Venezia

**Introduction:** Continuous intestinal levodopa infusion (CILI) through a percutaneous endoscopic gastrostomy and a jejunal tube (PEG/J) is an useful treatment for complicated Parkinson's disease (PD).

**Methods:** The aim of this retrospective study is to analyze features and outcome of PD patients with PEG/PEJ placed for CILI.

**Results:** Between 2006 and 2012, PEG-J was positioned in 38 PD patients, without acute complications. Patients' mean age was 64.4 years, disease duration 13 years and UPDRS III in ON 17. PEG-J was removed in 9 patients (4 patients underwent different treatments; 1 patient developed dementia, 2 patients developed a polyneuropathy). For the first 3 years, devices were replaced only on demand (tube deterioration or complications) and mean time between PEG-J positioning and the first request of replacement was 885,25 days. Since 2010, PEG-J replacement was programmed every 12 years, even in absence of complications (mean time 382,5 days). Mean time between intestinal tube replacement and previous PEG-J positioning or substitution for complications was 135,6 days, (24 times for migration of the jejunal extension, jejunal tube block due to a knot or a bezoar or accidental removal of the external tube). Four times the intestinal tube was repositioned because of dislocation. One patient needed PEG-J complete replacement for a bumper-buried syndrome. Complications (tube replacement) concerned 15 patients, from 1 to 4 times. Two of these patients presented also a more serious complication: gastric and duodenal pressure ulcers caused by the tension of the PEJ tube, anchored to the proximal ileum because of a bezoar or a knot. No significant differences were found in clinical features between patients with device complications and patients without.

**Conclusions:** PEG-J for CILI doesn't present major adverse events. An accurate monitoring of minor complications onset is needed. Further studies have to better identify patients more likely to develop complications.

#### SC65

### **Neuropsychological assessment significance in the treatment of cognitive disorders in Parkinson's disease: preliminary data and our experience**

*Pietro Marano*, *M. Seminara*, *L. Ravidà*

Unità Operativa di Neuroriabilitazione, Casa di Cura Villa dei Gerani, Catania

**Objective:** Our study was a perspective non-interventional that aims to evaluate the neuropsychological performance of patients with idiopathic Parkinson's disease using an evaluation protocol that we normally apply to these patients to define the stage of disease and follow longitudinally. Were evaluated neuropsychological changes over time as attention, memory, orientation, executive function, motor programming in outpatients with idiopathic Parkinson's disease.

**Design:** Perspective non-interventional study. Setting: Our department of Neurorehabilitation; Neuropsychology room. Participants: 30 patients with idiopathic Parkinson's disease, chosen at the discretion of the investigator, or in a position to accede to the Protocol.

**Interventions:** The tests were administered as follows: V1 start of the study, V2 after 6 months, V3 after one year. We did not make drug changes, because this is not an interventional study.

**Main Outcome Measures:** We used the following tests: Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Short Neuropsychological Assessment (SNA), Montreal Cognitive Assessment (Mo CA).

**Results:** The study is still under way, but we firmly believe that an evaluation must be carried out by using all the tests under consideration, as each of them has its own limits and strong points which give advantage to some specific cognitive areas but damage some others.

**Conclusions:** Our study, to suggest a proposed protocol highlights the need for administration of all tests used, because the four batteries of tests seem to be able to assess, within a reasonable period of time, both domains cognitive specific global cognitive functioning in patients with idiopathic Parkinson's disease. The administration of these tests in a protocol, designed by us, allows to overcome limitations of each battery providing a comprehensive picture of the investigated areas.

#### SC66

### **Impaired primary motor cortex LTP/LTD-like plasticity in multiple system atrophy**

*Luca Marsili*<sup>1</sup>, *A. Suppa*<sup>1,2</sup>, *F. Di Stasio*<sup>1</sup>, *A. Latorre*<sup>1</sup>, *P. Khandker*<sup>1</sup>, *C. Colosimo*<sup>1</sup>, *G. Fabbrini*<sup>1,2</sup>, *A. Berardelli*<sup>1,2</sup>

<sup>1</sup>Department of Neurology and Psychiatry, Sapienza University of Rome, Rome

<sup>2</sup>Neuromed Institute, Sapienza University of Rome, Rome

**Objective:** In humans intermittent and continuous theta-burst stimulation (iTBS and cTBS) are currently used for inducing long-term changes in motor evoked potential (MEP) amplitudes reflecting long-term potentiation (LTP)- and depression (LTD)-like plasticity in primary motor cortex (M1). In this study we investigated possible abnormalities of LTP/LTD-like plasticity in M1 in patients with Multiple System Atrophy (MSA). Recent studies have reported that LTP/LTD-like plasticity as tested by TBS is reduced in Parkinson's Disease (PD) (Suppa et al., 2011) and increased in patients with Progressive Supranuclear Palsy (PSP) (Conte et al., 2011). There are no previous studies testing M1 plasticity with TBS in patients with MSA.

**Materials and Methods:** We studied 10 patients with MSA, six with the Parkinson-variant (MSA-P) and four with the Cerebellar-variant (MSA-C) and 10 age-matched healthy subjects. We clinically evaluated patients using the Unified Multiple System Atrophy Rating Scale (UMSARS). To exclude cognitive impairment patients were also evaluated with the Frontal assessment Battery (FAB). The left M1 was conditioned in separate sessions with iTBS (20 trains of 2 sec repeated every 10 sec, in bursts of 3 pulses at 50 Hz, repeated at 5 Hz, 600 pulses in total) and cTBS (bursts given in a continuous train lasting 40 sec) at intensity of 80% of active motor threshold. Twenty

MEPs were recorded from right first interosseous muscle before, 5, 15 and 30 minutes after iTBS and cTBS at the intensity able to evoke at baseline MEPs of about 1 mV amplitude.

**Results:** Repeated measures analysis of variance (ANOVA) showed that in healthy subjects after iTBS, MEPs increased whereas after cTBS, they decreased in amplitude significantly at 5, 15 and 30 minutes (P Discussion: M1 LTP/LTD-like plasticity is impaired in patients with MSA).

**Conclusions:** Mechanisms underlying abnormal M1 plasticity in MSA are similar to those present in PD rather than in PSP.

## SC67

### Orthostatic tremor in a patient with Graves disease

*Sonia Mazzucchi, D. Frosini, M. Giuntini, C. Del Gamba, U. Bonuccelli, R. Ceravolo*

Dipartimento di Neuroscienze, Università di Pisa, Pisa

**Introduction:** Orthostatic Tremor (OT) is a rare disorder characterized by high frequency tremor affecting lower limbs and unsteadiness on standing with remission during sitting or lying.

A 70-year-old woman presented with a sense of unsteadiness and tremor in her legs mainly during standing and walking, which gradually worsened over a year without any benefit after administration of clonazepam.

Neurological exam showed tetrahyperreflexia, gait impairment with paraparetic features and inability to perform tandem gait. Her cognition and mental state was normal. She also reported intolerance of heat, excessive sweating and recent loss of weight with increased appetite, dysphagia and dysphonia.

**Methods:** Motor evoked potentials did not demonstrate impairment of the cortico-spinal tract. Brain and cervicodorsal MRI were normal. Electromyographic recordings from vastus medialis and tibialis anterioris, performed during standing, showed a rhythmic contractile activity at about 8 Hz. After prolonged supine rest a rhythmic contractile activity at lower amplitude re-appeared in both lower legs. Due to atypical phenotype and EMG activity and low frequency of tremor, a symptomatic origin was hypothesized.

Her thyroid function exams revealed severe hyperthyroidism (thyroid stimulating hormone (TSH) < 0.004  $\mu$ U/ml [0.400–4.000  $\mu$ U/ml], fT3 9.25 pg/ml [1.80–4.80 pg/ml], fT4 5.05 ng/dl [0.80–1.80 ng/dl]), increased values of thyroglobulin antibodies (451 UI/ml, [1020 <10 UI/ml]) and positivity of TSH receptor antibodies (19.10 UI/L). A chest and neck CT scan revealed an increase in thyroid size involving the upper mediastinum and affecting the left side of the esophagus.

**Result:** A diagnosis of Graves disease was performed and she was started on Carbimazole with dramatic improvement of tremor.

**Conclusion:** Graves syndrome has been recently described as a possible cause of OT, and should be taken into account mainly when OT presents with atypical phenotype.

## SC68

### A case of acute onset postural deformity in Parkinson's disease: Pisa Syndrome or post-traumatic lateral trunk flexion?

*Mario Meloni<sup>1</sup>, K.S. Paulus<sup>1</sup>, E.R. De Natale<sup>2</sup>, V. Agnetti<sup>1</sup>*

<sup>1</sup>Institute of Clinical Neurology, University of Sassari, Sassari

<sup>2</sup>Dept. of Biomedical Sciences, University of Sassari, Sassari

Pisa Syndrome (PS) and scoliosis are reported in Parkinson's Disease (PD): some authors define PS as a subacute-chronic marked lateral flexion of the trunk (LTF), generally contralateral to the affected side, which can be corrected by passive mobilization or

supine positioning, whereby scoliosis is defined as a pathologic posture due to a lateral curve of the spine, usually combined with a rotation of the vertebrae not relieved by passive movement; yet, this separation is not straight. In PS, two EMG patterns may be identified: hyperactivation of paravertebral muscles ipsilateral to the bending side, both at rest and during contraction and a different one, in which activation is seen contralaterally to the bending site. No denervation patterns have been reported.

We describe the case of a 72 year-old man with a 6-year history of PD ensued with right rigidity, tremor and bradykinesia with postural instability and longstanding good response to L-DOPA and Pramipexole. He developed acutely (1 week) a 30° LTF ipsilateral to the disease side, unresponsive to passive mobilization, supine positioning or therapy changes. Few days before onset, he reported repeated minor right flank traumas. Dorsal and lumbar paraspinal muscles looked hypertrophic on the left side, but hardly palpable on the right. Standing EMG showed hyperactivity on the left paravertebral muscles (opposite to the leaning side) at rest, enhanced after activation and neurogenic denervation on the right. Dorso-lumbar CT disclosed left-convex rotoscoliosis, left muscle hypertrophy and right muscular atrophy with fatty degeneration. This case features characteristics referable to both PS and scoliosis but also atypical signs: very rapid onset, previous traumas and ipsilateral neurogenic denervation at EMG. We speculate that an insult to the flank may have triggered the picture in an affected context and the electrophysiological data seen on EMG would be explained by a compensative muscular response.

## SC69

### Levodopa/Carbidopa intestinal gel and subthalamic nucleus deep brain stimulation: a 3 years comparison follow-up study

*Aristide Merola, M. Zibetti, C.A. Artusi, S. Angrisano, L. Rizzi, M. Lanotte, M.G. Rizzone, L. Lopiano*

Department of Neuroscience, University of Torino, Torino

**Background:** In a previous study we compared the effectiveness of Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) and Levodopa/Carbidopa intestinal gel (LCIG) after 15 months of treatment, observing an equal efficacy between the two procedures in two cohorts of parkinsonian patients with similar clinical features at baseline, apart from cognitive functions. Here, we report the clinical data of the same cohorts of patients after 3 years of follow-up.

**Methods:** Two groups of 20 patients each, treated either with STN-DBS or LCIG and matched for age, follow-up duration and motor complications duration were evaluated by means of a complete Unified Parkinson's Disease Rating Scale and a battery of neuropsychological tests.

**Results:** Clinical data were available for 17/20 patients of both groups (3 patients treated with LCIG died and 3 STN-DBS patients were lost at follow-up), showing a sustained clinical efficacy on motor complications, with a similar reduction of the "OFF" periods, but a greater efficacy of STN-DBS on dyskinesia duration. The autonomy in Activities of Daily Living decreased over the years in LCIG patients, as the baseline differences in cognitive profile became more evident. An higher number of procedure-related complications was observed with LCIG, mostly related to recurrent technical issues.

**Conclusions:** The two therapeutic procedures showed a similar sustained efficacy on motor fluctuations, but a lower effectiveness of LCIG on dyskinesia duration. However, the retrospective non-randomized clinical study design and the baseline cognitive differences in cognitive functions between groups should be considered in the interpretation of our findings.

## SC70

**Neurocognitive rehabilitation with motor imagery vs treadmill training for freezing of gait in Parkinson's disease: a pilot study**

*Susanna Mezzarobba*<sup>1</sup>, *L. Pellegrini*<sup>1</sup>, *A. Gorian*<sup>2</sup>, *G. Sgubin*<sup>1</sup>, *P. Busan*<sup>3</sup>, *L. Antonutti*<sup>2</sup>, *G. Pizzolato*<sup>2</sup>, *M. Catalan*<sup>2</sup>

<sup>1</sup>Corso di Laurea in Fisioterapia, Università degli Studi di Trieste, Trieste

<sup>2</sup>Clinica Neurologica, Dipartimento Clinico di Scienze Mediche, Chirurgiche e della Salute, Ospedale di Cattinara, Università degli Studi di Trieste, Trieste

<sup>3</sup>Centro per le Neuroscienze BRAIN, Dipartimento di Scienze della Vita, Università degli Studi di Trieste, Trieste

**Introduction:** Freezing of gait (FoG) is a highly disabling symptom of Parkinson's disease (PD) characterized by brief, episodic absence or marked reduction of forward progression of the feet during walking. FoG pathogenesis is not completely understood and pharmacological treatments generally have a poor outcome. For this reason many rehabilitation treatments have been proposed with contrasting results. Actually cueing and treadmill training are considered the best practice. Since motor imagery (MI) has been successfully used in stroke rehabilitation to enhance the beneficial effects of motor training, it could be useful to test it as a potential tool in PD rehabilitation.

**Objective:** Aim of our study was to test the efficacy of a rehabilitation program based on MI in improving FoG in PD patients.

**Materials and methods:** 14 PD patients with FoG (median age 72 ± 4, disease duration years 10 ± 4, H&Y 1,7 range 1-3) with no evidence of dementia (MMSE > 24) or depression (BDI < 16), were enrolled and randomly assigned to different treatment groups. Selected patients performed 20 sessions of a rehabilitation program, Group 1 based on MI while group 2 underwent treadmill training. Disease stage (H&Y and UPDRS III), FoG (FOGQ), quality of life (PDQ-39), locomotion (Timed up and go-TUG, six minute walk test-6MWT), balance (Berg balance test-BBT) and disability (Modified Parkinson's Activity scale-MPAS) were assessed at baseline and after treatment; furthermore patients underwent a brief neuropsychological test to assess frontal and execution functions.

**Results:** At baseline the two groups did not differ for clinical variables, neuropsychological scores or rehabilitation scales. After treatment a significant reduction in FoGQ ( $p = 0,01$ ) and an improvement in others rehabilitation scales (MPAS = 0,01 BBT  $p = 0,02$  TUG = 0,04), were detected in group 1 while no significant changes were shown in group 2.

**Conclusions:** The rehabilitation program with MI could represent an interesting rehabilitation strategy to treat FOG in PD patients.

## SC71

**Sleep alterations in dementia with Lewy bodies: sleep patterns and clinical correlates, a descriptive video-PSG study**

*Brigida Minafra*<sup>1,2</sup>, *M. Terzaghi*<sup>2,3</sup>, *I. Bertaina*<sup>1,2</sup>, *N.G. Pozzi*<sup>1,2</sup>, *D. Arnaldi*<sup>4</sup>, *R. Zangaglia*<sup>1,2</sup>, *R. Manni*<sup>3</sup>, *C. Pacchetti*<sup>1,2</sup>

<sup>1</sup>Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>2</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>3</sup>Sleep Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>4</sup>Department of Neurosciences, Ophthalmology and Genetics, Clinical Neurophysiology Unit, University of Genoa, Genoa

Sleep disorders are very common in dementia with Lewy bodies (DLB). However, knowledge of sleep architecture and disorders of nocturnal sleep in DLB is limited by the absence of systematic video-polysomnographic investigations. We describe the video-polysomnographic findings in twenty-three subjects diagnosed with probable DLB submitted to face-to-face clinical interview and overnight in-hospital video-polysomnography. A Spearman's Rank correlation was run to test the relationship between clinical and cognitive features and sleep-related measures. All the patients reported at least one sleep disturbance, which was the presenting symptom in eight subjects (34.7%). Video-polysomnography documented, within a pattern of reduced sleep continuity and REM sleep, sleep apnea in 35%, periodic limb movements in 80% and disruptive motor behavioural manifestations in 75.0% of the subjects.

Motor behavioural events consisted of REM Sleep Behaviour Disorder (RBD) in 53%, episodes mimicking RBD but related to arousal from NREM or REM sleep in 13% and confusional events in 34% of the cases, isolated or in the framework of parasomnia overlap disorder. No consistent correlations were found between analysed clinical, cognitive and sleep-related variables. Clinicians should be aware of the complexity of sleep alterations in DLB, which encompass an overlap of impaired sleep structure, sleep comorbidities and various motor-behavioural abnormal events, and bear in mind the possibility of misleading symptoms and that of overlooking sleep comorbidities; they should consider the possibility of polysomnographic sleep investigations in order to obtain a correct diagnosis and optimize treatment of disrupted sleep.

## SC72

**Prevalence of tremor in patients with adult celiac disease**

*Flavio Giordano*<sup>4</sup>, *M. Moccia*<sup>1</sup>, *R. Tortora*<sup>2</sup>, *G. Santangelo*<sup>3</sup>, *A. Rispo*<sup>2</sup>, *I. Improta*<sup>3</sup>, *T. Russo*<sup>2</sup>, *G. De Stefano*<sup>2</sup>, *P. Barone*<sup>4</sup>, *C. Vitale*<sup>5</sup>

<sup>1</sup>Dipartimento di Scienze Neurologiche, Università di Napoli "Federico II", Napoli

<sup>2</sup>Dipartimento di Gastroenterologia, Università di Napoli "Federico II", Napoli

<sup>3</sup>Dipartimento di Psicologia, Seconda Università di Napoli, Napoli

<sup>4</sup>IDC Hermitage Capodimonte – Scuola Medica Salernitana, Università di Salerno, Salerno

<sup>5</sup>IDC Hermitage Capodimonte – Università di Napoli "Parthenope", Napoli

**Introduction:** Coeliac disease (CD) is a chronic immune-mediated disorder that primarily affects the gastrointestinal tract. Anyway there is an increasing number of reports describing neurological complications of coeliac disease, especially ataxia, peripheral neuropathy, restless legs syndrome and epilepsy.

**Objective:** The aim of the present study was investigating prevalence and characteristics of tremor in CD.

**Methods:** CD patients attending Referral Regional Center for CD were consecutively evaluated at Movement Disorder Unit of University "Federico II" of Naples from January to May 2012. CD diagnosis was based on duodenal biopsy and on the presence of specific antibodies in serum (tTG, EMA, AGA). Exclusion criteria were uncertain CD diagnosis, history of neuroleptic exposure, other neurological or medical conditions known to be causative of tremor, alcohol or drug abuse. All patients underwent a complete neurological examination. In particular we investigated prevalence and clinical features of tremor.

**Results:** 50 patients (M:11, F:39) were included in the study. The average age was 34,4 year. Gluten free diet was followed by 28 of them, while 22 with a recent diagnosis of CD were on free diet. Postural tremor was found in 13 patients (26%; M:1; F:11) with an average age of 29,1 years. Three of them were found as having both postural and kinetic tremor (6%; M:1; F:2). No one was found as having symptoms or signs of neuropathy, or additional elements of cerebellar impairment. No relation was found between presence of tremor and gluten free diet adherence.

**Conclusions:** This is the first study investigating prevalence and clinical features of tremor in celiac disease. The mechanisms leading to neurological disorders in CD are not yet understood. Two different mechanisms have been proposed: a) a malabsorption-related deficiency of neurotrophic and/or neuroprotective factors; b) an autoimmune dysregulation. Our preliminary results broaden the spectrum of neurological disorders associated with CD and indicate that tremor should be sought in all patients with CD. Anyway further studies are needed to increase our knowledge on 'celiac tremor' and, in particular, to find out possible mechanisms.

### SC73

#### Serpentine tongue

Marcello Moccia

Dipartimento di Scienze Neurologiche, Università di Napoli "Federico II", Napoli

"Serpentine tongue" has been recently described in a patient with Multiple System Atrophy and in a patient with Parkinson's disease after initiation of levodopa therapy. We describe the case of a 37 year old woman with progressive gastrointestinal disorders associated to weight loss and decrease in daily life activities. After 4 months from symptom onset a movement disorder was described as strictly restricted to the tongue. Movements were sinuous, regular, stereotyped, relatively slow and primarily present when the tongue was kept on the floor of the mouth.

An evaluation of the patient in relation to the wide range of tongue movement disorders was made. The discussion highlights different clinical and instrumental approaches to the case.

### SC74

#### Experience with transdermal rotigotine in patients affected by atypical parkinsonian disorders

Davide Vito Moretti

IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia

**Background:** Rotigotine (RTG) is a non-ergot dopamine agonist (D3 > D2 > D1) developed as a new transdermal formulation, and it is indicated for use in early and advanced Parkinson's disease (PD). The potential advantages of the RTG patch include immediacy of effect onset as intestinal absorption is unneeded, constant drug delivery, better tolerability avoiding drug peaks and easy of use, helping patient's compliance. Based on this, RTG patch appears to be a suitable candidate in the treatment of elderly patients. Moreover, data about RTG use in atypical parkinsonian disorders are scant.

**Aim of the study:** Observational study to evaluate the efficacy and tolerability of RTG in elderly patients affected by atypical parkinsonian disorders.

**Methods:** We evaluated all subjects with diagnosis of atypical parkinsonian disorders admitted to our institute and treated with transdermal RTG. Patients were evaluated by UPDRS (part III), NPI and all adverse events (AEs) were recorded.

**Results:** 36 patients (mean age = 68,9 years; min = 52, max = 82) were evaluated. 30/36 (83%) presented cognitive impairment (mean MMSE = 18,9; min = 4, max = 30). Diagnosis was: parkinsonism in dementia (6), MSA-P (6), MSA-C (1), PSP (4), CBD (6), vascular parkinsonism (3), LBD (6) and FTD with parkinsonism (2), Farh's disease (1), iatrogenic Parkinson (1). At baseline, mean UPDRS-III score was 34,2/56 (min = 21/56; max = 49/56) and mean NPI score was 52,4/144 (min 0/144; max 98/144). 31/36 (86%) patients completed 6 months of treatment with RTG (mean dose = 3,4 mg/24 h; min = 2; max = 16), mean UPDRS-III score was 26,2/56 (min = 12/56; max = 43/56) and mean NPI score 46,2/144 (min = 18/144; max = 45/144). 21/31 (67,7%) patients completed 12 months of treatment with RTG (mean dose = 4,2 mg/24 h; min = 2 mg/24 h; max = 16 mg/24 h) mean UPDRS-III score was 26,9/56 (min = 15/56; max = 40/56) and mean NPI score was 43,3/144 (min = 18/144; max 45/144). Reported AEs were: hypotension (11 patients), nausea (7 patients), dystonia (3 patients, all treated with concomitant L-dopa). 5 patients suspended RTG treatment due to AE (vomiting, tachycardia and sleepiness).

**Conclusions:** In our population transdermal RTG seems to be effective and well tolerated. Due to its system of drug delivery, RTG appears to be a suitable therapy in elderly patients as it has a good tolerability profile, improves patient's compliance and helps management of fragile patients.

### SC75

#### Transient parkinsonism in a patient with non convulsive status epilepticus due to nonalcoholic steatohepatitis cirrhosis: a case report

Vincenzo Moschella<sup>1</sup>, C. Gerace<sup>2</sup>, V. Cozzolino<sup>3</sup>, F.M. Corsi<sup>2</sup>, G. Cerasari<sup>4</sup>

<sup>1</sup>UOC di Neurologia, Ospedale S. Camillo de Lellis, AUSL Rieti, Rieti

<sup>2</sup>UOC di Neurologia, Azienda Ospedaliera San Camillo-Forlanini, Roma

<sup>3</sup>UOC di Neuroradiologia Diagnostica ed Interventistica, Azienda Ospedaliera San Camillo-Forlanini, Roma

<sup>4</sup>UOC di Epatologia, Azienda Ospedaliera San Camillo-Forlanini, Roma

**Background:** Acquired hepatocerebral degeneration (AHD) is a chronic and progressive neurological syndrome, characterized by movement disorders, especially parkinsonism and ataxia, secondary to portosystemic shunt from numerous different genesis, usually liver dysfunction. Non-alcoholic steatohepatitis (NASH) is rarely reported to cause AHD.

**Aims:** To describe a case of transitory parkinsonism in a patient with non convulsive status epilepticus and NASH-cirrhosis.

**Methods and Results:** A 60 years old woman presented with acute confusional state without focal neurological deficits. Electroencephalogram revealed a non convulsive status epilepticus. Patient was subsequently treated with several antiepileptic drugs (AEDs; phenytoin, valproate, phenobarbital, carbamazepine, clonazepam) because of difficulty in discontinuing the state. Brain MRI showed bilateral pallidal hyperintensity in T1-weighted sequences. Serum ammonium level was very high, a liver biopsy revealed NASH with cirrhosis and abdominal CT scan revealed porto-caval shunt and hepatosplenomegaly. Hepatotoxic AEDs were replaced with levetiracetam and therapy for cirrhosis were started. General condition significantly improved but patient developed hypomimia, hypophonia, generalized symmetric bradykinesia and mild asymmetric resting tremor. These extrapyramidal symptoms were levodopa-unresponsive, lasted for several weeks and ended gradually.

**Conclusions:** Deep relationship between brain and liver has been known for a long time: in 1912 Wilson and in 1914 van Woerkom described two forms, respectively hereditary and acquired, of hepatic and cerebral pathology, and in 1965 AHD was definitively

illustrated by Victor, Adams and Cole. Portosystemic shunt seems to be the root of AHD, related to hepatic or non-hepatic diseases. NASH is rarely reported to bring it on. Moreover, usually AHD arises subacutely and carries on insidiously. In our case, AHD arose abruptly in course of hepatic encephalopathy in a patient with a misunderstood liver disease. This case should excite clinicians to consider liver dysfunction in case of atypical parkinsonism and/or encephalopathy of unknown origin, also in patient without history of liver disease.

## SC76

### Usefulness of waking day clinical-instrumental monitoring of motor fluctuations in Parkinson's disease

*Giovanni Mostile, G. Sciacca, A. Nicoletti, V. Dibilio, A. Luca, E. Bruno, L. Raciti, D. Contrafatto, M. Zappia*

Dipartimento GF Ingrassia, Sezione di Neuroscienze, Università degli Studi di Catania, Catania

**Background:** Patients with advanced Parkinson's disease (PD) may experiment motor and non-motor fluctuations during the waking day which may affect subjective perception of their motor conditions. A diurnal monitoring of their motor status performed in a clinical setting has been proposed to correctly identify L-dopa induced motor fluctuations.

**Objective:** To evaluate agreement between historical information and objective evaluations of motor fluctuations in PD patients by a diurnal clinical-instrumental motor status monitoring.

**Methods:** Patients admitted to our clinic were evaluated every 2-hours for 12 hours from 8:00 AM using the motor examination section of the UPDRS (UPDRS-ME) and the Abnormal Involuntary Movement Scale (AIMS) as clinical tools coupled with the Movement Time (MT) as objective index of bradykinesia. Historical information about patients motor condition and treatment were collected before the evaluation.

**Results:** Ninety one patients were evaluated (age:  $69.6 \pm 10.2$ ; 39 women). Average UPDRS-ME at the baseline before taking the daily dopaminergic treatment was  $40.7 \pm 13.8$ . Forty two patients (46.1%) referred a predictable motor deterioration of their motor status during the day while 43 (47.2%) patients referred L-dopa induced dyskinesia during the waking day. Wearing-off, clinically defined as a gradual emergence of parkinsonian disability between therapeutic doses, was observed in 71 (78%) patients. Waking day L-dopa induced dyskinesia were clinically detected in 48 (52.7%) patients, with an average AIMS score of  $7.5 \pm 4.8$ . Agreement between historical and clinically-assessed wearing-off was 63.7% ( $k = 0.3$ ; S.E. = 0.08;  $p = 0.0001$ ), while for the L-dopa induced dyskinesia agreement was 90.1% ( $k = 0.8$ ; S.E. = 0.1;  $p < 0.0001$ ).

**Conclusions:** While L-dopa induced dyskinesia may be accurately described by advanced PD patients during their interview, wearing-off phenomena may require a daily clinical monitoring of PD patients motor conditions to be identified and treated.

## SC77

### A study of incidence of Restless Legs Syndrome (RLS) in the course of DAergic therapy in de novo Parkinson's disease (PD) patients

*Anna Negrotti<sup>1</sup>, M. Angelini<sup>1</sup>, E. Marchesi<sup>1</sup>, M. Goldoni<sup>2</sup>, S. Calzetti<sup>1</sup>*

<sup>1</sup>Dip. Neuroscienze, UO Neurologia, Azienda Ospedaliero-Universitaria di Parma, Parma

<sup>2</sup>Dip. Clinica Medica, Nefrologia e Scienze della Prevenzione, Laboratorio di Tossicologia Industriale, Università di Parma, Parma

**Background:** The cross-sectional studies reporting an increased prevalence of RLS in patients with PD have shown that the sensory-motor disorder had emerged in the great majority of them following the onset of the neurodegenerative disease [1,3] and so very likely after the starting of DAergic therapy. However, prospective follow-up studies aimed at the assessment of the occurrence of RLS in the course of DAergic therapy in de novo PD patients are as yet lacking. We report the incidence rate of RLS in the course of PD as from the starting of DAergic therapy in de novo patients.

**Patients and methods:** 106 newly diagnosed according to UKPDS brain bank criteria and previously unmedicated outpatients with PD (67 male and 39 female) were enrolled in the study. None of them had suffered from RLS in their life-time, as ascertained according to IRLSSG criteria. RLS assessment was carried out every six months and the ongoing antiparkinsonian drug regimen was recorded. Incident cases were defined those reporting at least one episode of RLS in the six months preceding assessment.

**Results:** An incidence rate of overall RLS by 4.7 per 100 per year and by 3.7 per 100 per year after the exclusion of "secondary" cases of RLS was found, raised to 6.1 per 100 per year in the age bracket from 55 to 64 years. 83.3% of incident cases occurred within 24 months from the starting of DAergic therapy.

**Conclusions:** An increased incidence rate of overall RLS as compared to those reported in two recent population-based studies [4] was found and it further increased in the age bracket from 55 to 64 years after the exclusion of "secondary" cases of RLS, supporting the view of a co-morbid association between PD and RLS in patients on chronic DAergic therapy. We hypothesize that the increased occurrence of RLS in the course of PD could result from the interaction between a predisposing condition, i.e. PD, and the effect of chronic DAergic therapy in patients in which the neurodegenerative process has involved the DAergic hypothalamic A11 area, site of origin of the diencephalo-spinal pathway.

## References:

- [1] Ondo WG et al. Arch Neurol 2002; 59: 421-4.
- [2] Krishnan PR et al. Mov Disord 2003; 18: 181-5.
- [3] Nomura T et al. Mov Disord 2006; 21:380-4.
- [4] Szentkiralyi A et al. Sleep Med 2011; 815-20.

## SC78

### Progressive external ophthalmoplegia, sensory ataxia and parkinsonism in a patient with POLG gene mutation

*M. Bandettini di Poggio<sup>1,2</sup>, Claudia Nesti<sup>3</sup>, R. Zuccarino<sup>2</sup>, N. Cellotto<sup>2</sup>, R. Truffelli<sup>2</sup>, A. Schenone<sup>1</sup>, F.M. Santorelli<sup>3</sup>*

<sup>1</sup>University of Genova and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Department of Neuroscience, Ophthalmology and Genetics, Genova

<sup>2</sup>Fondazione Serena ONLUS, "La Colletta" Hospital, Service of Rehabilitation of Neuromuscular Diseases, Arenzano (GE)

<sup>3</sup>IRCCS Fondazione Stella Maris, Molecular Medicine, Neurodegenerative and Neuromuscular Disorders Unit, Calambrone (PI)

**Introduction:** Disorders of oxidative phosphorylation affects 1/5000 individuals and present heterogeneous involvement of tissues (such as brain, muscle and peripheral nerves) highly dependent upon ATP production.

**Objective:** To characterize the molecular defect of a patient with progressive external ophthalmoplegia (PEO), peripheral neuropathy, sensory ataxia, and parkinsonism.

**Methods:** After obtaining written informed consent, genomic DNA was extracted from peripheral blood. The whole sequence of

the mitochondrial genome and analysis of POLG, the gene encoding mitochondrial DNA polymerase gamma, were performed using standard Sanger methodologies.

**Results:** We present a 48-year-old Italian woman born to non-consanguineous parents, with a negative family history, who was received a diagnosis of bilateral PEO at the age of 26 years. At age 38 years she developed proximal and distal symmetrical limb weakness and sensory ataxia. Electromyography showed myogenic features and limb skeletal muscular biopsy was consistent with mitochondrial myopathy. Brain MRI was normal. A diagnosis of demyelinating sensory-motor neuropathy was made on the basis of nerve conduction studies and sural nerve biopsy. Symptoms of depression and anxiety-mood disorders were evident and treatment with SSRI was started with benefit. At age 48 years the patient was examined because of recent onset of resting and attitudinal hand tremor, and Parkinsonism. A homozygous missense mutation (p.Ala889Thr) in exon 17 of POLG was detected.

**Conclusion:** Mutations in POLG should be looked for in cases of parkinsonism, especially when multisystem neurological involvement is found.

## SC79

### Expanding the clinical presentation of DYT5 mutations: is multiple system atrophy a possible one?

*Valentina Nicoletti*<sup>1</sup>, *L. Kiferle*<sup>1</sup>, *C. Reale*<sup>2</sup>, *L. Petrozzi*<sup>1</sup>, *B. Garavaglia*<sup>2</sup>, *U. Bonuccelli*<sup>1</sup>, *R. Ceravolo*<sup>1</sup>

<sup>1</sup>Dipartimento di Neuroscienze - Università di Pisa, Pisa

<sup>2</sup>U.O. Neurogenetica, Istituto Carlo Besta, Milano, Italy

**Introduction:** Dopa responsive dystonia (DRD) is a clinically defined movement disorder characterized by childhood dystonia. It generally involves a lower limb with a typical diurnal fluctuation, improving with sleep and worsening during the day. DRD is caused by an autosomal dominant mutation in the GTP-cyclohydrolase 1 (GCH1) located on chromosome 14q22.1–q22.2. It causes a deficiency of tyrosine hydroxylase at the terminal of the nigrostriatal dopamine neurons. More than 100 mutations are known.

**Objective:** To evaluate clinical spectrum of DYT5 in a kindred with different clinical phenotypes.

**Methods:** A 70-years old woman presented at our clinic with a progressive ataxia associated to urinary incontinence and orthostatic hypotension. At neurological examination the patient presented ataxic gait and parkinsonian signs such rigidity at upper limbs, mild resting tremor and bradykinesia. Her nephew was diagnosed as having DRD and her brother had Parkinson's Disease diagnosed 10 years earlier, since then on L-dopa therapy with a good response and without complications. The FP-CIT SPECT of the latter showed nigrostriatal degeneration. The woman was subjected to a FP-CIT SPECT, positive, and to a heart MIBG SPECT, negative for noradrenergic degeneration. L-dopa did not improve her symptoms. A diagnosis of Multiple System Atrophy (MSA) was made. All the subjects underwent molecular testing of the GCH1 gene.

**Results:** While GCH1 sequence analysis was normal, Multiplex Ligation-dependent Probe Amplification (MLPA) analysis, a PCR-based method for detecting exon deletions or duplications, revealed a heterozygous deletion of exons 5 and 6 in the nephew (DRD) and in the brother (PD) of our patient. Therefore the same analysis was performed on the woman, which resulted positive for the same mutation.

**Discussion:** Parkinson's disease but also focal dystonia or recurrent tendonitis were previously described associated to GCH1 gene mutations. This is the first case report of MSA phenotype associated to GCH1 mutation, expanding the clinical spectrum.

## SC80

### Autosomal recessive cerebellar ataxia and low mitochondrial complex III in a Portuguese family

*Célia Nogueira*<sup>1,2</sup>, *C. Nesti*<sup>2</sup>, *M.C. Meschini*<sup>2</sup>, *R. Carrozzo*<sup>3</sup>, *J. Barros*<sup>4</sup>, *M.J. Sá*<sup>5</sup>, *L. Azevedo*<sup>6</sup>, *L. Vilarinho*<sup>1</sup>, *F. M. Santorelli*<sup>2</sup>

<sup>1</sup>National Institute of Health, Genetics Department, INSA, Oporto, Portugal

<sup>2</sup>Molecular Medicine & Neurogenetics, IRCCS Stella Maris, Pisa

<sup>3</sup>IRCCS Bambino di Gesù, Rome

<sup>4</sup>Oporto Hospital Center, Neurology Unit, Hospital S. António, Oporto, Portugal

<sup>5</sup>Hospital S. João, Neurology Unit, Hospital S. João, Oporto, Portugal

<sup>6</sup>IPATIMUP, Population Genetics, Oporto University, Oporto, Portugal

**Introduction:** Defects of mitochondrial complex III (CIII) are a relatively rare cause of mitochondrial dysfunction. The complex catalyzes the electron transfer from reduced coenzyme Q to cytochrome c and is composed of 11 subunits, one of which (MT-CYB) is mtDNA encoded. Mutations in MT-CYB and in assembly factor BCS1L account for the vast majority of cases with low CIII, and are associated with a wide range of neurological disorders. The gene coding for human tetratricopeptide 19 (TTC19) produces a poorly characterized protein thought to be involved in the correct assembly of CIII. Recently, mutations in *TTC19* have been described in three unrelated Italian kindred in association with a severe neurodegenerative disease.

**Objectives:** We studied a consanguineous Portuguese family where a severe neurometabolic disorder occurred in four siblings (three men and one woman) in association with a slowly progressive disorder characterized by dystonia of hands and feet, ataxic gait, severe olivo-ponto-cerebellar atrophy documented at brain MRI, and relentless psychiatric manifestations. Variability in age at onset and disease course was observed.

**Methods:** The enzymatic activity of CIII was determined in muscle using a reported spectrophotometric method. Sequence analysis of genomic DNA was performed to identify disease-causing mutations in *TTC19*. Immunodetection analysis in muscle homogenate and skin fibroblasts allowed the detection of the amount TTC19 protein using a commercially available anti-TTC19 antibody.

**Results:** In this family, we identified a novel homozygous *TTC19* mutation predicting frameshift and early protein truncation. The mutation was heterozygous in parents and healthy siblings, and it was absent in ethnically-matched controls. The protein was undetectable in tissues by Western blot analyses.

**Conclusion:** This is the fourth kindred presenting mutations in *TTC19*. The clinical phenotype of such condition is severe, embraces neurological and psychiatric symptoms, and represents a further example of autosomal recessive ataxia of metabolic origin.

## SC81

### Axonal sensory-motor polyneuropathy in two patients with duodenal levodopa infusion. To stop or not to stop the infusion?

*Gianni Orofino*, *E. Costantino*, *L. Fadda*, *M.M. Mascia*, *A. Cocco*, *L. Polizzi*, *P. Solla*, *F. Marrosu*, *A. Cannas*

Centro per i Disordini del Movimento, Clinica Neurologica, Università di Cagliari, Cagliari

**Background:** A severe complication of the duodenal levodopa infusion in patients with Parkinson's disease (PD) is the onset of an axonal sensory-motor polyneuropathy (ASMP) that may worsen substantially the quality of life of patients. The exact physiopathology is uncertain, although the most likely hypothesis is that of deficiency, in particular vitamin B12 and folate deficiency.

**Objective:** To open up a discussion and offer our experience on an inescapable question when diagnosis of ASMP is made: "Should the duodenal levodopa infusion be or not be suspended?" At the moment there are no guidelines.

**Clinical cases:** Among 10 patients (6 males and 4 females) implanted in recent years with a duodenal levodopa infusion pump, 2 males, respectively of 75 and 70 years, have developed an ASMP. Both had an advanced PD (stage IV of the Hoehn/Yahr score and an UPDRS-III score respectively of 69 and 62 in OFF-phase) and complicated by frequent motor fluctuations, with a few hours in the on phase, and major choreo-ballic dyskinesias. In the first patient the initial clinical sign of ASMP appeared about eight months after placement of the pump (dose starter of 12 ml: continuous infusion 5.3 ml/h; extra dose 3.5 ml), in the second case (dose starter of 12 ml: continuous infusion 6.1 ml/h; extra dose 3 ml) about six months later. Diagnosis of ASMP was confirmed by EMG. In the first case the duodenal levodopa infusion was maintained, in the second interrupted.

**Discussion:** In the absence of guidelines, our choice was dictated by practice. In the first case (in agreement with family members) we chose to continue infusion, with vitamin supplementation, because the worsening of patient life's quality did not allow an alternative; in the second case, paroxysmal painful symptoms of polyneuropathy did not leave any other choice than suspending duodenal levodopa infusion and returning to the previous oral therapy.

## SC82

### Phenotypical presentations in patients affected by progressive supranuclear palsy

Federico Pace<sup>1</sup>, L. Bet<sup>2</sup>, L. Romito<sup>3</sup>

<sup>1</sup>Stroke Unit, IRCCS Policlinico di San Donato, San Donato Milanese (Milano)

<sup>2</sup>Stroke Unit, IRCCS Policlinico San Donato, Dipartimento di Scienze Mediche per la Salute, Università degli Studi di Milano, San Donato Milanese (Milano)

<sup>3</sup>Neurologia I - Disturbi del Movimento, IRCCS Istituto Neurologico Carlo Besta, Milano

**Aims:** There aren't precise data regarding symptoms at PSP onset and, if there are, they are incomplete or include a single symptom. Moreover, they are not correlated to age. The aims of the study is to investigate the symptoms at the onset.

**Materials and Methods:** Were enrolled all patients alive with initial diagnostic suspect of PSP followed in the outpatients, totalling 120. During the follow-up 33 patients were eliminated, due to a diagnosis modification or because medical records were insufficient. These satisfied the diagnostic criteria for PSP (Litvan, 1996). These onset symptoms were considered: psychiatric, parkinsonian, dystonic, ocular, axial, gait akinesia, eyelid apraxia.

**Results and discussion:** The most frequent symptoms have been: extrinsic ocular motility disorders (97,7%), falls without loss of consciousness (100%), parkinsonism (100%). The most frequent onset symptoms were axial, both single (19,54%) or in association (68,96%). Psychiatric symptoms were the second in order of frequency as only symptom (11,49%). Parkinsonian symptoms

were the second in order of frequency, in association (40,2%). Extrinsic ocular motility abnormalities appeared as initial symptom in a very low percentage (2,29%). Gait akinesia represented the onset symptom in a low number of cases (5,74%). The patients who presented at onset only psychiatric symptoms (54 years) or gait akinesia (56,6 years) were younger.

**Conclusion:** This study concentrated on the clinical phenotypes of PSP at its onset, considered both as single and associated, and with age. We highlight how gaze paralysis appeared only in a very low number of cases at onset. The most frequent symptoms during the course were: ocular motility, axial and parkinsonism. Psychiatric symptoms were the second most frequent at onset, as only symptom. Parkinsonian symptoms were the second most frequent at onset, as associated symptoms. Patients who manifested the pathology at its onset with psychiatric symptoms or gait akinesia were younger.

## SC83

### EEG in Alzheimer's disease: what benefit?

Cristina Paci, R. Gobbato, G. D'Andreamatteo, T. Carboni, S. Sanguigni, S. Sobrini, A. Brandimarti, V. Urbano, B. Moretti

U.O.C. Di Neurologia, Ospedale Civile "Madonna del Soccorso" San Benedetto del Tronto (Ascoli Piceno)

**Aims:** EEG examination is used very frequently in Alzheimer's disease. The aim of our study was to determine whether there is a directly proportional correlation between the rate of background EEG and the MMSE score in patients with Alzheimer's disease.

**Materials and Methods:** We studied 30 patients with Alzheimer's disease, according to the NINCDS ADRADA criteria, 15 mild and 15 moderate. All patients have performed at same day MMSE and EEG. We calculated the MMSE score and the EEG background activity. The statistical method has been obtained with t-test and Student's Test.

**Results:** In the group of mild EEG background activity was  $7.4 \pm 1.6$  Hz and the MMSE score of  $22.20 \pm 1.80$ ; group of moderates in the EEG background activity was  $7.19 \pm 1, 28$  Hz and the MMSE score of  $16.06 \pm 2.07$  (EEG:  $p = 0.000$ ).

**Conclusions:** Our results demonstrate the low effectiveness of EEG monitoring according to the severity of the disease. The underlying rhythm is slow but we have not shown any difference in EEG between the two groups, unlike the MMSE score. This allows us to realize the validity of EEG to discriminate differential diagnosis but not for follow-up; we conclude that EEG is the "gold standard" in the early stages of a neurodegenerative disease and to differentiate a rapidly progressive viral encephalitis disease.

## SC84

### The effect of rasagiline on prospective memory in newly diagnosed patients with Parkinson's disease

Cristina Pagni, D. Frosini, M. Poletti, G. Giunti, R. Ceravolo, G. Tognoni, U. Bonuccelli

Department of Neuroscience, University of Pisa, Pisa

**Introduction:** Prospective memory could be impaired in Parkinson's Disease (PD) even at very early disease stages. Recent evidence has suggested a possible role of rasagiline in modulating cognitive functions in PD patients, especially in the dominion of attention.

**Objective:** The present study was aimed at investigating the effect of rasagiline, a monoamine oxidase type-B inhibitor, on the performance on an event-based prospective memory task by retrospectively evaluating a cohort of PD patients.

**Materials and methods:** A cohort of 33 PD patients was administered an experimental prospective memory task at time of diagnosis, before starting antiparkinsonian drugs (T0), and after one-year treatment (T1) with dopaminergic treatment alone (N = 16, T1: age 70.2 ± 5.4 years, disease duration 24.3 ± 7.1 months, UPDRS-III 15.5 ± 6.0) or in combination with rasagiline (N = 17, T1: age 64.7 ± 5.5 years, disease duration 25.5 ± 10.4 months, UPDRS-III 12.1 ± 3.3). Separate scores were computed for correct execution of intended action (prospective component-PC) and for recall of intention (retrospective component-RC).

**Results:** Patients without rasagiline (Pts-R) and patients with rasagiline (Pts + R) were similar in terms of dopamine agonists and Ldopa doses. After 1 year treatment Pts + R showed an improvement in PC while the group Pts-R worsened the performance (Pts + R: T0 = 2.9 ± 1.7 T1 = 3.6 ± 1.1; Pts-R: T0 = 2.0 ± 1.7, T1 = 1.2 ± 1.6). The change was statistically significant between the two groups (p < 0.005). No differences emerged in the RC.

**Conclusion:** These results are consistent with previous findings suggesting that rasagiline may exert beneficial effects on some aspects of attention and executive functions in non-demented, cognitively impaired PD patients. According to an explanatory model previously proposed, the process of prospective remembering involves different phases: *intention formation*, *intention initiation* and *intention execution* (that rely on executive processes) and *intention retention* (that rely on more retrospective memory storage capacity). Thus, rasagiline could be effective on the executive processes that support PC of memory for intention.

## SC85

### Global management of the patient with Parkinson's disease in advanced stage

*Kai Stephan Paulus*<sup>1</sup>, *M. Meloni*<sup>1</sup>, *E.R. De Natale*<sup>2</sup>, *F. Deriu*<sup>2</sup>, *G. Carpen-  
tras*<sup>1</sup>, *P. Galistu*<sup>1</sup>, *M. Serusi*<sup>1</sup>, *V. Agnetti*<sup>1</sup>

<sup>1</sup>Institute of Clinical Neurology, University of Sassari, Sassari

<sup>2</sup>Dept. of Biomedical Science, University of Sassari, Sassari

Parkinson's disease (PD) is a progressive neurodegenerative disorder. In the first stages PD has commonly a satisfactory response to dopaminergic treatment but with disease duration the pharmacological control of extrapyramidal signs decreases progressively with comparison of complications such as wearing off, on-off fluctuations, dyskinesia, dystonia, and psychiatric manifestations. Therefore medication has to be continuously modified administering various drugs with increasing dosages. Furthermore, PD commonly appears clinically after the sixth decade of life and thus the majority of patients are probably affected by interstitial comorbidities which requires further pharmacological treatment with the growing risk of side effects and interactions between different drugs. Notoriously this means worsening of quality of life (QoL). At this stage the pharmacological management appears to be very difficult. What can we do? Which kind of possibilities and weapons do we have?

First of all, the management of the later disease stages begins with the treatment approach at clinical onset. The correct initial management with the right use and combination of levodopa, peripheral and central enzym inhibitors, and dopamine agonists, obtaining an acceptable symptom control is the indispensable condition which permits a stable future treatment

conduct. The goal must be to delay as late as possible treatment complications exploiting strategies of levodopa saving. Then, simple side effects frequently caused by the combination of diverse drugs, can often be avoided by knowledge of pharmacokinetics and dynamics. The most important thing for maintaining a discrete QoL level is given by a global management including medical therapy, specific conventional and not conventional rehabilitation, and psychological support, as well as integration in a multidisciplinary team.

Doing so, there may be many advantages. Firstly, the disease course is monitored and possible therapy revisions can be performed easily on all treatment levels. Secondly, patients and caregivers do not feel abandoned which increases the QoL. Finally, the global management helps to avoid excessive drug consume, unnecessary instrumental investigation and hospitalization; in other words, it helps to restrain the health economics.

## SC86

### Serum IGF-1, EGF and GH levels and motor progression in a cohort of de novo Parkinsonian patients

*Marina Picillo*<sup>1</sup>, *R. Erro*<sup>1</sup>, *K. Longo*<sup>1</sup>, *M. Moccia*<sup>1</sup>, *M. Amboni*<sup>1</sup>, *P. Barone*<sup>2</sup>, *M.T. Pellecchia*<sup>2</sup>

<sup>1</sup>Department of Neurological Sciences, University Federico II, Naples

<sup>2</sup>Center for Neurodegenerative Diseases (CEMAND), University of Salerno, Salerno

**Introduction:** Insulin-like Growth Factor-1 (IGF-1) provides protection against loss of dopaminergic neurons in animal models of Parkinson's disease (PD) [1]; Epidermal Growth Factor (EGF) promotes morphologic and neurochemical development of cultured midbrain dopaminergic neurons [2]. Recently, increased serum IGF-1 levels were found in early PD patients compared to controls [3].

**Objective:** The aim of this study was to evaluate the influence of baseline serum IGF-1, EGF and Growth Hormon (GH) on motor progression in a cohort of "drug-naive" PD patients.

**Patients and methods:** Serum IGF-1, EGF and GH levels were measured in 33 "drug-naive" PD patients; subsequently, due to the observational nature of the study the patients were treated with antiparkinsonian drugs according to physician's decision and re-evaluated in "on" state three times over a period of 24 months with UPDRS part III and UPDRS dopa-resistant score.4 Variation within time and differences between quartiles of serum IGF-1, EGF and GH levels were analyzed with repeated measures ANOVA. Post-hoc analysis was performed with Bonferroni test. Analysis was computed using daily LED as covariate.

**Results:** Mean age (±SD) at diagnosis was 59,7 (±8) years, with a mean of 13,8 (±5,5) months since the very first putative clinical manifestation of PD. 42% of patients were women. At the end of the follow up period all the patients were in treatment. Overall mean progression on the UPDRS part III was 0,5 point/year (95%CI:-0,5 to 1,53) and on the UPDRS dopa-resistant score was 0,3 point/year (95%CI:0,13 to 0,55). Overall mean increase in LED was 111,6 mg/year (95%CI:42 to 300). Repeated measures ANOVA showed no significant progression within time of UPDRS part III (p = 0,2), while UPDRS dopa-resistant score showed a significant progression within time (p < 0,03). Post-hoc analysis revealed that, excluding patients with serum IGF-1 levels < 68 ng/ml, patients with higher baseline value of IGF-1 showed higher UPDRS part III scores during the first two years of disease. No differences between subjects were found for UPDRS dopa-resistant score and for baseline serum EGF and GH levels.

**Conclusions:** In PD higher serum IGF-1 at diagnosis may be associated with worse motor features during the first two years of disease.

#### References:

- [1] Quesada A, Lee BY, Micevych PE. PI3 kinase/Akt activation mediates estrogen and IGF-1 nigral DA neuronal neuroprotection against a unilateral rat model of Parkinson's disease. *Dev Neurobiol* 2008;68:632e44.
- [2] Iwakura Y, Zheng Y, Sibilina M, et al. Qualitative and quantitative re-evaluation of epidermal growth factor-ErbB1 action on developing midbrain dopaminergic neurons in vivo and in vitro: target-derived neurotrophic signaling (Part 1). *J Neurochem*. 2011 Jul;118(1):45-56.
- [3] Godau J, Herfurth M, Kattner B, et al. Increased serum insulin-like growth factor 1 in early idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2010 May;81(5):536-8.
- [4] Levy G, Louis ED, Cote L, et al. Contribution of aging to the severity of different motor signs in Parkinson disease. *Arch Neurol* 2005;62:467-72.

#### SC87

##### Excitability of cortical and subcortical circuits in oro-mandibular dystonia

Giovanna Pilurzi<sup>1</sup>, T.A. Saifee<sup>2</sup>, K. Bhatia<sup>2</sup>, M.J. Edwards<sup>2</sup>, F. Deriu<sup>1</sup>, J.C. Rothwell<sup>2</sup>

<sup>1</sup>Department of Biomedical Sciences, University of Sassari, Sassari

<sup>2</sup>Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, UK

**Introduction:** Oro-mandibular dystonia (OMD) is a rare form of focal dystonia affecting facial muscles. Both subcortical and cortical mechanisms have been implicated in its pathophysiology. Subcortical factors have been investigated testing brainstem reflexes, whereas cortical excitability of the facial motor area has not been studied yet.

**Objective:** To investigate excitatory and inhibitory interneuronal circuits in the brainstem and in the cortical representation of facial muscles, in patients with OMD.

**Methods:** Eight patients with OMD and 8 healthy controls were studied. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were measured in the most affected depressor angulis oris muscle, during 10% of maximal voluntary contraction. The blink reflex (BR) and the masseter inhibitory reflex (MIR) recovery cycles were recorded from the most affected orbicularis oculi and masseter muscle, respectively. The R2 area of BR recovery cycle and SP2 duration and inhibition of MIR recovery cycle were measured at 200-1000ms interstimulus intervals (ISI). To compare individual patients, "R2 index" and "SP2 index" were calculated as average of recovery values (at ISIs of 200-500ms for R2; 200-300ms for SP2).

**Results:** SICI and ICF were evidenced in both patients and controls. Two way ANOVA using group as between-subjects factor and ISI as within-subject factor showed a significant effect of ISI ( $p = 0.001$ ) but no significant effect of group. The R2 ( $n = 7$ ) and the SP2 ( $n = 5$ ) duration indices were significantly ( $p = 0.037$  and  $0.033$ , respectively) higher in patients than controls, indicating less suppression in OMD.

**Conclusions:** SICI and ICF did not differ significantly in the facial motor cortex of OMD and controls. By contrast, BR and MIR recovery cycles were significantly disinhibited in patients, in agreement with previous reports. These preliminary data suggest a minor role for cortical factors with respect to subcortical

mechanisms in OMD pathophysiology, however a larger sample is needed to draw firm conclusions.

#### SC88

##### Transcranial Direct Current Stimulation (tDCS) and cerebellar ataxia: a case report

Nicolò Gabriele Pozzi<sup>1,2</sup>, B. Minafra<sup>1,2</sup>, M. Fresia<sup>3</sup>, I. Bertaina<sup>1,2</sup>, G. Sandrini<sup>4,5</sup>, C. Pacchetti<sup>1,2</sup>

<sup>1</sup>Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>2</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>3</sup>Department of Neurophysiology, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>4</sup>Unit of Neurorehabilitation, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>5</sup>Department of Public Health and Neurosciences, University of Pavia, Pavia

Cerebellar ataxia is characterized by an incoordination of movement and due to cerebellar dysfunction. tDCS is a non invasive stimulation that can change cortical activity by rather weak electric currents modulation ion channels and gradients and hence the resting membrane potential. Anodal tDCS leads to brain depolarization (excitation) whereas cathodal tDCS results in brain hyperpolarization (inhibition). We report a case a 42 years-old female with sporadic, low progressive, form of cerebellar ataxia, treated with tDCS and studied with gait analysis, in double blind, sham controlled study. A neurological examination show: action tremor, dysarthria and gait disturbances: enlarged base, ataxic footing, with a prevalent incoordination on the left side.

On the basis of the potential capacity of tDCS stimulation to improve asymmetric disturbances we decided to perform tDCS cycle in attempt to improve ataxia and resynchronize the execution of the step program. The patient undergoes to a placebo stimulation for the first week, and then a week of anodal tDCS on the motor cortex (M1) of the right side of the brain and cathodal stimulation on motor cortex of the left side. A gait analysis was performed pre and post tDCS. We observed an improvement in symmetry of execution and in gait speed after tDCS stimulation; any change is been observed after sham stimulation. No variation of cerebellar symptoms was observed. The initial improvement not sustained at one month follow-up.

#### SC89

##### Selection criteria for continuous duodenal levodopa infusion: considerations on 24 consecutive patients

Francesca Preda<sup>1</sup>, G. Roversi<sup>1</sup>, E. Contini<sup>2</sup>, L. Trevisani<sup>3</sup>, R. Quatrone<sup>4</sup>, M.R. Tola<sup>2</sup>, M. Sensi<sup>2</sup>

<sup>1</sup>U.O. Clinica Neurologica, Arcispedale S. Anna, Ferrara

<sup>2</sup>U. O. Neurologia, Arcispedale S. Anna, Ferrara

<sup>3</sup>U.O. Endoscopia Digestiva, Arcispedale S. Anna, Ferrara

<sup>4</sup>U.O. Neurologia, Ospedale dell'Angelo, Mestre

**Background:** Continuous duodenal levodopa infusion (DLI) is widely recognized as an effective therapy for advanced Parkinson's Disease (PD) and represents a valid alternative for patients not candidate to surgery. In literature common selection criteria are lacking and the major inclusion criteria refer to those used for candidate to Deep Brain Stimulation.

**Methods:** We evaluated retrospectively 24 advanced PD patients treated with DLI from 2008 to 2011. 5 patients died, 2 of them for problems related to surgery and 3 for unrelated medical conditions. 16 patients were evaluated at baseline and after 24 months using UPDRS III, Freezing of Gait Questionnaire, Non-Motor Symptoms Scale, PDQ-8, a complete battery assessing cognitive and psychiatric status and the specific PD caregiver's quality of life scale (SQLC).

**Results:** All the 16 patients (9 men, 7 women, mean age 67.9 years) showed a marked improvement of motor complications and a concomitant improvement in quality of life. Cognitive status remained stable. All patients showed a significant improvement in depression scale. The impulsive behaviour or dopamine dysregulation syndrome, present in 3 patients, resolved completely in the first months. Among non motor symptoms we observed a statistically significant improvement in items regarding sleep, fatigue and mood. 8 patient showed a remarkable reduction of freezing and falls. Controversial data come from evaluation of caregivers burden scale, with a critical worsening in the first 6-9 months and a slight improvement in the long term follow up.

**Conclusions:** Our data confirms the long term beneficial effect of DLI in patients with advanced disease on motor symptoms. The best outcome was noted in patients not in advanced age, without other significant concomitant illnesses; psychosis but not dementia correlated with a poor outcome. An important issue to be considered in selection criteria is the impact of DLI on caregivers stress and burden.

## SC90

### The effect of mirror visual feedback on hemispheric balance

*Alessia Raffo De Ferrari<sup>1</sup>, E. Pelosin<sup>1</sup>, L. Avanzino<sup>2</sup>, C. Ogliastro<sup>1</sup>, R. Marchese<sup>1</sup>, G. Abbruzzese<sup>1</sup>*

<sup>1</sup>Department of Neurosciences, Ophthalmology and Genetics, University of Genoa, Genoa

<sup>2</sup>Department of Human Psychology, University of Genoa, Genoa

**Background:** The clinical use of mirror visual feedback (MVF) was initially introduced to alleviate phantom pain, and has since been applied to the improvement of hemiparesis following stroke. Neurophysiological mechanisms underlying MVF are still unknown. To our knowledge only one study demonstrated that MVF training can induce changes in the plasticity of primary motor cortex (M1).

**Objective:** To directly investigate cortical modification induced by MVF training, we studied both the excitability of the two M1s and transcallosal interaction between them in a group of healthy subjects.

**Methods:** 10 healthy right handed subjects were enrolled in this study. Subjects were asked to participate in MVF training protocol. MVF training consisted in executing a finger tapping motor training task using the mirror box technique. Subjects were asked to oppose thumb and index following an acoustic cue paced at 2 Hz for one minute per 10 times each with a resting period of 30 seconds within the training blocks. The subjects performed the training with the left hand while watching the mirror which gave the illusion of moving the right hand. Cortical activity changes were tested before and after the training by means of Transcranial Magnetic Stimulation (TMS). Both recruitment curve of left and right hemispheres and Inter Hemispheric Inhibition from left and right and right to left M1 were tested before and after training.

**Results:** MVF training induced no change in corticomotor excitability of left and right hemispheres and in RL-IHI while it induced an increase of transcallosal inhibition from LR M1s.

**Conclusions:** These preliminary results suggest that transcallosal interaction from the "illusioned" hemisphere to the contralateral one can be modulated by MVF training. One possible explanation is that transcallosal inhibitory interhemispheric interaction acts to suppress unwanted movements in the left hand.

## SC91

### Deep brain stimulation of subthalamic nucleus for advanced Parkinson's disease: effects on cognition

*Silvia Ramat<sup>1</sup>, C. Polito<sup>1</sup>, L.M. Raglione<sup>1</sup>, D. Bacci<sup>1</sup>, S. Meoni<sup>1</sup>, M. Fanini<sup>1</sup>, L. Caremani<sup>1</sup>, G. Pecchioli<sup>2</sup>, P.S. Bono<sup>2</sup>, F. Ammannati<sup>2</sup>, S. Sorbi<sup>1</sup>*

<sup>1</sup>SOD Neurologia 1, Dipartimento di Neuroscienze, AOU Careggi, Firenze

<sup>2</sup>SOD Neurochirurgia 1, Dipartimento di Neuroscienze, AOU Careggi, Firenze

**Introduction:** deep brain stimulation of the subthalamic nucleus (STN-DBS) is an efficacious treatment in well selected patients affected by Parkinson's disease (PD). Several studies describe a loss in verbal fluency after STN-DBS.

**Aim:** Aim of the study is to assess the neuropsychological outcome of bilateral STN-DBS in patients affected by PD.

**Method:** 37 PD patients selected for STN-DBS (age  $60.59 \pm 5.81$  years, PD duration  $13.19 \pm 6.52$  years, MMSE =  $27.44 \pm 1$ , LEDD  $1396.77 \pm 819.77$  mg/die) were assessed twice: one week before STN-DBS (in med-on condition) and after 12-24 months after STN-DBS (in med-on condition with stimulator switched on). Neuropsychological tests explored executive functions, attention, short and long-term memory.

**Results:** Motor scores significantly improved after STN-DBS. Our study of cognition show an increase of perseverative errors at Modified Card Sorting Test, an increase of time in Stroop test-interfering condition, a loss in verbal fluency, both phonemic and semantic.

**Conclusions:** STN-DBS influences only executive control functions, not causing a global cognitive decline. Our data confirm that STN-DBS is a safe procedure in a cohort of well-selected parkinsonian patients.

## SC92

### Syndrome of rostral midbrain dysfunction secondary to ventriculoperitoneal shunt malfunction

*Veronica Redaelli, M. Furlanetto, L.G. Valentini, F. Girotti*

Neurological Institute Carlo Besta, Milano

We describe two cases with rostral midbrain dysfunction secondary to malfunction of ventriculoperitoneal shunts presenting ocular and extrapyramidal signs, mutism, and alterations of consciousness.

Case 1: a 71-years-old woman was treated with ventriculoperitoneal shunt for normal pressure hydrocephalus. After a valve control she took temporary improvement of gait disturbance, but after a few months symptoms progressed with severe akinesia, muscular rigidity of the limbs, vertical gaze restriction, palpebral retraction, convergence-retraction eye movements and anarthria with partial alterations in consciousness. No improvement occurred after third ventriculostomy. DAT scan don't show reduction of dopamine transporter density.

MR image showed intracranial hypotension syndrome. After ventriculoperitoneal shunt closure and a treatment with L-Dopa the patient began to communicate and improved in vertical gaze restriction and muscular rigidity of the limbs.

Case 2: a 31-years-old man was treated with endoscopic third ventriculostomy for triventricular hydrocephalus secondary to aqueductal stenosis, and with ventriculoperitoneal shunt two months later. Then he presented somnolence, mutism, vertical gaze restriction, convergence-retraction eye movements and severe akinesia with endocranial hypotension signs. He was treated with L-Dopa and with another endoscopic third ventriculostomy and ventriculoperitoneal shunt closure. He gradually resumed a normal state of consciousness and motor autonomy, which persisted even after the interruption of L-Dopa. He reported that during the condition of mutism he was able to understand all verbal delivery but was unable to perform them.

**Conclusions:** Neurological features of the two patients characterized by vertical gaze restriction, palpebral retraction, convergence-retraction eye movements, severe akinesia, muscular rigidity of the limbs and trunk and mutism can be justified by disfunction of periaqueductal areas of rostral midbrain (posterior commissure and nuclei, and periaqueductal gray matter). Integrity of dopamine transporter density show that nigrostriatal dopaminergic pathway can't be responsible of psychic and motor akinesia that we can define as an "akinetin closed-in".

### SC93

#### **Intensive rehabilitation increases BDNF serum levels in patients with early Parkinson's disease**

Giulio Riboldazzi, C. Comi, R. Maestri, S. Buttini, E. Bellinzona, F.L. Lombino, M. Perini, D. Uccellini, R. Cantello, G. Frazzitta

Centro Parkinson e Disordini del Movimento, Ospedale di Circolo e Fondazione Macchi, Varese

In the last decade, a considerable number of reports showed that physical exercise is effective in improving balance, gait, and general motor performance in Parkinson's disease (PD). Recent studies highlighted that i) moderate to vigorous activities in preceding years decrease PD risk and ii) intensive exercise leads to optimal results in PD rehabilitation. The neuroplastic effect of intensive exercise may be linked to increased release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF).

The aim of this study is to assess whether intensive rehabilitation treatment (IRT) is able to modulate BDNF serum levels. Twenty five patients with early PD and under Rasagiline monotherapy for at least 2 months were enrolled in the study. Fourteen patients underwent IRT (group 1), while nine patients continued taking only pharmacological treatment (group 2). IRT consisted of a 4-week cycle of physiotherapy that entailed three daily sessions 5 days a week. BDNF serum levels at enrolment and 1, 2, 3 weeks later were tested in both groups. We found that baseline BDNF serum levels did not differ significantly between the two groups.

In all patients from group one, BDNF levels showed an increase, which was statistically significant after 10 days of IRT and remained stable over the treatment period; on the contrary, BDNF serum levels remained quite stable in patients from group 2.

This study suggests that IRT in patients with early PD is able to induce an increase of BDNF serum levels, which is maintained over the whole treatment period. We recently showed that IRT is effective in patients with early PD, and our current observations provide a biological basis to the beneficial effect of IRT. Indeed our findings are in line with studies on animal models, showing that intensive exercise is effective in promoting neuronal growth factors release and eventually cell proliferation and neuronal differentiation.

### SC94

#### **Intrajejunal levodopa infusion in advanced Parkinson's disease: long-term effects on motor and non-motor symptoms and impact on patient's and caregiver's quality of life**

Lucia Ricciardi<sup>1,2</sup>, F. Lena<sup>3</sup>, N. Modugno<sup>3</sup>, A.R. Bentivoglio<sup>1</sup>, A. Fasano<sup>1,4</sup>

<sup>1</sup>Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma  
<sup>2</sup>Dipartimento di Neuroscienze, Psichiatria e Scienze Anestesiologiche, Università di Messina, Messina  
<sup>3</sup>Istituto Neuromed, Pozzilli, Isernia, Italy  
<sup>4</sup>Dipartimento di Neuroscienze, Ospedale AFaR-Fatebenefratelli, Roma

**Background:** Continuous infusion of intrajejunal levodopa/carbidopa gel (CIILG) for advanced Parkinson's disease (PD) has been proved to be beneficial on motor complications, non-motor symptoms and quality of life in the short-term follow-up. Aim of this two-center, retrospective, open-label study was to evaluate the long-term effect of CIILG on patients' condition and caregivers' quality of life.

**Materials and methods:** The assessments (performed at baseline and at latest follow-up available after CIILG) included: the unified PD rating scale (UPDRS I-IV), the non-motor symptoms scale (NMSS), the PD questionnaire (PDQ-8), the PD sleep scale (PDSS), and a battery assessing the cognitive and psychiatric status as well as caregiver's quality of life. Medications were expressed as levodopa equivalent daily dose (LEDD).

**Results:** 14 advanced PD patients (age:  $67.0 \pm 11.5$  years, disease duration:  $12.9 \pm 4.8$  years) were followed for  $24.9 \pm 14.4$  months after CIILG. Total LEDD was unchanged at follow-up, however therapy was globally simplified by reducing dopamine agonists (DAs). A statistically significant beneficial effect was shown on motor complications while the severity of motor symptoms did not change over time. A significant improvement of depressive symptoms and psychiatric side effects caused by DAs was detected. Sleep quality and diurnal somnolence ameliorated as revealed by the significant reduction of PDDS. Caregivers' stress and patients' quality of life were not significantly improved. However, when categorized according to their outcome, patients with improvement of motor condition and functionality gained an improvement of quality of life. Apart from the severity of motor impairment at baseline, no other predicting factors were detected.

**Conclusions:** CIILG is an effective treatment option for patients with advanced PD over the long-term period as it may improve both the motor complications and the psychiatric side effects caused by other dopaminergic therapies.

### SC95

#### **Myoclonus in a patient undergoing hysteroscopic myomectomy**

Steno Rinalduzzi, S. Almonti, A.M. Cipriani

UOC Neurologia e Neurofisiopatologia, Ospedale Sandro Pertini, Roma

**Introduction:** Transcervical endoscopic surgery uses a new hysteroscopy technique that entails inserting a scope into the uterine cavity and instilling a suitable distending medium to visualize the endometrium. If these fluids are rapidly absorbed they can cause volume overload, electrolyte imbalance and variable concomitant adverse effects. We describe here a patient in whom myoclonus developed during hyponatremia after hysteroscopic myomectomy.

**Case report:** A 58-years-old woman was admitted for elective hysteroscopic myomectomy to treat a large submucosal

leiomyoma. Anesthesia was induced with propofol 150 mg iv. Three liters electrolyte-free 1.5% glycine solution was instilled to distend the uterus. At one hour after the distending medium infusion started, laboratory findings disclosed low sodium 120 mmol/L and the procedure was stopped. One hour later myoclonus developed. Neurological examination showed myoclonus at rest, generalized myoclonic jerks, predominantly involving the bilateral sternocleidomastoid and abdominal muscles and left limbs, but no other focal neurological signs. The patient was alert and cooperative; jerks were spontaneous and triggered by sensory stimuli. The electroencephalography (EEG) recording showed no abnormal EEG activity correlating with the jerks. Brain computed tomography was normal. The patient was treated with diazepam, she was immediately sedated and the myoclonic jerks stopped. Arterial blood tests 2 hours later showed hyponatremia, hypokalemia and hypocalcemia. Electrolyte imbalance normalized within 10 hours and the myoclonus gradually decreased and resolved within 24 h.

**Conclusion:** Myoclonic jerks are an extremely rare complication in a patient undergoing surgical hysteroscopy. The clinical characteristics of the myoclonus and lack abnormal EEG activity correlating with the jerks resemble reticular reflex myoclonus and probably reflect an electrolyte disorder. The case report we present underlines the need to detect in time and promptly treat neurological symptoms, an uncommon event complicating transcervical hysteroscopic surgery.

## SC96

### Prognostic factors of long term cognitive impairment in Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation

*Laura Rizzi, A. Merola, E. Montanaro, M. Zibetti, M.G. Rizzone, C.A. Artusi, M. Lanotte, L. Lopiano*

Università degli Studi di Torino, Dipartimento di Neuroscienze, Torino

**Background:** Cognitive impairment has been increasingly recognized as part of Parkinson's disease (PD) clinical features. It has been reported an 85% prevalence of dementia after 15 years since PD diagnosis; age, precocious impairment of neuropsychological functions and akinetic-rigid disease feature seem to be negative prognostic factors. Subthalamic nucleus deep brain stimulation (STN-DBS) is a therapeutic option for a subset of PD patients with long-lasting preserved cognitive function and levodopa response. Nevertheless, the medium-long term cognitive effects of STN-DBS are not completely understood. The aim of this study is to investigate the possible prognostic factors of cognitive impairment in PD patients treated with STN-DBS, considering the clinical and neuropsychological evaluations of a large cohort of patients (182 subjects) up to  $\geq 5$  years since surgery.

**Materials and Methods:** The clinical and neuropsychological data of PD patients treated with STN-DBS in Turin between 1998 and 2010 were collected at baseline and at each follow-up available. The follow-up data were clustered in four different time-points: baseline, 1 year, 3 years and  $\geq 5$  years since surgery. A Cox regression analysis was performed analyzing the prognostic value of several clinical and neuropsychological baseline factors and their risk of predict cognitive impairment.

**Results:** Clinical and neuropsychological data were available for 182 patients at baseline, 155 patients at 1-year, 107 patients at 3-years and 63 patients at  $\geq 5$ -years since surgery. **Conclusion:** The interaction of different specific clinical and cognitive features

might predict the risks of developing cognitive impairment in PD patients treated with STN-DBS.

## SC97

### Five years follow up efficacy of subthalamic nucleus stimulation for tremor dystonia: a case report

*Mario Giorgio Rizzone<sup>1,2</sup>, D.V. Roccatagliata<sup>1,3</sup>, L. Castana<sup>1</sup>, E. Agostoni<sup>1</sup>, G. Lo Russo<sup>1</sup>, L. Lopiano<sup>2</sup>*

<sup>1</sup>Dip. di Neuroscienze, A.O. Niguarda Ca' Granda, Milano

<sup>2</sup>Dip. di Neuroscienze, Università di Torino, Torino

<sup>3</sup>Università degli Studi di Milano-Bicocca, Milano

**Objective:** To evaluate the efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of dystonic tremor (DT).

**Background:** DBS is a valid therapeutic option for the treatment of movement disorders unresponsive to pharmacologic measures. The globus-pallidus-internus and the nucleus-ventralis-intermedius of the thalamus are considered the first choice target for dystonia and non-parkinsonian tremors, respectively. STN-DBS is effective for the treatment of Parkinson's disease, but its efficacy for dystonic disorders has been already described too. We evaluated the efficacy of STN-DBS for the treatment of a patient with severe DT refractory to medical treatment.

**Methods:** In 2007 a 63 years old patient with severe DT underwent bilateral STN-DBS. The disease onset was reported at age seventeen, with a bilateral postural tremor of the upper limbs that worsened with time, involving the lower limbs. Severe dystonia, involving limbs, trunk and cranial district appeared later on. All pharmacologic treatments failed, and at the time of surgery the disease was very disabling. Ventriculography, MRI and intraoperative multi-track microrecording and microstimulation were performed to individuate the STN. Clinical evaluation was performed preoperatively, at 2-years and 5-years follow-up by the Burke-Fahn-Marsden-Dystonia scale (BFM) and the Fahn-Tolosa-Marin-Tremor scale (FTM).

**Results:** Both tremor and dystonia significantly improved with STN-DBS, and this improvement was maintained over the time. Preoperatively, the BFM-movement-score was 53, the BFM-disability-score was 19 and the FMT-score was 102. At 2-years-follow-up, in the stim-on condition (3.2V-right-STN, 2.9V-left-STN; 60us; 130 Hz), the BFM-movement-score was 18, the BFM-disability-score was 12 and the FMT-score was 58. At the 5-years-follow-up, in the stim-on condition (3.5V-right-STN, 3.0V-left-STN, 60us, 130 Hz), the BFM-movement-score was 19, the BFM-disability-score was 12 and the FMT-score was 59.

**Conclusions:** Despite the necessity of larger studies, STN-DBS could be considered as an effective long-term therapeutic option for uncommon movement disorders, as DT.

## SC98

### Acute onset of hyperglycaemic hemichorea-hemiballismus: improvement and response to treatment

*Daria Valeria Roccatagliata<sup>1,2</sup>, E. Ferrante<sup>1</sup>, M.G. Rizzone<sup>3</sup>, C. Erminio<sup>1</sup>, E. Forapani<sup>1</sup>, C. Ferrarese<sup>2</sup>, E. Agostoni<sup>1,2</sup>*

<sup>1</sup>Dip. di Neuroscienze, A.O. Niguarda Ca' Granda, Milano

<sup>2</sup>Università degli Studi di Milano-Bicocca, Milano

<sup>3</sup>Dip. di Neuroscienze, Università di Torino, Torino

**Introduction:** Acute onset of involuntary movements as hemichorea-hemiballismus caused by basal ganglia dysfunction have

been widely described both due to a vascular lesion and in non-ketonic hyperglycaemia. In the latter condition, movements can persist despite treatment.

**Objectives:** To describe acute onset of left-sided hemichorea-hemiballismus in a lady with underrated type-2 diabetes mellitus and her dramatic improvement after treatment with tetrabenazine and clonazepam.

**Methods:** A 85-year-old lady presented at the emergency department after a fall caused by acute onset of involuntary movements of the left limbs. She suffered from arterial hypertension but there was no history of diabetes mellitus, other diseases, exposure to drugs or family history of movement disorders.

**Results:** On admission she was fully oriented and neurological examination showed chorea-ballism involving both left limbs with normal muscle strength and no other neurological impairment. Movements were unsuppressible, increased with emotions and voluntary movements of the right limbs and disappeared during sleep. Blood examination showed severe hyperglycaemia (750 mg/dL - normal values 60-110 mg/dL) and glycosylated haemoglobin A1c was 112 mol/mol (normal values 20-42). Blood pH and urinary ketones were unremarkable as well as other routine blood tests (calcium concentration, thyroid hormones, liver and renal tests). Endocrinological consultancy led to a diagnosis of type-2 diabetes mellitus. Normal glycaemia was restored after 3 days on insulin therapy, then treatment with gliclazide + metformine was started. Brain CT scan was unremarkable. T1-weighted brain magnetic resonance imaging (MRI) showed a hyperdensity in the right pallidum-putamen, detectable on T2-weighted and Flair images, too. After intravenous gadolinium administration, subtle contrast enhancement appeared within and around the lesion. Chorea-ballistic movements disappeared in the lower limb and improved significantly in the upper one after a week on tetrabenazine 25 mg tid and clonazepam 8 drp/die.

**Discussion:** Tetrabenazine has been effective and well-tolerated in our case of acute-onset hyperglycaemia-related movement disorders.

## SC99

### Somatosensory temporal discrimination threshold can differentiate multiple system atrophy patients from Parkinson's disease patients

*Lorenzo Rocchi, A. Conte, A. Nardella, P. Li Voti, G. Leodori, G. Fabbrini, A. Berardelli*

Department of Neurology and Psychiatry and Neuromed Institute, "Sapienza" University of Rome, Rome

**Introduction:** Somatosensory Temporal Discrimination Threshold (STDT) is defined as the threshold for perceiving two tactile stimuli as clearly distinct. STDT physiological mechanisms include afferent sensory input gating and a time-locked interplay between cortical and subcortical structures. STDT is altered in various movement disorders such as Focal Dystonia, Parkinson's Disease (PD) and Multiple System Atrophy (MSA).

**Objectives:** To investigate whether STDT can be used as a diagnostic aid in differentiating patients with PD and MSA.

**Methods:** Nineteen MSA patients, twenty-two PD patients and eighteen age-matched healthy subjects were tested for STDT. Clinical evaluation included Hoehn and Yahr Scale, Unified Multiple System Atrophy Rating Scale for MSA patients and Unified Parkinson's Disease Rating Scale for PD patients. STDT was

investigated by delivering paired electrical stimuli starting with an inter-stimulus interval (ISI) of 0 msec (simultaneous pair), and progressively increasing the ISIs in 10 msec steps. Subjects had to report whether they perceived a single stimulus or two temporally separated stimuli. Between group ANOVA was used to compare STDT values in PD, MSA and healthy subjects. A receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy (sensitivity and specificity) of STDT testing in differentiating MSA from PD patients.

**Results:** Between group ANOVA showed a significant effect of factor group ( $F_{2,52} = 19,00$ ;  $p < 0,00001$ ). Post-Hoc analysis showed that STDT values in MSA and PD patients were significantly higher than those obtained in healthy subjects. The ROC curve analysis for the STDT value calculated on the right hand in PD and MSA patients yielded 78,95% sensitivity and 86,36% specificity with a cut off STDT value of 140 msec.

**Conclusions:** The degree of STDT abnormality is higher in MSA than in PD patients and, due to the high sensitivity and specificity, STDT testing can effectively differentiate MSA from PD patients.

## SC100

### New class of nitric oxide donor derived from Piloty acid as possible drugs for Parkinson's disease treatment: an in-vitro microdialysis study

*Gaia Rocchitta<sup>1</sup>, O. Secchi<sup>1</sup>, M.D. Alvau<sup>1</sup>, E. Garribba<sup>2</sup>, A. Porcheddu<sup>2</sup>, L.V. Deluca<sup>2</sup>, D. Sanna<sup>3</sup>, P.A. Serra<sup>1</sup>*

<sup>1</sup>Department of Clinical and Experimental Medicine, University of Sassari, Sassari

<sup>2</sup>Department of Chemistry and Pharmacy, University of Sassari, Sassari

<sup>3</sup>Institute of Biomolecular Chemistry, National Research Council, Sassari, Sassari

Nitric oxide (NO) is one member of a new class of gaseous signaling molecules with fundamental functions in biology. Several pharmacological implications of NO have been demonstrated and numerous studies in vitro and in vivo showed that NO-generating drugs (NO donors) cause an increase of the extracellular level of dopamine in the striatum. This could suggest a possible application of such NO-donors in the treatment of Parkinson's disease. PC12 cells can reproduce experimental model of Parkinson's disease, since they are known to synthesize, secrete, and metabolize DA. The present work aims to study the effects of a new class of NO donors on the release of dopamine from PC12 cell suspensions by means of capillary microdialysis. The newly synthesized molecule are derived from Piloty Acid that spontaneously is able to release NO.

Each molecule was synthesized starting from Piloty Acid, commonly commercially available, by adding different substituent groups, capable of modulating the release of dopamine from these molecules.

The microdialytic protocol provided the perfusion of NO donors for 60 minutes and recovered samples were analyzed by means of HPLC-EC instrument.

All the newly synthesized donor produced a statistically significant increase in dopamine concentrations comprised between 3.29- and 6.21-fold respect basal levels. The molecule that had a nitro-group as substituent determined a significant decrease in DA concentration (more than 70% compared to basal levels).

## SC101

### Dopamine Transporter expression in patients chronically treated with rotigotine: results from a preliminary prospective SPECT study

Carlo Rossi<sup>1,2</sup>, D. Genovesi<sup>3</sup>, D. Frosini<sup>1</sup>, C. Menichetti<sup>4</sup>, E. Filidei<sup>3</sup>, D. Volterrani<sup>5</sup>, U. Bonuccelli<sup>1</sup>, R. Ceravolo<sup>1</sup>

<sup>1</sup>Department of Neuroscience, University of Pisa, Pisa

<sup>2</sup>UOC Neurophysiopathology, Ospedale F. Lotti, ASL 5 Pisa, Pisa

<sup>3</sup>UO Nuclear Medicine, Fondazione Toscana "G. Monasterio", Pisa

<sup>4</sup>UO Neurology, Ospedale-ASL1 Città di Castello (Perugia)

<sup>5</sup>UO Nuclear Medicine, University of Pisa, Pisa

**Background:** Neither Ldopa or immediate release dopamine-agonist have demonstrated to interfere with FP-CIT SPECT binding. Recently, in order to avoid or reduce the risk of motor complication and to allow a more physiologic continuous dopaminergic stimulation longer acting and extended release formulations of dopaminergic drugs have been launched. With once-daily application, the patch of rotigotine matrix provides constant non-fluctuating plasma drug levels at steady state, resulting in continuous and stable plasma and brain levels with a continuous striatal dopamine-receptor stimulation.

**Objective:** The aim of this study was to evaluate the effect of chronic treatment with rotigotine on striatal dopamine transporter (DAT) in patients with Parkinson's disease (PD) by means of FP-CIT SPECT.

**Methods:** In this prospective study, we investigated presynaptic nigrostriatal function in 8 de novo patients fulfilling clinical criteria for "probable PD" (age  $59 \pm 6.2$  years; M/F 5/3) using FP-CIT SPECT before and after 3 months of treatment with rotigotine (mean daily dose  $7.75 \pm 1.98$  mg). For data analysis, specific (left and right caudate, left and right putamen) to non-specific (occipital cortex) binding ratios, putamen to caudate ratios and asymmetry indexes were calculated.

**Results:** During rotigotine treatment, all patients improved motor symptoms (UPDRS III mean score  $11.88 \pm 2.59$  vs  $7.63 \pm 1.92$  on therapy,  $p = 0.0022$ ). Striatal FP-CIT levels showed a significant improvement in each patient at the follow up scan. Comparisons between the whole group before and after treatment showed a significant improvement in FP-CIT uptake in both caudate and putamen ( $p < 0.001$  in each nucleus). Putamen to caudate ratio and asymmetry indexes did not show a significant difference before and after treatment.

**Conclusions:** Our results suggest that rotigotine could affect FP-CIT binding and should be withdrawn before SPECT examination. These findings could be explained as expression of loss of efficacy of this drug in our PD population. Since DAT serves to maintain relatively constant dopamine synaptic levels and its expression is inversely correlated with dopamine turnover, the increase of DAT after rotigotine might have the effect to preserve DA in the nigro-striatal terminals.

## SC102

### Creative thinking in patients with Parkinson's disease and healthy controls: does the artistic profession makes the difference?

M. Canesi<sup>1</sup>, Maria Luisa Rusconi<sup>2</sup>, R. Cilia<sup>1</sup>, E. Reali<sup>2</sup>, F. Moroni<sup>2</sup>, G. Pezzoli<sup>1</sup>

<sup>1</sup>Parkinson Institute, Istituti Clinici di Perfezionamento, Milan

<sup>2</sup>Department of Human Sciences, Università degli Studi di Bergamo, Bergamo

**Introduction:** Creative drive and enhanced artistic like production may emerge in patients with PD during dopaminergic therapy.

A recent study (Canesi et al., 2011) suggests that newly acquired artistic-like production in PD patients might represent the emerging of innate skills in a subset of predisposed patients and this is not associated with impulsivity or impulse control disorders. Moreover, changes in painting style after treatment onset have been described in some case reports. Nonetheless no data are available in de novo PD patients (PD-dn) and in PD patients with professional artistic job (PD-art). We investigated creative thinking in different PD patients and healthy controls by means of the abbreviated Torrance test for adults (ATTA).

**Aims:** To evaluate creative thinking in Parkinson's disease (PD-dn) patients with any dopaminergic treatment and in professional artists (PD-art) patients by means of the ATTA.

**Method:** We investigated creative thinking in a cohort of cognitively preserved patients with PD: 11 PD-dn, 10 PD-art and 25 PD-na by means of the ATTA. We also investigated a sample of healthy controls (HC), with (12 HC-art) and without (47 HC-na) professional artistic job, by means of the ATTA. All PD patients underwent the following evaluation: \*Neurological assessment: UPDRS-part III; HY stages. \*Cognitive assessment: MMSE, Frontal Assessment Battery (FAB). \*Mood scales: Geriatric Depression Scale (GDS) **Results:** Mean ATTA score of PD-art patients was found to be similar to HC-art ( $73,6 \pm 22,4$  vs  $97,0 \pm 29,1$  respectively) and of PD-dn vs PD-na ( $54,9 \pm 29,6$  vs  $55,6 \pm 24,6$ ). PD-art patients and HC-art showed a significantly higher ATTA score than PD-na and HC-na respectively ( $p < 0,01$ ). \*No correlation was found with reference to any demographic and clinical data in PD subgroups.

**Conclusion:** Our results suggests that creative thinking is not correlated with dopaminergic therapy in PD patients with and without professional artistic job. These results are in accordance with the hypothesis that dopaminergic system is involved in creative drive but not in idea generation.

## References:

- [1] Canesi M et al, Artistic productivity and creative thinking in Parkinson's disease. *European Journal of Neurology* 2012, 19: 468-472
- [2] Goff K et al, The Abbreviated Torrance Test for Adults (ATTA). IL Scholastic Testing Service, 2002
- [3] Torrance EP, The Torrance Test of Creative Thinking-Streamlined Scoring Guide Figural A and B
- [4] Drago V et al, Creativity in Parkinson's disease as a function of right versus left hemibody onset. *Journal of the Neurological Sciences* 2009, 15: 179-183

## SC103

### Insulin sensitivity and early-phase insulin secretion are not impaired in normoglycemic patients with Huntington's disease

Cinzia Valeria Russo, E. Salvatore, T. Tucci, C. Rinaldi, M. Massarelli, F. Rossi, L. Di Maio, A. Filla, A. Colao, G. De Michele

Departments of Neurological Sciences and of Molecular and Clinical Endocrinology and Oncology, Federico II University, Naples

**Background:** Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat in exon 1 of the Huntingtin gene (HTT) which encodes a stretch of glutamines in the huntingtin protein. Apart from main neurological impairment, there is increasing evidence pointing towards an early involvement of the endocrine system in HD. Recent studies were conducted to investigate association with an increased risk of diabetes mellitus and with an impairment in insulin sensitivity and insulin secretion in HD patients with contradictory results.

**Objective:** To investigate the association between diabetes mellitus and HD by performing an oral glucose-tolerance test (OGTT) to evaluate the glucose-tolerance status and OGTT-related insulin release.

**Patients and Methods:** Twenty-eight consecutive patients with HD seen at our Clinics and 28 healthy controls were matched for age, sex and BMI. Diagnosis of HD was confirmed in all patients by analysis for the CAG repeat expansion. Clinical assessment of patients was performed using the Unified Huntington's Disease Rating Scale (UHDRS) motor section and the Total Function Capacity (TFC). Wide basal metabolic investigations and a 2-hour 75-g oral glucose tolerance test (OGTT) were performed. We used the homeostasis model assessment of insulin resistance (HOMA-IR) as index of insulin sensitivity. Insulin secretion was determined by the Insulinogenic index.

**Results:** HD patients did not differ from the control group with respect to fasting plasma glucose level, insulin sensitivity and secretion. However, HD patients showed lower plasma glucose (-19%) and insulin levels (-48%) at 30 minutes after oral glucose load and higher plasma insulin at 90 (+132%) and 120 minutes (+380%) in comparison with controls. CAG expansion size, disease stage or BMI did not influence HOMA-IR or insulinogenic index in HD patients.

**Conclusions:** Our data challenge the assumption of an increased risk of diabetes among HD patients although they suggest abnormal glucose regulation.

## SC104

### Changes in walking performance on people with Parkinson disease after lower limb robotics rehabilitation

*Patrizio Sale*<sup>1</sup>, *F. Stocchi*<sup>1</sup>, *D. Le Pera*<sup>1</sup>, *I. Sova*<sup>1</sup>, *M. Galli*<sup>1</sup>, *M. Franceschini*<sup>1</sup>, *M.F. De Pandis*<sup>2</sup>

<sup>1</sup>IRCCS San Raffaele Pisana, Roma

<sup>2</sup>San Raffaele Cassino, Cassino (Frosinone)

**Introduction:** The effectiveness of non-pharmacological options such as exercises has been demonstrated; in particular an example for patient tailored exercises is physiotherapy. The goal of physiotherapists is to enable PD patients to maintain their maximum level of mobility, activity, and independence. The use of electromechanical devices such as treadmill training (a supplement to conventional therapies) in the last years has also been used with PD patients. The specific aims of this project are: to verify whether the robotics lower limb treatment with body weight support is more effective than the treadmill treatment in the reduction of motor impairment in PD patients, and to improve the quality of the gait and the endurance and to analyze possible improvements in terms of physiological biomechanical gait through analysis of spatio-temporal parameters.

**Materials and methods:** Study design: RCT. Subjects: 18 patients with a diagnosis of PD. Inclusion criteria: evidence of motor deficit in one lower limb, age between 18 and 79 years. At the beginning of the treatment and after 20 sessions, optocynematic analysis of gait and clinical scales Hoehn and Yahr, were delivered. Treatment: all patients will receive traditional treatment (Physiotherapy, Occupational Therapy and Speech Therapy). All subjects excepted will undergo inpatient rehabilitation consisting of a treatment cycle using the G-EO system (Reha Technologies) or treadmill device GAIT TRAINER, according to individually tailored exercise scheduling (Group A and CG.). All the treatment consists of 20 sessions for the lower limbs, each lasting 45 minutes, 5 days a week for 4 weeks.

**Results:** The clinical characteristic of the experimental groups were: Hoehn and Yahr Stage range 2-3 median 3, Age 70.00 ± 8.396 yrs, Weight 70.22 ± 17.14 kg, Height 159.6 ± 9.13 cm.

The clinical characteristic of the control groups were: Hoehn and Yahr Stage range 2-3 median 3, Age 70 ± 10,2 yrs, Weight 85,11 ± 19,27 kg, Height 162 ± 11 cm. The ones treated with G-EO showed a significant improvement of Barthel (45 vs 62) and FIM (57 vs 86) scores at discharge compared to admittance. No statistical difference at T0 were found. The spatio-temporal parameter (Mean velocity, Stride length, Stance and Swing time) showed a statistical improvement in Robot group.

**Conclusions:** Our preliminary results show that G-EO system treatment is well tolerated by patients with a statistical improvement of intra group performance and compared to Treadmill group.

## SC105

### Subthreshold depression and subjective cognitive complaints in Parkinson's disease

*Gabriella Santangelo*<sup>1,2</sup>, *C. Vitale*<sup>2,3</sup>, *L. Trojano*<sup>1</sup>, *M.G. Angrisano*<sup>1</sup>, *M. Picillo*<sup>4</sup>, *D. Errico*<sup>1</sup>, *P. Barone*<sup>5</sup>

<sup>1</sup>Department of Psychology, Second University of Naples, Caserta

<sup>2</sup>IDC Hermitage-Capodimonte, Naples

<sup>3</sup>University of Naples, "Parthenope", Naples

<sup>4</sup>Department of Neurological Sciences, Federico II University of Naples, Naples

<sup>5</sup>Center for Neurodegenerative Diseases, University of Salerno, Salerno

**Introduction:** Subthreshold depression (SD) is characterized by depressive symptoms, not meeting criteria for major depression; its prevalence and neuropsychological correlates in Parkinson's disease (PD) are not well-established.

**Objects:** The present study aimed to explore the prevalence of SD in non-demented PD patients and to investigate the possible association of SD with cognitive complaints and/or cognitive impairments assessed by means of a screening instrument specifically validated in PD.

**Methods:** We assessed 109 consecutive PD patients for severity of depressive symptoms by means of Beck Depression Inventory, and for objective and subjective cognitive dysfunctions by means of Montreal Cognitive Assessment.

**Results:** Established cutoffs of the Beck Depression Inventory identified subthreshold depression in 35 patients and major depression in 38; 36 patients were classified as non-depressed. The three groups did not differ on demographic and clinical aspects. Subthreshold depressed did not differ from non-depressed patients on objective cognitive measures, whereas depressed patients achieved significantly lower scores than the other two groups. Subthreshold depressed and depressed patients reported more cognitive complaints than non-depressed patients.

**Conclusions:** Subthreshold depression is a non-motor aspect of PD that is not related with objective cognitive deficits but is associated with cognitive complaints, thus impacting on patients' subjective well-being.

## SC106

### Dopamine receptors oligomerization: biological significance and potential role in Parkinson's disease

*Marco Scarselli*, *G.U. Corsini*

Dipartimento di Neuroscienze, Università di Pisa, Pisa

Accumulating evidence indicates that signaling molecules such as G protein-coupled receptors (GPCRs) might be organized in oligomeric or multimeric superstructures. Specifically, it has been demonstrated by different groups that dopamine receptors can

exist as homo- and hetero-dimers or higher-order oligomers. Despite the high interest related to this field, our understanding of the biological role of these receptor complexes is still controversial and the question “Do GPCRs function as monomers, dimers or oligomers is still unanswered?”.

One reason why receptor oligomerization is a controversial topic is because the direct measurement of these protein aggregates has been outside the resolution of the available microscopy techniques limited by diffraction barrier. Recent developments in the field of optical super-resolution techniques allow both a 10–20 fold increase in resolution as well as an increased ability to quantify the amount of labeled molecules visualized in the fluorescence measurement. One of these new microscope techniques is the Photo-activated Localization Microscopy (PALM) that is capable to resolve precisely localized molecules at separations of few nanometers (precision of 10–20 nm) and to determine the localization of single molecules.

By using PALM, we analyzed the plasma membrane localization and distribution of three prototypical class I GPCRs, namely beta2 adrenergic, D2 dopaminergic and M3 muscarinic receptors. We investigated the assembly in clusters (size and density) of these membrane proteins, and the effect of agonists and antagonists upon these domains. The application of these novel super-resolution techniques could unveil the biological meaning of dopamine receptor oligomerization with relevant consequences for the discovery of new selective drugs in Parkinson's disease.

#### SC107

##### **Real time amperometric monitoring of neurotoxin MPTP effects on oxygen glucose and lactate levels in striatum of freely moving rats**

*Ottavio Secchi, G. Calia, R. Migheli, G. Rocchitta, P.A. Serra*

Dept. of Clinical and Experimental Medicine, Section of Pharmacology, University of Sassari, Sassari

The loss of dopaminergic neurons of *Substantia Nigra pars compacta* in Parkinson's disease, is related to oxidative stress, mitochondrial dysfunction and impaired energy metabolism. The neurotoxin MPTP, known to induce a significant dopaminergic neurodegeneration, is converted into MPP<sup>+</sup> by MAO-B in glial cells interfering with complex I of the mitochondrial electron transport chain. This lead the dopaminergic cell to impaired glucose metabolism and energetic deficit because of reduced ATP production. The aim of this study has been monitoring oxygen, glucose and lactate levels by means of amperometric micro- and biosensors, integrated to a wireless telemetric system, in order to evaluate real-time effects of sub-chronic MPTP administration on physiological metabolism in the brain of freely moving rats.

Oxygen was electrochemically reduced at -400 mV vs Ag/AgCl reference electrode on carbon-epoxy sensor surface. Glucose and lactate detection was attained by glucose oxidase or lactate oxidase-based biosensors polarized at + 700 mV vs Ag/AgCl reference electrode.

Oxygen microsensor and glucose and lactate biosensors have been stereotaxically implanted in the right striatum of male Sprague Dawley rats (250 gr.). MPTP was administered for 3 days consecutively (25, 15, 10 mg/Kg/2.5 ml saline i.p.).

Oxygen, glucose and lactate baseline of 60 minutes was recorded every day before MPTP administration. The first MPTP administration led to an increase of oxygen, glucose and lactate levels. On Day 2 and Day3 a further increase of oxygen and lactate levels was found, compared to both basal and after MPTP administration levels recorded on Day 1. Conversely, glucose showed a statistically significant decrease either in basal or

following MPTP administration. These results suggest that in MPTP-related mitochondrial dysfunction oxygen and glucose cannot be normally used by neurons and increased production of lactate reflect a switch towards anaerobic metabolism.

#### SC108

##### **Formulation of a treatment protocol for OPCA: two cases description**

*P. Marano, Mariella Seminara*

Unità Operativa di Neuroriabilitazione, Casa di Cura Villa dei Gerani, Catania

The rehabilitation of secondary parkinsonism is one of many possibilities, now sufficiently experienced, to interfere with the debilitating disease that results. It is important to emphasize the need, as it should always take place in rehabilitation, be clear objectives attainable, from both of the team that part of the patient, in order to avoid the error of missing the target.

The experience of the writer wants to emphasize the necessity of proceeding through an appropriate method of work as a team, which should include clinical assessment, integrated with a functional assessment, as a prerequisite to identify the objective first thing to attainable.

The first thing to do is the global observation of the patient to assess the interaction with the environment, motivation, orientation, space-time, any compensation or alternative strategies already put in place, then we proceed with the observation and measurement of any volume of muscle mass and tone, find for any changes, this leads to the possible presence of involuntary movements, there is the existence of postural alteration, taking into account that posture is the attitude assumed by the body in space, defined by the relative positions of different body segments and observed the ability of postural control in key positions, the ability to independently perform steps postural and movement, function and implementation of grasping and manipulation, we also seek balance reactions and parachute in quadruped position, middle position, while standing, you look at how they are played: walking, stairs, and with any travel aids (wheelchair, tripods, staffs, canadian support).

This is good to understand the importance of a functional assessment is carried out in quantitative terms, ie by analyzing the functions and features not found, and in quality, by analyzing the characteristics of motor behavior implemented by the patient, in terms of patterns available (poor, stereotypes abnormal), limitations of osteo-articular, compensation used as adaptive features, the fluidity of modular sequences, the sequences of the monitoring mode (visual, proprioceptive) and any dystonic or hyperkinetic components that interfere with the possibility of completing a sequence efficiently.

The program will also define the practical possibilities of intervention, so it is necessary to carefully consider when evaluating each of the qualities making up each stage of the disease.

#### SC109

##### **LSTV-BIG: a new rehabilitative approach to Parkinson's disease**

*Rita Semprini*

Associazione I.P.(Iniziativa Parkinsoniani), Bologna

*Introduction:* LSTV-BIG is a rehabilitative approach used specifically for PD based on the Silverman voice training method (LSVD LOUD, 1987, USA). Using this approach, increasing vocal

loudness results in widespread effects on other interconnected motor symptoms (sialorrhoea, swallowing, facial expressions). Becky Farley then applied these concepts to the motor system of the trunk and limbs (LSTV BIG), thus proceeding from vocal loudness to amplitude of limb and body movement. This rehabilitative method has recently spread from the USA to several European countries.

**Objectives:** To understand how to place this method within neuroscience studies and research, keeping to the principles of neuronal plasticity, motor learning, and brain imaging. To extend knowledge, increase people's experience, and share results.

**Methods:** General aspects: Rebuilding and correcting body awareness and body movements; Acting directly on sensory and kinaesthetic disturbances, thereby enabling patients to monitor and calibrate their own movements; Creating the conditions for the method to be applied in all contexts and at all stages of the illness.

**Characteristics:** Standardized protocol both of the exercises and the results achieved; Continuous assessment of the motivation of the patient through feedback; Seeking out goals which are of fundamental importance and also emotionally relevant to the patient; Aiming for maximum change with minimum cognitive load.

**Results:** Significant benefits at cerebral level - the reorganisation of damaged neurological circuits - have been confirmed through brain imaging. The therapist's personal experience with a group of ten people of differing ages and at different stages of the illness was extremely positive; the training acted on sensory motor elaboration and on planning movement.

**Conclusions:** Overall, the method is effective. Self treatment at home needs to be monitored more carefully; a three-monthly follow-up to sustain motivation, verify how closely the programme is being adhered to, and evaluate that results are being maintained over time is recommended.

## SC110

### 123I-FP-CIT SPECT and clinical motor features in Sardinian Parkinson's disease patients

*Paolo Solla, A. Cannas, F.C. Ibbi, E. Costantino, M. Corona, G. Orofino, M.G. Marrosu, F. Marrosu*

Movement Disorders Center, Department of Neurology, Institute of Neurology, University of Cagliari, Cagliari

**Background:** Parkinson's disease (PD) is a neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra. Due to predominant motor symptoms, PD can be distinguished in a tremor-dominant type (TDT), a bradykinetic-rigid type (BRT) and a mixed type (MT). TDT patients are supposed to have a lower rate of decline than patients with BRT.

**Objective:** To investigate the correlation between 123I-FP-CIT and clinical features in Sardinian patients with PD.

**Methods:** We performed a retrospective study in Sardinian PD patients followed at the Movement Disorders Unit of the University of Cagliari who had undergone 123I-FP-CIT SPECT in the last three years. Clinical data and features, such as age at onset, disease duration, presenting symptoms, Hoehn and Yahr stage and UPDRS assessment, were retrieved from the patient's history, taken during the regular follow up visits. A 123I-FP-CIT SPECT semi-quantitative analysis for the ipsi and contralateral putamen and caudate nucleus was used. Patients were subtyped into one of three clinical groups: TDT, BRT and MT (features of bradykinetic – rigid and tremor) subtypes. This classification was derived from the UPDRS-motor score. Subtypes were defined according to the ratio of each patient's UPDRS III Tremor score (sum of Items 20 and

21 divided by 4) to his/her mean UPDRS bradykinetic/rigid score (sum of items 22–27 and 31 divided by 15). A ratio > 1.0 was indicative of TDT, a ratio < 0.80 was indicative of BRT, and a ratio between 0.80 and 1.0 was indicative of MT.

**Results:** Eighty-two PD patients (39 males and 43 females) with a mean age of  $66.0 \pm 8.7$  years and mean disease duration of  $4.0 \pm 2.5$  years were included in this analysis. The mean Hoehn and Yahr stage score was  $1.7 \pm 0.7$ . A significantly higher dopaminergic uptake was observed in the TDT group compared with the BRT group ( $2.4 \pm 0.7$  versus  $1.8 \pm 0.5$ ;  $p < 0.01$ ).

**Discussion and conclusions:** We found that the different subtypes of PD had a different correlation with the differential  $^{123}\text{I}$ -FP-CIT SPECT uptake, showing a significant separation of PD subtypes into TDT and BRT. These results are consistent with previous neuropathological models and could confirm other studies that suggested a more marked loss of dopamine nerve terminals in the striatum of patients with predominant rigidity and bradykinesia.

## SC111

### A novel mitochondrial TRNAHYS point mutation in a patient with PSP-like phenotype

*Chiara Sorbera, O. Musumeci, S. Romeo, A.M. Ciranni, G. Vita, A. Toscano, P. Giralanda, F. Morgante*

Department of Neuroscience, University of Messina, Messina

**Introduction:** Mitochondrial disorders are multisystem conditions frequently affecting the skeletal muscle and the central nervous system (CNS). One of the clinical manifestations of CNS involvement is a parkinsonian syndrome.

**Case Report:** A 65-year-old female with positive family history for juvenile stroke like episodes (mother and 2 siblings) presented to our observation with a 3-year history of progressive speech disturbances, dysphagia, balance and gait impairment. One year before our first observation, she experienced an episode of speech difficulty and a CT scan showed an intrasellar neoplasm, treated with surgery and radiotherapy with partial improvement of symptoms. General examination demonstrated short stature. Neurological examination revealed dysarthro-dysphonia with palilalia, marked dysphagia, short-step gait with several freezing episodes, postural instability, sopranuclear vertical gaze palsy, facial hypomimia, moderate bradykinesia and rigidity with bilateral extensor plantar responses. A diagnosis of probable Progressive Sopranuclear Palsy (PSP) according to Litvan criteria was carried out.

**Results:** MRI revealed cortical atrophy, with diffuse confluent hypointensities at basal ganglia, brainstem and subcortical infarcts; specifically, there was an ischemic area in the dorsal pons, extending up to the tegmentum. Serum lactate was elevated. Muscle biopsy showed few ragged red fibers, SDH positive and COX negative fibres. Biochemical assay performed on muscle homogenate following standard protocol revealed reduced activity of succinate dehydrogenase and succinate cit-C-reductase. Muscle coenzyme Q10 was reduced. Southern blotting of mtDNA showed a normal band of mtDNA. Whole mitochondrial genome sequencing analysis in muscle identified a novel c.12182A > G transition in the tRNA histidine gene. The mutation is in a highly conserved region of the T(ψ)C stem of the tRNA(His) gene and may alter secondary structure formation.

**Conclusion:** This is the first reported case of a mitochondrial tRNA mutation manifesting with a PSP-like phenotype. This case expands the genetic heterogeneity of mitochondrial diseases.

## SC112

**CSF dopamine and DOPAC, following levodopa challenge, as a new diagnostic tool in Parkinson's disease**

*Mario Stampanoni Bassi<sup>1,2</sup>, G. Angileri<sup>2</sup>, E. Olivola<sup>2</sup>, T. Pascucci<sup>3</sup>, P. Stanzione<sup>1,2</sup>, M. Pierantozzi<sup>1,2</sup>, A. Stefani<sup>1,2</sup>*

<sup>1</sup>IRCCS Santa Lucia Foundation, European Centre for Brain Research CERC, Rome

<sup>2</sup>Clinica Neurologica, Università di Roma "Tor Vergata", Rome

<sup>3</sup>Dipartimento di Psicologia and Centro "Daniel Bovet", Università La Sapienza, Rome

In Parkinson's disease (PD), reliable staging biomarkers are elusive. Here we tested whether cerebrospinal fluid (CSF) concentrations of dopamine (DA) and its major metabolites - 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) - correlated with motor performance scores in a group of non-fluctuating, stage 1-2 PD patients.

Patients were challenged, in washout (CAPIT), with 200 mg levodopa (LD) and lumbar puncture (LP) was performed after 120 min, when LD concentration in CSF reaches a maximum. DA, DOPAC and HVA were analysed using high performance liquid chromatography (HPLC).

DA concentration (mean: 5.6 nM ± 0.9) was inversely correlated with UPDRS score. DOPAC was tightly correlated with the motor impairment, being significantly higher in more advanced patients. Subjects assigned as early stage PD (below 18 months, n = 9) were significantly different from stage 2 PD patients (n = 10, mean UPDRS 27) in the concentration ratio DA/DOPAC (4.9 and 15.3, respectively). Anecdotal tests in non-PD patients (NIH and cephalgia) revealed a DOPAC/DA ratio always < 4.

These observations suggest that early alterations in the pre-synaptic dopaminergic terminal machinery is a core hallmark of PD. They support the notion that DA metabolites report disease progression attributable to nigro-striatal terminals, hence representing inexpensive biomarkers to support diagnosis specificity, and also to monitor effectiveness of on-going therapies.

On-going studies will assess to what extent the metabolite/DA ratio differs between PD patients with different motor pattern (i.e., TD vs PIG) or different degree of asymmetry or reveals peculiar alterations in other synucleinopathies, such as multiple system atrophy.

## SC113

**Bladder dysfunctions in Parkinson's disease do not imply specific 24-hours Blood Pressure (BP) monitoring modifications**

*L. Brusa<sup>1</sup>, T. Attanasio<sup>4</sup>, E. Finazzi Agrò<sup>3</sup>, F. Petta<sup>3</sup>, C. Iani<sup>1</sup>, Paolo Stanzione<sup>2</sup>*

<sup>1</sup>UOC Neurologia Ospedale Sant'Eugenio, Roma

<sup>2</sup>Clinica Neurologica Università di Roma Tor Vergata, Roma

<sup>3</sup>Clinica Urologica Università di Roma Tor Vergata, Roma

<sup>4</sup>Cardiologia Università di Roma Tor Vergata, Roma

**Objective:** Aim of our study was to evaluate if bladder dysfunctions in patients with Parkinson disease correlate with blood pressure and heart rate dysregulation as assessed by 24-hour blood pressure (BP) monitoring.

**Methods:** 20 patients affected by Parkinson disease according with Brain Bank Criteria (Hoehn and Yahr stage: 2.5), underwent 24-hour blood pressure monitoring by utilizing a Spacelabs device during day and night periods. All patients were normotensive without orthostatic hypotension. Ten of the studied patients

were affected by bladder overactivity and "urge incontinence" (group A) as stated by urodynamic evaluations and clinical interviews; the other ten consecutive patients were not affected by urologic dysautonomia (group B) as revealed by the same clinical and instrumental procedures. All patients were studied in CAPIT condition. The two PD groups did not significantly differ for age, gender and disease duration.

**Results:** Mean systolic and diastolic 24-hours blood pressure, diurnal and nocturnal systolic and diastolic BP were within normal range in both groups and no significant difference were detected between the two groups. Moreover, twelve patients (6 in group A and 6 in group B) showed a non-dipping BP pattern.

**Conclusions:** Our data indicate that urologic dysfunctions are not associated with specific alterations of ambulatory blood pressure monitoring, including circadian rhythm of BP and heart rate variability. Thus, different mechanisms other than autonomic must be involved to support bladder dysfunction in PD.

## SC114

**Epidemiological (cross-sectional) study to evaluate and describe fatigue in patients with Parkinson disease in Italy - The FORTE Study**

*Fabrizio Stocchi<sup>1</sup>, G. Abbruzzese<sup>2</sup>, R. Ceravolo<sup>3</sup>, P. Cortelli<sup>4</sup>, M.F. De Pandis<sup>5</sup>, G. Fabbrini<sup>6</sup>, W. Liboni<sup>7</sup>, C. Pacchetti<sup>8</sup>, G. Pezzoli<sup>9</sup>, M. Canesi<sup>9</sup>, C. Iannaccone<sup>10</sup>, M. Zappia<sup>11</sup>, FORTE Study Investigators*

<sup>1</sup>Institute of Neurology, IRCCS San Raffaele Pisana, Rome

<sup>2</sup>Department of Neurosciences, Ophthalmology, Rehabilitation and Genetics, University of Genoa, Genoa

<sup>3</sup>Department of Neuroscience, University of Pisa, Pisa

<sup>4</sup>Department of Neurological Sciences, Alma Mater Studiorum, IRCCS, Institute of Neurological Sciences, University of Bologna, Bologna

<sup>5</sup>Parkinson Operative Unit, San Raffaele Institute, Cassino (Frosinone)

<sup>6</sup>Department of Neurology and Psychiatry, and IRCCS Neuromed, 'La Sapienza' University of Rome, Rome

<sup>7</sup>Complex Structure of Neurology, Gradenigo Hospital, Turin

<sup>8</sup>Parkinson Operative Unit, IRCCS "National Neurological Institute C. Mondino" Foundation, Pavia

<sup>9</sup>Parkinson Institute, I.C.P., Milan

<sup>10</sup>SPARC Consulting, Milan

<sup>11</sup>Department "G. F. Ingrassia", Neurosciences Area, University of Catania, Catania

**Introduction:** Fatigue is a common non-motor symptom in patients with Parkinson's Disease (PD) and one of the most disabling symptoms of this disease, as reported by patients, with serious impact on patients' quality of life. It is generally accepted that about 50% of PD patients will complain of fatigue and clinical observation revealed that its severity remained mostly unchanged during progression of disease. This study aims to assess, in a non-interventional epidemiological setting, the incidence and severity of fatigue in PD patients and its correlation with PD severity.

**Methods:** This is an epidemiological, cross-sectional, multi-centre study, in patients diagnosed with PD according to the "UKPDS brain bank diagnostic criteria". The primary objectives included the evaluation of the incidence and severity of fatigue in PD patients measured by Parkinson Fatigue Scale (PFS-16) and assessment of its predisposing factors (age, gender, marital status, disease duration, presence of depression, presence of sleep disorders, PD severity, UPDRS total score).

**Results:** 402 patients (mean age: 66.9 years; mean disease duration: 7.5 years) were enrolled in 27 PD centers in Italy. 33.8% of them showed fatigue (PFS-16 score ± 3.3 points). Logistic regression

analysis showed that UPDRS total score, gender female, presence of depression and presence of sleep disorders increase significantly the odds of occurrence of fatigue in patients with PD.

**Conclusion:** FORTE is the largest study ever conducted in Italy to assess the fatigue in PD patients. The large amount of data collected will allow us to investigate in depth the fatigue in these patients.

## SC115

### Recovery of motor performance after a demanding finger motor task in patients with Parkinson disease with and without fatigue

Tiziano Tamburini<sup>1</sup>, L. Avanzino<sup>2</sup>, E. Pelosin<sup>1</sup>, G. Abbruzzese<sup>1</sup>

<sup>1</sup>Department of Neurological Sciences, Ophthalmology and Genetics, Genova

<sup>2</sup>Department of Experimental Medicine, Section of Human Physiology, Genova

**Introduction:** Parkinson patients may experience fatigue among their non-motor symptoms. Recently we described an experimental paradigm apt to study fatigue at a behavioral level and recovery of motor performance after a demanding finger motor task. Here we evaluated motor performance during a demanding finger motor task and recovery in a group of PD patients who presented fatigue and a group of PD patients without fatigue.

**Methods:** 7 patients with Parkinson disease and fatigue (F-PD) and 10 patients without fatigue (NF-PD), age and gender matched, were included in this study. No differences in UPDRS part III scores were found between groups. The occurrence of fatigue was defined as a score  $\geq 8$  on the Parkinson Fatigue Scale. Subjects were instructed to sequentially tap the thumb on each of the other fingers for 5 minutes following an acoustic cue at 2 Hz, and, after 1 minute of rest, to repeat the same task for 1 minute (min REC1) wearing a sensor-engineered glove on their more affected hand. We evaluated the inter-tapping interval (ITI), the touch duration (TD) and the movement rate (MR).

**Results:** ITI progressively increased from minute 1 to minute 5 and returned to baseline values in the 1-min recovery. However F-PD and NF-PD showed a different behavior: while in NF-PD ITI recovered after the demanding motor task to a level comparable to baseline (min REC1 vs min1  $p = 0.24$ ), in F-PD group ITI decreased to a major extent with respect to baseline (min REC1 vs min1  $p < 0.05$ ).

**Discussion:** Our findings may indicate that deterioration of motor performance during the 5 minutes demanding motor task is similar in F-PD and NF-PD patients, but recovery is more effective in F-PD, possibly through compensatory mechanisms involving basal ganglia.

## SC116

### Normal lateral inhibition mechanism during sensory-motor plasticity in dystonia

Carmen Terranova, V. Rizzo, F. Morgante, L. Ricciardi, P. Girlanda, A. Quartarone

Department of Neurosciences, Psychiatry and Anaesthesiological Sciences, University of Messina, Messina

**Object:** To explore if sensory information is processed and integrated during sensory-motor plasticity phenomena by using lateral inhibition mechanisms in normal humans and in patients with dystonia.

**Background:** Several evidence suggest that lateral inhibition is a system within sensory-motor cortex operating during the acquisition of new motor tasks in order to select the appropriate muscle sequence to be stored within the final motor engram. This mechanism is thought to be lost in dystonia and this should explain the development of redundant motor memories which could culminate in overflow phenomena and overt dystonia.

**Methods:** We have used transcranial magnetic stimulation to explore lateral inhibition during sensory-motor plasticity in 12 dystonic patients (7 focal hand dystonia, 5 cranial dystonia) and in 8 healthy subjects. In particular we looked at motor evoked potential (MEP) facilitation, in the abductor pollicis brevis (APB) and abductor digiti minimi (ADM), obtained after 5 Hz repetitive paired associative stimulation after median (PAS M), ulnar nerve stimulation (PAS U) and median + ulnar nerve (PAS MU) stimulation. In this way we evaluated the ratio MU/M + Ux100 (lateral inhibition index).

**Results:** Our data confirmed that patients with dystonia had two main abnormalities: first the amount of facilitation was larger than normal subjects; second and more important the spatial specificity was lost. A three-factorial ANOVA demonstrated a significant time x group x conditioning interaction ( $F = 7.9$ ;  $p = 0.005$ ). Lateral inhibition index was similar (about 50%) in healthy subjects and dystonic patients.

**Conclusions:** These data suggest that lateral inhibition is normal in dystonia during sensory-motor plasticity. Another mechanism could contribute to the formation of motor memories with redundant information, which could culminate in overt dystonia.

## SC117

### Syndrome as onset of autosomal dominant cerebellar ataxia type I

R. De Micco<sup>1</sup>, Alessandro Tessitore<sup>1</sup>, G. Cirillo<sup>1</sup>, A. Giordano<sup>1,2</sup>, G. Tedeschi<sup>1</sup>

<sup>1</sup>Department of Neurological Sciences, Second University of Naples, Naples

<sup>2</sup>Neurological Institute for Diagnosis and Care "Hermitage Capodimonte", Naples

**Clinical case:** a 63-years-old man presenting with a slowly progressive 5-year history of upper limb tremor, occurring during voluntary movements; rarely tremor at rest; lower limb tremor, which was present only during standing position; speech impairment. His neurological examination revealed mild broad-based gait; mild dysarthria; action tremor of the upper limb; mild and inconstant left hand tremor at rest; mild bradykinesia of left upper limb; "pseudo-orthostatic" tremor of the lower limb. Absent other neurological signs. Biochemical blood tests, including CBC, glycemia, thyroid and parathyroid hormones; antigliadin/tissue transglutaminase/endomysium antibodies; vitamin E, B12 and folic acid levels, tumor screen, was normal. Brain MRI revealed olivo-ponto-cerebellar atrophy. A <sup>123</sup>Ioflupane SPECT was performed and revealed diffuse reduction of the striatal uptake. Neurological examination and instrumental findings prone to hypothesize a diagnosis of late onset autosomal dominant cerebellar ataxia type I with parkinsonism. Therefore, we have analyzed CAG repeat expansion in the SCA1, SCA2 and SCA6 loci of our patient and we have found pathologic trinucleotide expansion at the SCA2 locus.

**Diagnosis:** SCA2 with parkinsonism. **Addendum:** one year later, the patient's daughter, a 33-years-old woman, was referred to us with a slowly progressive six-months history of unsteady gait;

speech impairment; upper limb kinetic tremor; rarely head tremor.

## SC118

### Outpatient rehabilitation treatment in Parkinson's disease: Efficacy evaluation

*Mattia Tiburzi, F. Tirinelli, M.E. Tondinelli, M. Ernesto, A. Marini, N. Vanacore, F. Viselli*

Ospedale San Giovanni Battista, ACISMOM Roma

**Introduction:** Patients suffering from Parkinson's disease show the gradual loss of motor skills, especially a deficit of gait and balance reactions. Therefore we planned a specific outpatients rehabilitation treatment for PD.

**Objective:** The aim of this study is to investigate the effectiveness of outpatient treatment, setting the target on gait, balance and autonomy improvement.

**Methods:** We included 20 patients with idiopathic PD  $9 \pm 5.7$  years, 11 males and 9 females, with mean age of  $69.1 \pm 10.5$  and severity between 2 and 3 of the H&Y scale, stabilized in drug treatment. The treatment consisted of 10 rehabilitative sessions of 3 hours twice a week, each session was divided into individual therapy, group therapy and occupational therapy. The individual treatment steps included training for postural, stretching exercises, muscle strengthening the trunk and limbs, exercises for balance and gait. Coordination exercises, strengthening and rhythmic movement were performed during the therapy group. Autonomy in ADLs, problem-solving, socialization, handwriting and speech were treated in occupational therapy. All patients were evaluated in three stages: 3 months before the treatment (T0), at the beginning (T1), and at the end of the rehabilitation plan (T2). The rating scales used were the Berg Balance Scale (BBS), the Rivermead Mobility Index (RMI) and the Falls Efficacy Scale (FES).

Statistical analysis were performed with analysis of variance for repeated measures.

**Results:** The BBS evaluation showed a significant improvement in gait and balance (T1  $23.2 \pm 8.2$  vs T2  $28.5 \pm 7.4$   $p < 0.001$ ). RMI evaluation has highlighted a significant improvement in ADL autonomy (T1  $11.4 \pm 3.3$  vs T2  $13.3 \pm 2.1$   $p < 0.001$ ). The FES scale, despite the improvement (T1  $29.2 \pm 21.2$  vs T2  $26.7 \pm 19.2$ ), did not produce statistical significance.

**Conclusions:** The results demonstrate that outpatient rehabilitation treatment is able to improve the balance and motor functions, furthermore it represents an indispensable support to drug therapy.

## SC119

### Palatal tremor after brachial plexus anesthesia

*Pierluigi Tocco, M. Turri, M. Acler, L. Bertolasi*

Department of Neuroscience, University of Verona, Verona

**Introduction:** Palatal tremor, also called palatal myoclonus, is defined by short, rhythmic contractions of the palatal musculature and may be associated with synchronous movements of adjacent structures. It can be distinguished into the essential form (EPT) and the symptomatic form (SPT). In the EPT ear click can be present, involuntary contraction stops during sleep and brain MRI does not detect anomalies, while in the SPT ear clicks are rarely present and palatal movements are part of a constellation of clinical findings, including dysarthria, nystagmus

and ataxia. Pathologic studies outlined an important role of lesions affecting the dentate-rubral-olivary pathway, or Guillain-Mollaret triangle.

**Case presentation:** We describe a 49 year-old woman with acute onset palatal tremor following brachial plexus anesthesia with levobupivacaine 0.5% due to surgery of ulnar collateral ligament. She also presented bilateral, involuntary, and rhythmic activity of chin muscles evoked by the opening of the mouth. The palatal contraction could not be inhibited by external sensory stimuli, whereas chin contraction could be suppressed by selective tactile stimuli of the trigeminal area. The patient also complained bilateral ear click. The remainder of the neurological and otorhinolaryngologic examinations were normal. Symptoms appeared immediately after surgery and did not improve after clonazepam and carbamazepine intake. Brain MRI was unremarkable, and we conducted a broad electrophysiologic evaluation: EEG, blink-reflex, BAEPs, lower and upper limbs SEPs and MEPs were all normal.

**Conclusion:** As previously described, intratecal anesthetics could induce myoclonus. This case suggests possible pharmacological toxic effect on the dentate-rubral-olivary pathway (Guillain-Mollaret triangle) even after local administration of levobupivacaine.

## SC120

### Effects of Parkinson's disease and surgery for STN-DBS on the top-down and bottom-up mechanisms of visual selective attention

*Giorgio Tommasi<sup>1,2,4,8</sup>, M. Fiorio<sup>2</sup>, J. Yelnik<sup>3</sup>, P. Krack<sup>4</sup>, F. Sala<sup>1</sup>, E. Schmitt<sup>4</sup>, V. Fraix<sup>4</sup>, L. Bertolasi<sup>1</sup>, J.F. Le Bas<sup>5</sup>, A. Fiaschi<sup>1,2</sup>, J. Theeuwes<sup>6</sup>, P. Pollak<sup>4,7</sup>, L. Chelazzi<sup>2</sup>*

<sup>1</sup>Department of Neurosciences, University Hospital Trust of Verona, Verona

<sup>2</sup>Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Verona

<sup>3</sup>Behavior Emotion and Basal Ganglia Team, Institut du Cerveau et de la Moelle Epinière, University Hospital Pitié-Salpêtrière, Paris, France

<sup>4</sup>Department of Neurology, University Hospital Joseph Fourier University, Grenoble, France

<sup>5</sup>Neuroradiology and MRI Unit, University Hospital Joseph Fourier University, Grenoble, France

<sup>6</sup>Department of Cognitive Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

<sup>7</sup>Department of Neurology, University Hospital of Geneva, Geneva, Switzerland

<sup>8</sup>U.O.C. Neurologia d.O, Azienda Ospedaliera Universitaria Integrata Verona, Verona

**Introduction:** Some findings suggest that patients with Parkinson's disease (PD) may be impaired in visual selective attention (VSA) tasks, and may present enhanced distractibility (attentional capture, AC) in the presence of salient objects/events, which capture their attention (by bottom-up mechanisms), disrupting target search (driven by top-down mechanisms). At present, it is rather unclear to what extent PD, and deep brain stimulation of the subthalamic nucleus (STN-DBS) can impact on the VSA mechanisms.

**Objective:** We aimed to assess the effects of PD and of electrode placement in the STN on the VSA mechanisms.

**Methods:** The main instrument for our study was an AC task, which was suitably combined with a choice reaction and simple reaction time tasks to assess in isolation the effectiveness of

bottom-up and top-down mechanisms of VSA, as well as the mechanisms of motor response selection and initiation. We compared the performances on these tasks of two groups of 12 PD patients, one treated only by drugs, the other also by STN-DBS, with those of a group of controls. PD patients were evaluated after antiparkinsonian drugs withdrawal and stimulation arrest.

**Results:** Both groups of patients showed an equivalent increase of AC as well as similar delays in target selection and movement initiation compared to controls, whereas motor response selection time was significantly increased only in the operated patients. Noteworthy, the daily dose of dopaminergic drugs was significantly lower in the STN-DBS group than the non-operated group.

**Conclusions:** Our results suggest that in PD there might be both a relative enhancement of the bottom-up mechanisms, and a weakening of the top-down mechanisms, which mutually could account for the observed increase in AC. The similar amount of AC and target selection delay obtained in both groups of our patients suggest that surgery for STN-DBS should not impact negatively on the VSA mechanisms. The dysfunctions of the VSA mechanisms found in PD patients were part of a more composite scenario of deficits, especially in the surgically treated patients, who present slowing down of the processes of motor response selection and movement initiation, possibly related to the decrease in dopaminergic drug doses.

## SC121

### Exploratory approach with “Neuro-Fragmentation of Movement” (NF) in Parkinson’s disease

*Maria Elena Tondinelli, M. Tiburzi, F. Tirinelli, M. Egidi, A. Monge, M. Paradiso, F. Viselli*

Ospedale San Giovanni Battista - Cavalieri di Malta, Roma

**Objective:** To estimate the outcomes of treatment with Neuro-Fragmentation (NF) in patients with PD, who have difficulties with postural changes. PD presents difficulties in motor automatism and with complex motor sequences (sequence effect-dual task effect). The category of automatic movements is represented by anticipated postural reactions. Studies present evidences on using cueing to improve movements.

**Materials:** In 5 years we included in our observation 34 patients affected by PD, between 3–4 HeY, with difficulties with passages. Patients have been assessed at the beginning and to the term of therapeutic cycle with: UPDRSIII, BBS, RMI.

12 of them have had a balance training and active general chinesi (age:71; std:6,5; HeY:3,33; std:0,49). 22 were approached with NF (age:70,77; std:6,11; HeY:3,4; std:0,50). After a stabilization period of pharmacological treatment the patients were treated 1 h/day for 30 days.

Patients have not been randomized but the allocation has been accidental for the inner organization of unit. Two groups are comparable for age and HeY. Statistic analyses have been conducted with the t-test between the T0 and T1 inside of everyone of 2 groups.

The (NF) treatment was carried out with: 1. Anticipated and reactive reaction (understanding the own possibilities of movement, concept of visual objective and “motor alternative”). 2. Simple motor sequences, starting from the most difficult passage for the patient, perception of the error store clerks: “error like possibility” to modify itself, cognitive task, cueing. 3. Self-training:

anticipated reaction, divide postural passages in simple movement, visual and cognitive task.

**Results:** BBS and RMI showed a significant improvement (BBS-T0:22,64; STD:2,81-T1:41,14; STD:4,61 RMI-T0:3,86; STD:2,48-T1:9,71; STD:1,50). Modifications were not found in bradykinesia, rigidity and ability to execute contemporary motor task as reported by the UPDRSIII.

**Conclusion:** (NF) is an educational process: reprograms every automatic movement as voluntary, simple movement; exalts postural reaction hidden by the lesion, is enriched by visual and cognitive task; it allows an improvement of self-sufficiency.

This observation has various critical point, as the blindness operator, the few items sensitive to postural passages. For these reason, we are designing a RCT, that it will answer to the requirements of objective analysis.

## SC122

### Full remission of pathological gambling after switch from pramipexole to transdermal rotigotine: Analysis of a case series

*Vincenzo Toni, M.C. Pastore, M.R. Mazzeo, A. Bernardi, R. Scarpello*

U.O.C. Neurologia, Osp. “F. Ferrari”, ASL LE, Casarano (Lecce)

**Introduction:** Impulse Control Disorders (ICDs) not rarely occur in Parkinson’s disease (PD) patients treated with dopamine agonist drugs (estimated prevalence 13,6%). The prevalence of Pathological Gambling (PG) in these PD patients is 6%–8%. Pramipexole and ropinirole are more likely to induce PG, but a few reports have been published regarding transdermal rotigotine inducing PG.

**Objective:** To describe the improvement of PG in three of four patients treated with pramipexole I.R. after switch to rotigotine.

**Subjects and methods:** Four patients (3 M, 1F), mean age  $64,2 \pm 10,7$  years, disease duration  $5,8 \pm 2,5$  years, treated with pramipexole (mean dose  $2,9 \pm 0,5$  mg), developed PG (mainly scratch cards). So pramipexole was discontinued and rotigotine was introduced in all patients (mean dose  $14 \pm 2,3$  mg).

Patients have been followed-up for at least one year (12–26 months) after the switch.

**Results:** Three out of four patients reported full remission of PG during the follow-up without developing other ICDs. No worsening in UPDRS motor score has been observed during the entire follow-up.

One out of four patient continued to have PG nevertheless the withdrawal of all dopaminergic medications, except levodopa, and the introduction of quetiapine (up to 300 mg per day). Adverse events: application site reactions occurred in two patients; only one patient discontinued the treatment.

**Discussion:** Rotigotine, as pramipexole and ropinirole, has a high affinity to D3 receptors, involved in reward processes, but differs from the other DA-agonists because of its longer half-life and more constant plasma levels. In our knowledge there are few papers reporting PD patients with ICDs related to rotigotine administration and they mostly show arising of ICDs in these patients.

Our case series is very limited, but it may suggest that the peculiar pharmacokinetic profile of rotigotine could lead to a differential risk of ICDs. Further and larger observations are requested to confirm our hypothesis.

## SC123

**Different perception and awareness of LID and other core symptoms of Parkinson's disease between parkinsonian patients and caregivers**

*Margherita Torti, F. Stocchi, P. Grassini, L. Vacca, S. Pinnola, M. Casali, F.G. Radicati*

IRCCS San Raffaele Pisana, Roma

**Introduction:** Approximately 5 years after starting levodopa therapy, about 40% of patients with Parkinson's disease can develop involuntary movements known as Levodopa induced dyskinesia (LID) and motor fluctuations.

**Objective:** The purpose of this study was to investigate the different perception and awareness of LID and other core symptoms of Parkinson's disease between patients and caregivers through the use of a newly developed questionnaire (PD-C SCL Parkinson's disease/Caregiver Symptoms check list).

The areas investigated were the following: speech problems, psychiatric symptoms (apathy, agitation/aggressive behaviour, gambling and other compulsive disorders), involuntary movements (trunk, limbs, head and face, freezing), off state, falls, attention or memory dysfunction, and tremor (head and face, upper and lower limbs).

**Methods:** The questionnaire was administered at 70 out-patients (42 male and 28 female, mean age: 65.3, mean disease duration: 10.4 years) and 70 caregivers by a trained neuropsychologist.

Patients and caregivers were interviewed separately to avoid any influence and interference between their opinion. Complete neurological assessment included: MOCA, UPDRS, H&Y.

**Results:** The preliminary data showed that among patients the symptoms more recognized and having a negative impact on their quality of life are freezing, off times, speech problems and limbs involuntary movements. Among caregivers the more disabling symptoms are limbs involuntary movements, off times and freezing, and trunk dyskinesia.

**Conclusions:** Parkinsonian patients tend not to be aware of LID or to underestimate their severity and their impact on activity of daily living while family members and caregivers frequently point at them as the main sign or the most bothersome among parkinsonian symptoms.

## SC124

**Valproic Acid for the treatment of aggressiveness and depression in Huntington disease: one year follow-up**

*Elisa Unti, S. Mazzucchi, C. Del Gamba, F. Vanelli, U. Bonuccelli, R. Ceravolo*

U.O. Neurologia, Dipartimento di Neuroscienze, Azienda Ospedaliero-Universitaria Pisana, Pisa

**Introduction:** Huntington disease (HD) is an autosomic dominant inherited disorder characterized by involuntary movements resulting from a continuous flow of random muscle contractions, progressive cognitive decline mainly in latest phase and psychiatric symptoms such as aggressiveness, and depression that represent one of the most disabling features of the disease. In most cases involuntary movements and psychiatric symptoms are controlled by antipsychotic drugs, but sometimes side effects as

parkinsonism or worsening of depression and apathy can reduce the therapeutic window of these drugs.

**Objective:** To evaluate the beneficial effect of Valproic Acid on psychiatric symptoms such as agitation and aggressiveness as well as depression in HD.

**Methods:** 10 symptomatic genetically confirmed HD patients (mean CAG repeat  $40 \pm 2$ ), mean disease duration ( $8 \pm 2$  years) on antipsychotics, all with aggressiveness defined as disabling by the patients along with the caregiver, were included in an open unblinded trial. Clinical evaluation including motor (Unified Huntington Disease Rating Scale), psychiatric (Neuro Psychiatric Inventory scale) and cognitive scale (Mini Mental Scale Evaluation) was performed at baseline and after 6 and 12 months of treatment with Valproic Acid (from 300 up to 1000 mg die).

**Results:** In our cases we reported a reduction of 10 points of NPI score in each patient one year after the introduction of Valproate without any side effect reported.

**Discussion:** The beneficial effect of Valproic Acid and its derivatives on aggressive patients is well documented in elderly aggressive patients and there are only two case reports that support this effect in such psychiatric disturbances in HD. This longitudinal study showed the beneficial effect and the safety of valproate for the treatment of aggressiveness in Huntington disease. Moreover, the successful use of Valproic acid in controlling aggressiveness allowed us not to increase the daily dose of neuroleptic, preventing motor and psychiatric side effects.

## SC125

**Early fluctuation in de-novo parkinsonian patients**

*Laura Vacca, P. Grassini, M. Torti, F.G. Radicati, S. Pinnola, M. Casali, F. Stocchi*

I.R.C.C.S. San Raffaele Pisana, Roma

**Introduction:** Motor complications are a limiting factor in treatment of Parkinson's disease. Recent evidence showed that even patients in the honeymoon phase of drug treatment may have early fluctuations in their response to dopaminergic therapy.

**Objectives:** This protocol has been designed to evaluate the presence of pre-clinic motor fluctuations, as fluctuations of motor ability not detected yet by patient but already present even in the earlier phases of the disease.

**Methods:** 10 de novo parkinsonian patients entered the study and were evaluated for eight consecutive hours in three separate assessment. A staging of Parkinson's disease through Hoehn & Yahr was performed as well as the UPDRS pars I-II-III. The more affected side was identified by medical history and by examination in all subjects. The presence of early fluctuations was measured by tapping and screw test scores. Tapping rate was the number of times that a patient could alternately tap two counters 20 cm apart in 30 seconds. SCREW was assessed by the time taken to tighten by hand a 6-centimeter screw bolt. Tapping rates and screw test scores were evaluated before administration and every 20 minutes for eight hours after administration of levodopa: Day 1 (basal): screw test and tapping every 20 minutes after administration of 10 mg of domperidone. Day 2 (week 1): screw test and tapping every 20 minutes after administration of 1 tablet of domperidone and 1 tablet of Sinemet 100 + 25. Day 3 (week 3): screw e tapping every 20 minutes after administration of 1a mg of domperidone and Sinemet 200 + 50. Plasma levodopa concentration (ug/ml) were measured at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0.

**Results and conclusions:** Statistical analysis of data showed a significant fluctuation of motor performance even at the earlier stage of disease.

## SC126

### **Anodal transcranial direct current stimulation (TDCS) applied to the motor cortex ameliorates freezing of gait in patients affected by Parkinson's disease**

*Francesca Valentino*<sup>1</sup>, *N.G. Pozzi*<sup>2,3</sup>, *G. Cosentino*<sup>1</sup>, *F. Brighina*<sup>1</sup>, *B. Minafra*<sup>2,3</sup>, *M. Fresia*<sup>4</sup>, *I. Bertaina*<sup>2,3</sup>, *F. Faulisi*<sup>1</sup>, *G. Sandrini*<sup>5,6</sup>, *B. Fierro*<sup>1</sup>, *A. Priori*<sup>7,8,9</sup>, *G. Savettieri*<sup>1</sup>, *M. D'Amelio*<sup>1</sup>, *C. Pacchetti*<sup>2,3</sup>

<sup>1</sup>Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Sezione di Neurologia, Università degli Studi di Palermo, Palermo

<sup>2</sup>Parkinson's Disease and Movement Disorders Unit, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>3</sup>Interdepartmental Research Center for Neurodegenerative Disease, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>4</sup>Department of Neurophysiology, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>5</sup>Unit of Neurorehabilitation, National Institute of Neurology Foundation "C. Mondino", Pavia

<sup>6</sup>Department of Public Health and Neurosciences, University of Pavia, Pavia

<sup>7</sup>Unità Operativa di Neurologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano

<sup>8</sup>Centro Clinico per la Neurostimolazione, le Neurotecnologie ed i Disturbi del Movimento, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano

<sup>9</sup>Dipartimento di Scienze Neurologiche, Università degli Studi di Milano, Milano

**Background:** Progression of Parkinson's disease (PD) is frequently characterized by the occurrence of freezing of gait (FOG), which generally does not improve with dopaminergic therapy and with current available surgical therapies. Recent evidences show that motor symptoms may be ameliorated by means of non-invasive brain stimulation techniques in PD (transcranial current direct stimulation, TDCS; repetitive transcranial magnetic stimulation, RTMS).

**Objective:** To investigate the efficacy of anodal TDCS in the treatment of FOG in PD. Excitatory anodal tDCS was applied unilaterally to the motor and premotor cortices contralateral to the most affected leg.

**Methods:** Randomized, double-blind, sham-controlled study. TDCS was applied consecutively for 5 days to 10 patients who were randomly assigned to anodal or sham TDCS. Efficacy of the interventions was investigated after the 1st, the 5th stimulation, 1 week, 2 weeks and 1 month after the start of the trial. Clinical assessment was performed by Stand Walk Sit test (SWS), UPDRS, Freezing of Gait Questionnaire (FOG-Q), Gait and Falls Questionnaire (GFQ), and the Parkinson's Disease Questionnaire (PDQ-39). 5 patients also underwent gait analysis. All patients received stimulation when "on" medication.

**Results:** Anodal TDCS compared to the sham significantly improved gait and FOG starting from the first stimulation. The effect was evident up to 1 month from the first treatment.

**Conclusion:** Anodal TDCS of the motor and premotor cortex is safe and it may have therapeutic potential for FOG in patients with PD. TDCS might determine release of dopamine in the caudate and putamen. Alternatively excitation of the less active motor cortex may restore an inter-hemispheric balance, as it has been recently hypothesized as possible mechanism at the origin of FOG.

## SC127

### **A 43-year-old man with hemiparkinsonism, moderate cerebral asymmetry and normal echogenicity of the substantia nigra: a case of hemiparkinsonism-hemiatrophy syndrome?**

*Emilio Vecchio*<sup>1</sup>, *M. Proaspatu*<sup>2</sup>, *M.V. Calloni*<sup>1</sup>, *A. Giorgetti*<sup>1</sup>, *M.C. Guaita*<sup>1</sup>, *P. Perrone*<sup>1</sup>, *L. Politini*<sup>1</sup>, *P. Secchi*<sup>1</sup>

<sup>1</sup>U.O. Neurologia, A.O. Ospedale Civile di Legnano, Legnano (Milano)

<sup>2</sup>S.C. a D.U. di Radiologia, Azienda Ospedaliero-Universitaria "Maggiore della Carità" di Novara, Novara

A 43-year-old man was evaluated for a slowly progressive left hemiparkinsonism. He referred moderate bradykinesia and tremor at the left upper limb of 3-year duration. His family history was negative for neurologic disorders; there was no mention of perinatal damage, delayed motor milestones, substance abuse.

On neurological examination there are mild hemifacial asymmetry, slowness of hand-grip on the left, evidence of cogwheel rigidity of the left upper limb and tremor of the hand. The swinging of the left arm was reduced, with a slight dystonic posture of the hand. A mild increase of the deep tendon reflexes was detected on the left leg. Plantar reflexes were downward bilaterally. There was no evidence of other body asymmetries, skeletal deformities, abnormal extraocular motility, postural instability or cerebellar dysfunction.

Blood analysis and neurophysiological tests (EEG, EMG, motor and somatosensory evoked potentials, BAEPs) were normal. Brain MRI demonstrated moderate skull asymmetry and a dilatation of left ventricle. SPECT study with DaTSCAN revealed decreased bilateral striatal transporter binding. A transcranial sonographic evaluation of the mesencephalon was performed, with normal findings (no hyperechogenicity) of the substantia nigra. The patient was started on pramipexole, which was discontinued due to significant side effects; therapy with rotigotine was well tolerated, with some motor improvement.

In this young patient, the presence of a strictly lateralized hemiparkinsonism with dystonic posture of the hand, raised the suspicion of a hemiparkinsonism-hemiatrophy syndrome (HPHA). HPHA syndrome, described by Klawans in 1981, is a relatively rare form of parkinsonism characterized by atrophy on one side of the body, but not necessarily noticed by the patient, and young onset of hemiparkinsonism on the side of hemiatrophy, unilateral and stable for many years. Dystonia is a common neurologic feature observed initially on the side of HPHA. As in other reported cases, our patient presented abnormal SPECT, mild asymmetry of the brain MRI and slight body asymmetry.

The ultrasound normality of the substantia nigra virtually ruled out a form of idiopathic Parkinson's disease, rather supporting the diagnostic hypothesis of a form of parkinsonism: the HPHA syndrome was considered secondary to a primary damage of the striatal structures, possibly perinatal, without involvement of the substantia nigra.

## SC128

**Hearing impairment in Parkinson's disease: expanding the non-motor phenotype**

*Carmine Vitale*<sup>1,2</sup>, *V. Marcelli*<sup>3</sup>, *R. Allocca*<sup>3</sup>, *G. Santangelo*<sup>2,4</sup>, *P. Riccardi*<sup>3</sup>, *R. Erro*<sup>5</sup>, *M. Amboni*<sup>1,2</sup>, *M.T. Pellecchia*<sup>5</sup>, *A. Cozzolino*<sup>5,6</sup>, *K. Longo*<sup>2,5</sup>, *M. Picillo*<sup>5</sup>, *M. Moccia*<sup>5</sup>, *V. Agosti*<sup>1,2</sup>, *G. Sorrentino*<sup>1,2</sup>, *M. Cavaliere*<sup>7</sup>, *E. Marciano*<sup>3</sup>, *P. Barone*<sup>2,6</sup>

<sup>1</sup>University of Naples "Parthenope", Naples

<sup>2</sup>IDC, Hermitage Capodimonte, Naples

<sup>3</sup>Audiology and Vestibology Unit, Department of Neuroscience, University of Naples "Federico II", Naples

<sup>4</sup>Department of Psychology, Second University of Naples, Caserta

<sup>5</sup>Department of Neurological Sciences, University of Naples "Federico II", Naples

<sup>6</sup>Neurodegenerative Diseases Center, University of Salerno, Salerno

<sup>7</sup>Department of Otolaryngology, University of Naples "Federico II", Naples

**Objective:** To evaluate hearing impairment in patients affected by Parkinson's disease as compared with hearing scores observed in normal age and sex matched controls.

**Methods:** 118 consecutive patients with clinical diagnosis of Parkinson's disease were screened. Severity of motor symptoms and staging were measured with the Unified Parkinson's Disease Rating Scale (section III) and the Hoehn and Yahr scale.

Audiometric evaluation consisted of a comprehensive audiologic case history and questionnaire, visual otoscopic examination, acoustic immittance measures (tympanogram and acoustic reflexes), pure tone audiometry and measurement of brainstem auditory evoked potentials. Healthy age- and sex-matched subjects were selected as control group.

**Results:** 106/118 patients were enrolled. Pure tone audiometry revealed age-dependent high-frequency hearing loss in patients with Parkinson's disease as compared with both normative values and healthy age- and sex-matched controls (75/106, 71%;  $\chi^2 = 5.959$ ;  $p = 0.02$  and 92/106 (86.8%) vs 60/106 (56.6%);  $\chi^2 = 23.804$ ;  $p < 0.001$ , respectively). Pure tone audiometry scores correlated with Hoehn and Yahr scale scores ( $p < 0.05$ ). Brainstem auditory evoked potentials were normal in all patients.

**Conclusion:** Our patients with Parkinson's disease showed age-dependent peripheral, unilateral or bilateral hearing impairment. Whether these auditory deficits are intrinsic to Parkinson's disease or secondary to a more complex impaired processing of sensorial inputs occurring over the course of illness remains to be determined. Because  $\alpha$ -synuclein is located predominately in the efferent neuronal system within the inner ear, it could affect susceptibility to noise-induced hearing loss or presbycusis. It is feasible that the natural aging process combined with neurodegenerative changes intrinsic to Parkinson's disease might interfere with cochlear transduction mechanisms thus anticipating presbycusis.

## SC129

**Subjective sleep problems and daytime sleepiness in advanced Parkinson Disease: effects of intraduodenal levodopa gel infusion and deep brain stimulation**

*Maurizio Zibetti*, *C.A. Artusi*, *A. Merola*, *S. Angrisano*, *L. Rizzi*, *E. Montanaro*, *M.G. Rizzone*, *L. Lopiano*

Dipartimento di Neuroscienze, Università di Torino, Torino

**Objective:** To analyze the impact of continuous intraduodenal L-dopa/carbidopa gel infusion (LCGI) and deep brain stimulation

(DBS) on subjective sleep problems and daytime sleepiness in advanced Parkinson's disease (PD) patients.

**Background:** Sleep problems are common in PD patients and especially so with disease progression. In advanced PD, nocturnal akinesia, restless leg syndrome and REM sleep behavior disorder are frequent and often coexist with daytime sleepiness. Both LCGI and DBS greatly improve motor complications in advanced PD patients. Relatively few studies examined the impact of DBS on sleep and only preliminary data are available for LCGI.

**Materials and methods:** We prospectively assessed a total of 42 PD patients, 20 on LCGI and 22 undergoing DBS. The PD Sleep Scale-version 2 (PDSS-2) was used to assess sleep problems and the Epworth Sleepiness Scale (ESS) to evaluate daytime sleepiness. Motor symptoms, activities of daily living and motor complications were assessed with the Unified PD rating Scale (UPDRS) section II, III and IV. Evaluations took place at baseline and 6-9 months after the procedures.

**Results:** Subjective sleep problems improved substantially with both DBS and LCGI procedures compared to previous oral polytherapy. Analyses of PDSS-2 subdomains showed a significant reduction of nocturnal akinesia only for patients treated with DBS. Measures of daytime sleepiness improved with LCGI and did not vary significantly after DBS.

**Conclusion:** Subjective measures of sleep improve substantially with LCGI and DBS in advanced PD patients. Objective polysomnographic recordings are needed in order to characterize the underlying mechanisms.

## SC130

**Neuroprotective role of pargyline on energy metabolism in MPTP model of Parkinson's disease in freely moving rats**

*Manuel Zinellu*, *G. Bazzu*, *R. Migheli*, *G. Rocchitta*, *P.A. Serra*

Dept. of Clinical and Experimental Medicine, Section of Pharmacology, University of Sassari, Sassari

Mitochondrial dysfunction and oxidative stress are thought to be crucial in the dopaminergic neuronal death in Parkinson's disease. The neurotoxin MPTP, widely used as *in vivo* model of Parkinson's disease. MPTP, activated by astrocytes MAO-B, induce neurodegeneration and energy metabolism alteration of dopaminergic neurons of *substantia nigra pars compacta*.

Therefore, we deemed of interest the study of neuroprotective role of pargyline on dopamine and energy metabolism in MPTP-induced parkinsonism. This study was carried out by an innovative microdialysis approach for the simultaneous monitoring of striatal dopamine (DA) and energy substrates in freely moving animals using asymmetric perfusion flow rates on a dual microdialysis probe. Adult male Wistar rats (280-330 g) were used in this study. The probe was stereotaxically implanted in the right striatum of rats. Systemic MPTP was administered for three consecutive days as follows: 25 mg/Kg (day 1), 15 mg/Kg (day 2) and 10 mg/Kg (day 3). Pargyline (15 mg/Kg/day i.p. for 3 days) was intraperitoneally administered 40 minutes prior the MPTP dose to a second group of animals. Striatal levels of catecholamines were quantified by means of HPLC-EC. Glucose, lactate, pyruvate and L/P ratio were spectrophotometrically evaluated (CMA Iscus Analyzer).

The first dose of MPTP induced an increase in dopamine levels in both groups while the second and third doses reduced striatal DA only in animals without pargyline pre-treatment. Furthermore, animals treated only with MPTP showed a progressive decrease in glucose and pyruvate levels, and an increase in striatal lactate and of L/P ratio. Pargyline pre-treatment reduced glucose and pyruvate loss as well as lactate and L/P ratio increase in the rat striatum.

These *in vivo* results showed MPTP-related mitochondrial dysfunction with consequent loss of DA and energy impairment. They also suggest pargyline neuroprotective effects preventing bioactivation of MPTP and preserving neuronal dopamine and energy metabolism.

## Author Index

Abate, T	SC2	Bandettini di Poggio, M	SC10, SC78
Abbruzzese, G	SC5, SC7, SC10, SC12, SC16, SC28, SC90, SC114, SC115	Barbic, F	SC23
Acler, M	SC119	Barbuto, M	SC11
Agnetti, V	SC32, SC68, SC85	Barone, P	L16, SC2, SC5, SC10, SC12, SC40, SC41, SC48, SC60, SC72, SC86, SC105, SC128
Agosti, V	SC2, SC40, SC128	Baroni, C	SC4
Agostoni, E	SC97, SC98	Barros, J	SC80
Aiello, E	SC32	Bartalucci, M	SC52
Albanese, A	SC1, SC3, SC39	Bartolo, M	SC30
Albani, G	SC1	Barzaghi, C	SC39
Alberio, T	SC44	Bazzu, G	SC130
Albertini, G	SC33	Bellavia, G	SC38
Alfonsi, E	C25, SC30	Bellinzona, E	SC93
Allena, M	SC30, SC34	Bempensanti, MG	SC4
Allocca, R	SC2, SC128	Bendinelli, M	SC4
Allocca, S	SC27	Bentivoglio, AR	C22, SC37, SC94
Almonti, S	SC95	Benuzzi, F	SC49
Alvau, MD	SC100	Berardelli, A	L21, SC18, SC47, SC66, SC99
Amami, P	SC3	Berlangieri, M	SC34
Amboni, M	L8, SC2, SC12, SC41, SC86, SC128	Bernardi, A	SC122
Ammannati, F	SC91	Bernardi, E	SC13
Andretto, F	SC4	Berret, B	SC16
Angelini, M	SC77	Bertaina, I	SC14, SC34, SC71, SC88, SC126
Angileri, G	SC112	Berti, C	SC9
Angrisano, MG	SC105	Bertolasi, L	SC48, SC63, SC119, SC120
Angrisano, S	SC69, SC129	Bertotti, G	SC51
Annunziato, L	SC31	Bestavashvili, L	SC15
Antonello, P	SC4	Bet, L	SC82
Antonini, A	L6, SC5, SC12, SC17, SC64	Bhatia, K	SC87
Antonutti, L	SC70	Bisio, A	SC16
Ardolino, G	SC26, SC48, SC63	Biundo, R	C20, SC17
Arnaldi, D	SC71	Bloise, MC	SC18
Artusi, CA	SC6, SC69, SC96, SC129	Bolla, M	SC30, SC34
Attanasio, T	SC113	Bonanni, L	L9
Attar, M	SC5, SC12	Bonetto, N	SC45
Avanzino, L	SC7, SC16, SC90, SC115	Bono, PS	SC91
Avarello, TP	SC8	Bonomi, M	SC4
Azevedo, L	SC80	Bonuccelli, U	L17, SC9, SC10, SC35, SC67, SC79, SC84, SC101, SC124
Azzolini, J	SC39	Borelli, P	SC10
Bacci, D	SC91	Borghero, G	SC24
Baccini, M	C34	Bove, F	SC37
Bagella, CF	SC39	Bove, M	SC7, SC16
Baldacci, F	SC9	Boveri, N	SC51
Ballestriero, R	SC62	Bovi, T	SC60
		Bozzali, M	SC21
		Bragadin, LM	SC62
		Brandimarti, A	SC83
		Brighina, F	SC126
		Brotini, S	SC19
		Brugnoli, G	SC57
		Brunelli, P	SC4

Brunetti, A	SC20	Cirillo, M	SC56
Bruno, E	SC76	Clemenzi, I	SC15
Brusa, L	SC21, SC113	Cocco, A	SC81
Busan, P	SC70	Cocito, D	SC6
Buttini, S	SC93	Codazzi, V	SC54
Cacciatore, FM	SC22	Codeluppi, L	SC25, SC49
Cagnin, A	SC45	Cogiamanian, F	SC26, SC48, SC63
Calabresi, P	L4	Colao, A	SC103
Calandra-Buonauro, G	C2	Colombo, D	SC5, SC12
Calandrella, D	SC64	Colosimo, C	C14, SC66
Calia, G	SC107	Comani, S	L9
Calloni, MV	SC127	Comi, C	SC44, SC51, SC93
Calzetti, S	SC77	Conforti, R	SC31
Campagnoli, P	SC64	Contardi, S	SC25, SC49
Canesi, M	SC23, SC102, SC114	Conte, A	SC47, SC99
Cannas, A	SC24, SC29, SC81, SC110	Contini, E	SC89
Cantello, R	SC93	Contrafatto, D	SC76
Carboni, T	SC83	Contu, P	SC10
Carecchio, M	SC39	Coppola, A	SC59
Caremani, L	SC91	Corbo, D	SC56
Carlucci, S	SC4	Cordano, C	SC28
Carnicella, F	SC36	Corona, M	SC110
Carpentras, G	SC85	Corsi, FM	SC75
Carrabba, G	SC26	Corsini, GU	SC106
Carrozzo, R	SC80	Cortelli, P	C1, SC114
Casali, M	SC50, SC58, SC123, SC125	Cosentino, G	SC126
Cascio, E	SC62	Cosentino, M	SC28
Casetta, I	SC13, SC57	Cossu, G	SC10
Castana, L	SC97	Costa, N	SC34
Castiglioni, D	SC50	Costantino, E	SC24, SC29, SC81, SC110
Catalan, M	SC70	Cozzolino, A	SC2, SC128
Cavaliere, M	SC2, SC128	Cozzolino, V	SC75
Cavallieri, F	SC25, SC49	Cristina, S	SC34
Cecchetto, S	C32	D'Amelio, M	SC38, SC126
Cecconi, D	SC44	D'Andreamatteo, G	SC83
Cellotto, N	SC78	Dal Fante, M	SC64
Cenzi, D	SC60	De Angelis, MV	SC33
Cerasa, A	SC38	De Icco, R	SC30, SC34
Cerasari, G	SC75	De Mari, M	SC36
Ceravolo, MG	C7	De Micco, R	SC27, SC31, SC56, SC117
Ceravolo, R	L3, SC10, SC35, SC67, SC79, SC84, SC101, SC114, SC124	De Michele, G	L11, SC103
Ceriani, E	SC4	De Natale, ER	SC32, SC68, SC85
Cerri, G	SC23	De Pandis, MF	SC33, SC53, SC104, SC114
Cesnik, E	SC13, SC57	De Paoli, I	SC30, SC34
Chelazzi, L	SC120	De Simone, M	SC22
Chiari, L	SC25	De Stefano, G	SC72
Cilia, R	SC102	Dedola, S	SC43
Ciocca, M	SC26, SC48	Defazio, G	L7, SC7, SC47
Cipresso, P	SC1	Dekker, I	SC3
Cipriani, AM	SC95	Del Caro, A	SC43
Ciranni, AM	SC111	Del Dotto, P	C24, SC9
Cirillo, G	SC27, SC56, SC117	Del Gamba, C	SC35, SC67, SC124
		Del Prete, E	SC35

Dell'Aquila, C	SC36	Fontana, D	C25
Deluca, LV	SC100	Forapani, E	SC98
Deriu, F	SC32, SC85, SC87	Formento-Dojot, P	SC17
Di Gesaro, L	SC38	Fossati, C	SC50
Di Giacomo, R	SC37	Fraix, V	SC120
Di Maio, L	SC103	Franceschini, M	SC53, SC104
Di Matteo, A	SC60	Franciotti, R	L9
Di Stasio, F	SC66	Franzini, A	SC1
Dibilio, V	SC38, SC76	Frazzitta, G	SC51, SC61, SC93
Dubbioso, R	SC42	Freddi, N	SC46
Ebreo, M	SC11	Fresia, M	SC34, SC88, SC126
Edwards, MJ	SC87	Frosini, D	L10, SC10, SC35, SC67, SC84, SC101
Egidi, M	SC121	Fumagalli, M	SC63
Elia, AE	SC39	Furlan, R	SC23
Ermani, M	SC45	Furlanetto, M	SC92
Erminio, C	SC98	Galistu, P	SC85
Ernesto, M	SC118	Gallerini, S	SC52
Errico, D	SC40, SC105	Galli, M	SC33, SC53, SC104
Erro, R	SC2, SC41, SC86, SC128	Garavaglia, B	SC39, SC79
Esposito, F	SC31, SC56	Garribba, E	SC100
Esposito, M	SC42, SC59	Gasparro, AM	SC8
Fabbrini, G	L18, C31, SC18, SC47, SC66, SC99, SC114	Gastaldo, E	C18
Facchini, S	SC17	Gennuso, M	SC54
Fadda, F	SC29	Genovesi, D	SC101
Fadda, L	SC81	Gerace, C	SC75
Falasca, NW	L9	Ghirardi, S	SC54
Falomi, B	SC4	Giannicola, G	SC55
Fanini, M	SC91	Gioia, MC	SC38
Farina, D	SC43	Giordano, A	SC27, SC31, SC56, SC117
Fasano, A	L15, SC14, SC60, SC94	Giordano, F	SC72
Fasano, M	SC44	Giorgetti, A	SC127
Faulisi, F	SC126	Giovanditti, L	SC52
Fava, C	SC4	Girlanda, P	SC11, SC111, SC116
Favaretto, S	SC45	Girrotti, F	SC92
Fazio, P	SC57	Giunti, G	SC84
Ferigo, L	SC46	Giuntini, M	SC9, SC67
Ferracuti, S	C15	Gnoato, F	SC45
Ferrante, E	SC98	Gobbato, R	SC83
Ferrarese, C	SC98	Gobbi, B	C3
Ferrazzano, G	SC47	Goldoni, M	SC77
Ferré, F	SC3	Gorian, A	SC70
Ferrucci, R	SC48, SC63	Govoni, V	SC57
Fiaschi, A	SC60, SC120	Granieri, E	SC13, SC57
Fierro, B	SC126	Granieri, G	SC13, SC57
Filidei, E	SC101	Grassini, P	SC50, SC58, SC123, SC125
Filla, A	C28, SC103	Graziosi, A	SC11
Finazzi Agrò, E	SC113	Grazzi, G	SC13
Fioravanti, V	SC25, SC49	Groppo, E	SC13, SC57
Fiorillo, C	C30	Grossi, D	SC40
Fiorio, M	SC120	Guaita, MC	SC127
Floris, G	SC24	Guzzon, S	SC46
Foncke, EMJ	SC3	Iani, C	SC21, SC113

Iannacone, C	SC114	Marchesi, E	SC77
Ibba, FC	SC110	Marciano, E	SC2, SC128
Improta, I	SC40, SC72	Marconi, R	SC52
Inguaggiato, EF	C30	Marin, D	SC62
Inversi, F	SC36	Marini, A	SC118
Iodice, R	SC59	Marinò, C	SC42
Ioni, MF	SC15	Marino, F	SC28
Ippolito, S	SC15	Marrosu, F	SC24, SC29, SC81, SC110
Jelcic, N	SC45	Marrosu, MG	SC24, SC110
Juergenson, I	SC60	Marsili, L	SC66
Khandker, P	SC66	Martinelli, P	C5
Kiferle, L	SC79	Martino, D	SC7
Koch, G	SC21	Martino, I	SC7
Krack, P	SC120	Mascalchi, M	C29
La Bua, V	SC8	Masci, MM	SC29
Lanfranchi, S	SC61	Mascia, MM	SC81
Lanni, D	SC20	Masi, G	SC36
Lanotte, M	SC69, SC96	Massarelli, M	SC103
Latorre, A	SC18, SC66	Mastronardi, R	SC36
Le Bas, JF	SC120	Mastropasqua, C	SC21
Le Pera, D	SC104	Mauro, A	SC1
Le Pira, F	SC38	Mazza, S	SC53
Lena, F	SC94	Mazzeo, MR	SC122
Leodori, G	SC47, SC99	Mazzoni, G	SC13
Li Voti, P	SC99	Mazzucchi, S	SC67, SC124
Liboni, W	SC114	Melis, M	SC10
Ligabò, M	SC4	Melis, R	SC29
Liguori, S	SC56	Mellone, S	SC25
Ling, H	L22	Meloni, M	SC68, SC85
Lo Russo, G	SC97	Melotti, L	SC4
Locatelli, M	SC26	Menicchetti, C	SC101
Logi, C	SC9	Menini, S	SC4
Lombino, FL	SC93	Meoni, S	SC91
Longo, K	SC2, SC41, SC86, SC128	Mereu, A	SC10
Lopiano, L	C11, SC6, SC10, SC44, SC69, SC96, SC97, SC129	Merola, A	SC6, SC10, SC69, SC96, SC129
Luca, A	SC76	Meschini, MC	SC80
Lucetti, C	SC9	Mezzarobba, S	C35, SC62, SC70
Maci, T	SC38	Migheli, R	SC43, SC107, SC130
Maestri, R	SC51, SC61, SC93	Minafra, B	SC14, SC71, SC88, SC126
Maieron, M	SC62	Moccia, M	SC2, SC41, SC72, SC73, SC86, SC128
Mameli, F	SC63	Modugno, N	C17, C18, SC20, SC94
Manca, D	SC10	Monge, A	SC121
Manca, M	SC13	Montagnana, B	SC4
Mancini, F	C16, C18, SC64	Montanaro, E	SC96, SC129
Manfredi, L	SC64	Montemezzi, S	SC60
Manganelli, F	SC10, SC42	Moretti, B	SC83
Manni, R	SC71	Moretti, DV	SC74
Mannino, M	SC8	Morgante, F	SC11, SC111, SC116
Marano, P	SC65, SC108	Morgante, L	C10, SC11
Marceglia, S	SC55	Moroni, F	SC23, SC102
Marcelli, V	SC2, SC128	Moschella, V	SC75
Marchese, R	L12, SC10, SC28, SC90	Mostile, G	SC76

Musumeci, O	SC111	Pierantozzi, M	SC112
Nagliati, C	SC57	Pieri, S	SC52
Nappi, G	SC30	Pignataro, G	SC31
Nardella, A	SC99	Pignatelli, S	SC42
Negrotti, A	SC77	Pilleri, M	C21, SC17
Nesti, C	SC78, SC80	Pilurzi, G	SC87
Nicardi, P	SC54	Pinnola, S	SC50, SC58, SC123, SC125
Nichelli, P	SC25, SC49	Pippione, AC	SC44
Nicoletti, A	C27, SC38, SC76	Pirisinu, M	SC43
Nicoletti, V	SC10, SC35, SC79	Pisciotta, C	SC42
Nogueira, C	SC80	Pizzolato, G	SC70
Ogliastro, C	SC90	Plewnia, K	SC52
Olgiate, S	SC44	Poletti, M	SC84
Olivola, E	SC112	Politini, L	SC127
Onofrj, M	L9	Polito, C	SC91
Orofino, G	SC24, SC81, SC110	Polizzi, L	SC81
Pacchetti, C	L5, SC14, SC30, SC34, SC71, SC88, SC114, SC126	Pollak, P	SC120
Paccone, A	SC31	Polo, A	SC46
Pacei, F	SC82	Ponzo, V	SC21
Paci, C	SC83	Porcheddu, A	SC100
Padovani, A	SC48	Porta, A	SC23
Pagni, C	SC84	Porta, M	SC55
Palmerini, L	SC25	Pozzi, NG	SC14, SC30, SC71, SC88, SC126
Panico, F	SC4	Pozzo, T	SC16
Panzeri, M	SC48	Pramstaller, P	C23
Pappatà, S	SC41	Preda, F	SC89
Paradiso, M	SC121	Prelle, A	SC54
Paribello, A	SC10	Priori, A	SC26, SC48, SC55, SC63, SC126
Parodi, B	SC28	Proaspatu, M	SC127
Pascucci, T	SC112	Puddu, R	SC24
Pastore, MC	SC122	Quaranta, D	SC37
Patrocinio, D	SC22	Quartarone, A	SC116
Pau, R	SC29	Quatrala, R	SC89
Paulus, KS	SC32, SC68, SC85	Quattrone, A	SC38
Paviotti, L	SC62	Raciti, L	SC76
Pecchioli, G	SC91	Radicati, FG	SC50, SC58, SC123, SC125
Pedroli, E	SC1	Raffo De Ferrari, A	SC90
Pellecchia, MT	C6, SC2, SC41, SC86, SC128	Raffo, A	SC16
Pellegrini, L	C33, SC70	Raglione, LM	SC91
Pelliccioni, G	C3	Ramat, Silvia	C4, SC91
Pelosin, E	C9, SC7, SC90, SC115	Ramat, Stefano	C4
Perini, M	SC51, SC61, SC93	Raoli, V	SC48
Perrone, P	SC127	Ravidà, L	SC65
Petrozzi, L	SC79	Reale, C	SC79
Petta, F	SC113	Reali, E	SC23, SC102
Pezzoli, G	SC23, SC51, SC102, SC114	Realmuto, S	SC38
Piacentini, S	L13, SC3	Recchia, S	SC4
Picazio, S	SC21	Redaelli, V	SC92
Piccininni, C	SC37	Riboldazzi, G	SC51, SC61, SC93
Pichiecchio, A	SC30	Riccardi, P	SC128
Picillo, M	SC2, SC10, SC41, SC86, SC105, SC128	Ricci, R	SC15
		Ricciardi, L	SC11, SC94, SC116
		Rinaldi, C	SC103

Rinalduzzi, S	SC95	Schenone, A	SC28, SC78
Rispo, A	SC72	Schmitt, E	SC120
Risso, P	SC26	Sciacca, G	SC76
Riva, G	SC1	Secchi, O	SC100, SC107
Rizzi, L	SC69, SC96, SC129	Secchi, P	SC127
Rizzo, V	SC116	Seminara, M	SC65, SC108
Rizzone, MG	C13, SC6, SC69, SC96, SC97, SC98, SC129	Semprini, R	SC109
Roccatagliata, DV	SC97, SC98	Sensi, M	SC89
Rocchi, L	SC99	Serlenga, L	SC22
Rocchitta, G	SC43, SC100, SC107, SC130	Serra, PA	SC43, SC100, SC107, SC130
Romeo, S	SC111	Serusi, M	SC85
Romito, L	SC1, SC3, SC82	Servello, D	SC14, SC55
Ronconi, L	SC48	Sgubin, G	SC70
Rosa, M	SC55	Simioni, V	SC57
Rossetto, S	SC46	Sobrini, S	SC83
Rossi, C	SC4, SC101	Solla, P	SC24, SC29, SC81, SC110
Rossi, F	SC103	Sorbera, C	SC11, SC111
Rothwell, JC	SC87	Sorbi, S	SC91
Roversi, G	SC89	Sorrentino, G	SC2, SC40, SC128
Rovescala, R	SC51	Sotgiu, G	SC32
Ruggieri, S	SC20	Sova, I	SC104
Rusconi, ML	SC23, SC102	Spissu, Y	SC43
Russo, A	SC56	Squintani, G	SC60
Russo, CV	SC103	Stampanoni Bassi, M	SC112
Russo, T	SC72	Stanzione, P	C26, SC21, SC112, SC113
Sá, MJ	SC80	Stefani, A	SC21, SC112
Sabbatini, D	C3	Stocchi, F	L19, C12, SC5, SC12, SC33, SC50, SC53, SC58, SC104, SC114, SC123, SC125
Sacchetti, M	SC4		
Saifee, TA	SC87	Strafella, G	SC36
Sala, F	SC120	Stuppiello, M	SC36
Sale, P	SC53, SC104	Suppa, A	L1, SC66
Sallustio, V	SC22	Tamburini, T	SC115
Salsone, M	SC38	Tassorelli, C	C8, SC30, SC34
Salvato, L	SC61	Tedeschi, G	SC27, SC31, SC56, SC117
Salvatore, E	SC103	Terranova, C	SC116
Sandrini, G	SC30, SC34, SC88, SC126	Terruso, V	SC8
Sanfilippo, C	SC38	Terzaghi, M	SC71
Sanguigni, S	SC83	Tessitore, A	L2, SC27, SC31, SC56, SC117
Sanna, D	SC100	Theeuwes, J	SC120
Santangelo, G	C19, SC2, SC40, SC41, SC72, SC105, SC128	Thomas, A	L9
Santorelli, FM	C30, SC78, SC80	Tiburzi, M	SC118, SC121
Santoro, L	SC10, SC42, SC59	Tinazzi, M	L14, SC60
Sarchioto, M	SC18	Tirinelli, F	SC118, SC121
Saveriano, F	SC36	Tocco, P	SC119
Savettieri, G	SC38, SC126	Tognoni, G	SC84
Scarpello, R	SC122	Tola, MR	SC89
Scarpini, C	SC52	Tolu, E	SC32
Scarpino, O	C3	Tomasini, E	SC63
Scarselli, M	SC106	Tomelleri, S	SC4
Scelzo, E	SC63	Tommasi, G	SC120
Schembri, L	SC28	Tondinelli, ME	SC118, SC121
		Toni, V	SC122

Torti, M	SC50, SC58, SC123, SC125	Vecchio, E	SC127
Tortora, R	SC72	Veneziano, G	SC61
Toscano, A	SC111	Vergallo, A	SC9
Trevisani, L	SC89	Vigna, C	SC1
Troiano, M	SC6	Vilarinho, L	SC80
Trojano, L	SC40, SC105	Vimercati, S	SC33, SC53
Truffelli, R	SC78	Viselli, F	SC118, SC121
Tucci, T	SC103	Vita, G	SC111
Turla, M	SC51	Vitale, C	L16, SC2, SC40, SC41, SC72, SC105, SC128
Turri, M	SC119	Volpe, E	SC15
Uccelli, A	SC28	Volterrani, D	SC101
Uccellini, D	SC51, SC93	Weis, L	SC17
Uliari, S	SC13	Wenning, GK	L23
Ulivì, M	SC9	Yelnik, J	SC120
Unti, E	SC124	Zangaglia, R	SC14, SC30, SC71
Urbano, V	SC83	Zappia, M	SC38, SC76, SC114
Vacca, L	SC50, SC58, SC123, SC125	Zarantonello, G	SC45
Vacca, M	SC29	Zarcone, D	SC61
Valente, EM	L20	Zarino, B	SC26
Valentini, LG	SC92	Zibetti, M	C10, C12, SC6, SC10, SC44, SC69, SC96, SC129
Valentino, F	SC126	Zinellu, M	SC130
Valzania, F	SC25, SC49	Zuccarino, R	SC78
Vanacore, N	SC118		
Vanelli, F	SC124		
Vattemi, G	SC60		

---