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Substantia nigra hyperechogenicity in essential tremor and Parkinson disease: a longitudinal study

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ABSTRACT

Introduction. Essential Tremor (ET) and Parkinson's disease (PD) sometimes overlap in their clinical expression with ET preceding PD onset, leading often to misdiagnosis. Transcranial Sonography (TCS) has been shown as valid and non-invasive diagnostic tool to identify early idiopathic PD and to differentiate it from ET. The purpose of this study was to investigate the relevance of hyperechogenicity of Substantia Nigra (SN+) in ET patients.

Methods. 138 patients (79 PD, 59 ET) and 50 matched controls underwent TCS examination at baseline. All patients were followed in a three years longitudinal assessment.

Results. 10 subjects were excluded from the analysis for the bilateral absence of temporal acoustic window. During the follow-up period 11 out of ET patients developed new-onset parkinsonian features, without fulfilling criteria for PD diagnosis (ET+). 9 patients developed clinical features meeting diagnostic criteria for probable PD (ET-PD). ET- patients did not develop parkinsonian features. For each group, the maximum values of SN+ size was calculated and they resulted as it follows: $5.62 \text{ mm}^2 \pm 5.40$ in the control group; $19.02 \text{ mm}^2 \pm 14.27$ in PD patients; $9.15 \text{ mm}^2 \pm 11.26$ in ET- patients; $20.05 \text{ mm}^2 \pm 13.78$ in ET+ patients; $20.13 \text{ mm}^2 \pm 13.51$ in ET-PD patients. ET-PD maximum values were significantly different from controls. Maximum values in ET+ patients were different from both controls and ET- patients.

Conclusions. SN hyperechogenicity in ET seems to represent a risk marker to develop early parkinsonian symptoms or signs in the next three years from TCS assessment.

1. Introduction

The association between ET and PD has frequently been reported [1,2,3]. It is well known that a subgroup of ET patients develops parkinsonian disturbances [4,5]. The presence of an ET-PD pathology, with the overlap of their clinical features, and ET often preceding PD onset by several years may even suggest ET like a risk factor for PD development [6]. The differentiation between PD and ET might be difficult since they can have overlapping manifestations. Thus, misdiagnosis is common [4].

During the last decade, Transcranial Sonography (TCS) has been reported as an effective, non-invasive and inexpensive method to differentiate PD from ET [7,8]. Substantia Nigra Hyperechogenicity (SN+) is found in more than 90% of PD patients, with great specificity (82.4%), sensitivity (90.7%) and high predictive positive value for PD diagnosis (92.9%) [9]. SN+ is detected in about 13–16% of ET patients [10]. Furthermore, a relationship between SN+ and early non-motor manifestations of PD including hyposmia, constipation and depression has been described. Noteworthy, the occurrence of SN+ in ET seems to be associated with a greater risk to develop PD. These observations suggest that a subgroup of ET patients have an increased risk to develop PD in the following years [10].

In this study we aimed to investigate the relevance of hyperechogenicity of SN in ET patients, monitored for a 3 year-follow up. Particularly, we tested the possible role of SN+ in identifying ET patients with an increased risk to develop parkinsonian features.

2. Methods

2.1 Participants

The study involved 188 subjects (105 men, 83 women), including 79 PD patients (47 men, 32 women), 59 ET patients (40 men, 19 women) and 50 age- and gender-matched healthy controls (28 men, 22 women). Patients were recruited from the Movement Disorders

Centre of Perugia Hospital “Santa Maria della Misericordia”. PD patients met the Movement Disorder Society (MDS) Diagnostic Criteria for clinically established PD [11]. The diagnosis of ET was established according to the Consensus Statement of Movement Disorder Society on Tremor [12]. ET patients did not exhibit PD-related motor signs and non-motor symptoms at the time of enrollment and they had never been treated with dopamine receptor blockers or dopamine-depleting agents. At baseline, some PD and ET patients, when clinical diagnosis was quite uncertain, underwent ¹²³I-FP-CIT SPECT which confirmed clinical diagnosis (14 PD and 6 ET patients). Control subjects were recruited from Neurology Clinic of the same hospital, according to the following inclusion criteria: older than 50 years, absence of pre-diagnosed movement disorders or other neurodegenerative diseases, absence of previous or current pharmacological treatment with neuroleptics. Both patients and healthy subjects gave their informed consent for the study. The study was approved by the ethical committee of Perugia (CEAS, Umbria).

2.2 Clinical assessment

At the time of enrollment, patients were receiving specific anti-PD or anti-ET medications when necessary. At baseline, disease-related severity and disability in PD patients were assessed referring to the MDS Unified Parkinson’s Disease Rating Scale part III (UPDRS-III) [13] and the Hoehn & Yahr Rating Scale (H&Y) [14], respectively. ET patients were closely monitored over time and they received a longitudinal clinical assessment for a follow-up period of at least three years. Every 4 months ET patients were evaluated to identify the possible new onset of parkinsonian motor signs (bradykinesia, rigidity, resting tremor, postural instability) and were accurately evaluated for the possible complaints of new-onset PD-related early non-motor symptoms (olfactory dysfunctions, REM sleep behavior disorders, constipation and mood disturbances). During the follow-up period, UPDRS-III was used to evaluate the possible onset of parkinsonian motor signs in ET patients [13]. The possible onset of REM sleep behavior disorders, constipation and mood disturbances were examined by means of Non-Motor Symptoms Scale [15], whereas olfactory impairment was assessed by using Italian Olfactory Identification Test [16]. ET patients were classified as ET-PD if they developed clinical features meeting MDS diagnostic criteria for clinically probable

PD [11]. Meanwhile, ET patients were identified as ET+ if they developed new-onset motor signs and/or non-motor symptoms of PD, without reaching the criteria for PD diagnosis. Particularly, ET patients were classified as ET+ if they developed at least one motor sign among rigidity, resting tremor and postural instability or if they complained at least one early non-motor symptom among olfactory dysfunctions, REM sleep behavior disorders, constipation and mood disturbances during the three-years follow-up period. The remaining group of ET patients were classified as ET-. Clinical investigators were blinded to transcranial sonography results.

2.3 Transcranial sonography

At baseline, both patients and healthy controls underwent TCS. TCS examination was performed using a color-coded phase array ultrasound system Acuson (Aspen, Italy) equipped with a 2.5 Hz transducer. All the scans were executed by the same investigator (G.C.), who was blinded to the clinical conditions and the evolution of the patients along the follow-up. Insonation was carried out with the subject in supine position and the probe positioned in the pre-auricular region, throughout temporal acoustic window, from both sides (right and left). The parameters for sonographic analysis were chosen according to the most recent guidelines [8] proposed for this method. Temporal axial plane was explored and, after identifying the butterfly-shaped hypoechogenic brainstem, the image was “frozen” and enlarged 2-3 times; SN echogenicity in the mesencephalic tegmentum was manually marked and then calculated automatically by the machine in mm^2 .

2.4 Statistical analysis

Descriptive statistics were calculated. Continuous variables were summarized as means and standard deviations while categorical data were reported as absolute frequencies and percentages. The distribution of SN echogenicity was tested for normality with Shapiro Wilk test. Due to the non-normality of the distribution, SN echogenicity was compared between groups by means of Mann-Whitney U test accounting for the multiplicity with Benjamini-Hochberg procedure. Spearman’s correlation coefficients between SN echogenicity and

clinical parameters were calculated. We performed ROC analysis to calculate the ability of TCS in predicting conversion from ET to ET+ or PD [17] Thresholds calculated with ROC analysis were used for classifying subjects in two stages of TCS, which were later used in logistic regression models to calculate the Odds Ratios of conversion. Multivariate logistic regression models were carried out for verifying the role of other variables such as disease onset, age, male sex and familiar history of PD. The statistical analysis was carried out using R software v 3.5 (www.r-project.org), with statistical significance level set at 5%.”

3. Results

Ten of the 188 subjects (5,3%, 5 PD, 3 ET and 2 controls) were excluded from the study due to the absent or insufficient temporal acoustic window. Epidemiologic and clinical data are summarized in Table 1.

During the 3-year follow-up, 9 of the 59 ET patients were identified as ET-PD. All of them developed both bradykinesia and resting tremor. Rigidity was present in 5 patients. Hyposmia, constipation and mood disturbances were also recorded (2, 3 and 3 patients, respectively) (Table 2). Furthermore, 11 of the 59 ET patients were identified as ET+. Among ET+ patients, resting tremor was recorded in 9 cases. Hyposmia, constipation and mood disturbances were also reported (1, 2 and 4 patients, respectively) (Table 2). Among 6 ET patients who underwent baseline ^[123]I-FP-CIT SPECT, 1 patient resulted as ET- and 5 patients were ET+.

Left side SN+, right side SN+ and mean values of SN+ are summarized in Table 3 for all the groups: PD, ET-, ET+, ET-PD and healthy controls. Mean values of PD, ET-PD and ET+ were significantly different from those of the control group (p<0.001, p=0.010 and p=0.036, respectively).

For each group, the maximum values of SN+ size between the two sides was evaluated. The maximum values of SN+ were distributed as follows: 5.62 mm² ± 5.40 in the control group; 19.02 mm² ± 14.27 in PD patients; 9.15 mm² ± 11.26 in ET- patients; 20.05 mm² ± 13.78 in

ET+ patients; $20.13 \text{ mm}^2 \pm 13.51$ in ET-PD patients (Table 3). The adjusted pairwise comparisons revealed that values of maximal SN+ size in PD were significantly different from controls ($p < 0.001$) and ET- ($p = 0.003$). ET-PD maximum values were significantly different from controls ($p = 0.003$). Maximum values in ET+ patients were different from both controls ($p = 0.013$) and ET- patients (0.039) (Figure 1). Maximum values of SN+ provided an AUC of 0.72 (95% CI = 0.58-0.86). Specificity was 0.72 (95% CI = 0.50 – 1.00), sensitivity 0.75 (95% CI = 0.30 – 0.95) (Figure 2). According to a ROC derived cutoff of 14.75, the odds ratio of conversion was 1.37 (95% CI = 1.07 – 1.74). After considering other variables we found that only age entered in a multivariate regression model (OR=1.01, 95% CI = 1.00 -1.02) which also included TCS Max (OR=1.42, 95% CI = 1.13 -1.78).

In PD group Spearman's correlation Test showed that SN echogenicity size did not correlate with disease duration, H&Y and UPDRS III score ($p > 0.05$). Moreover, age of onset, gender and familiar history of PD, tested by multivariate logistic regression models, were not statistically significant and seem that did not play a role in explaining the onset of PD symptoms or the diagnosis of PD in subjects with ET.

4. Discussion

In this study we aimed to assess the relevance of SN+ in ET patients and to investigate the significance of SN+ in identifying ET patients who will develop parkinsonian features. SN+ is considered an early marker of nigrostriatal dopaminergic pathway degeneration in PD. Its early appearance on the PD timeline has supported the hypothesis that it may represent a potential prodromal marker for PD [18,19]. Furthermore, it is likely that ET and PD share common clinical pattern in a subgroup of patients. Hence, epidemiological, biological, genetic and imaging data strongly support the association between these two conditions [20, 21].

In our cohort, 18.6% of ET patients developed motor signs and/or early non-motor symptoms without reaching the current diagnostic criteria for PD, whereas 15.3% of ET patients developed clinical features which were adequate to meet the MDS Diagnostic Criteria for probable PD. The maximum values of SN echogenicity did not differ significantly

between PD, ET+ and ET-PD groups. This observation supports the existence of neurobiological links between ET and PD, at least in a subgroup of ET patients. Otherwise, the maximum values of SN echogenicity in ET- significantly differed from those of PD, ET-PD and ET+ groups, suggesting the presence of a subgroup of ET patients with a more benign course. Conversely, ET patients with increased SN+ showed not only a higher risk to develop early non-motor symptoms or PD-related motor signs but also a greater risk to receive a specific PD diagnosis in a three-years follow-up, in line with previous findings [22]. In line with our findings, Sprenger and colleagues recently investigated 54 ET patients with TCS at baseline and evaluated them for the incidence of new-onset PD along a 6-year follow-up. They found that 9 patients developed PD on-ET, of whom 7 had SN+ at baseline, and that the relative risk for developing PD in ET patients with SN+ was 7.00 [21]. The rate of conversion we found was lower (1.37) as compared to previously reported risk of 7.00, probably due to the more strict criteria for ET patients who did not exhibit non-motor symptoms at baseline evaluation in our work. Furthermore, in their study follow-up period was longer (6.2 ± 2.1 years) and disease duration was higher (27.0 ± 15.5 years), maybe contributing to identify a greater relative risk compared to our work. Evidence such these strengthen the role of SN+ not only as a diagnostic instrument for PD but also as useful biomarker for prodromal PD which identifies the stage in which patients manifest early non-motor symptoms and/or subtle motor signs without meeting the current diagnostic criteria for PD [23]. Noteworthy, previous observations suggest also that SN+ is able to predict conversion to PD in patients with idiopathic REM sleep behavior disorders [24], in patients with drug-induced parkinsonisms [25] and in general elderly population [26].

The relationship between ET and PD has been already investigated in many studies. Increasing findings suggest that these two common movement disorders are pathogenically related [3]. The ET-PD syndrome has been labeled using different eponyms, such as “benign tremulous parkinsonism” [27]. However, its wide clinical heterogeneity and unclear etiology make difficult to hold it in a single diagnostic set.

In a recent study, PD patients with and without preceding ET did not show significant clinical differences in their motor and non-motor phenotypes, except for the presence and severity of postural and kinetic tremor [28]. Over the broad spectrum of possible presentations of

ET-PD phenotype, it appears so necessary to identify useful tool that may help to discover ET patients with higher risk of developing PD.

Substantia Nigra Hyperechogenicity (SN+) might represent a reliable marker for PD diagnosis with high predictive value [8]. TCS emerges as a useful tool to discriminate PD from other movement disorders with good sensitivity and specificity [7]. TCS has been demonstrated to show good reliability in distinguishing patients with PD from those with ET, even when compared to [123]FP-CIT SPECT [28]. However, it is well established that SN+ is not an exclusive feature of PD patients and is detected in about 15% of ET patients and ET patients show higher prevalence of SN+ compared to healthy subjects. Kim and collaborators observed an interesting and significant association between SN+ and the early non-motor PD-typical symptoms in ET patients. Moreover, ET cases showing a higher number of premotor symptoms had a greater value of SN+ [10].

Our study has some limitations. First of all, the major limit is probably represented by the small number of included subjects. Furthermore, ¹²³I-FP-CIT SPECT was performed to support the clinical diagnosis of ET and PD only at baseline in selected patients and it was not repeated along the follow-up. So misdiagnosis in some of the ET patients developing parkinsonian features or remaining PD-free cannot be excluded, in the absence of post-mortem examination. We believe, however, that the presence of both control subjects and PD patients groups, in addition to the ET group, represents the strength of our work. Nevertheless, larger longitudinal prospective studies assessing the natural history of ET patients presenting with SN+ should be performed to establish a clear pathophysiological link between ET and PD.

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Table 1: Epidemiologic and clinic data.

Table 2: Motor signs and non-motor symptoms in ET-PD and ET+ patients.

Table 3: Transcranial sonographic data.

Legend for Figure 1: The distribution of the average of maximum values of SN+ size (TCS MAX) between the two sides for each group (PD, ET+, ET-, PD-ET, Controls).

Legend for Figure 2: ROC curve for predictability of ET+ ET-PD conversion with TCS. Cutoff point is displayed along with 95% CI of sensitivity and specificity.

Table 1.

	PD	ET	Controls
Number	79	59	50
Gender	47 M, 32 F	40 M, 19 F	28 M, 22 F
Age (yrs)	69,4 (\pm 9,9)	71,5 (\pm 10,5)	65,2 (\pm 12,2)
Follow-up (yrs)	3,2 (\pm 2,5)	3,1 (\pm 2,1)	
Disease duration (yrs)	6,9 (\pm 5,3)	7,1 (\pm 6,1)	
Hoehn & Yahr Scale	2 (1-4)		
MDS-UPDRS part III	20,4 (\pm 10,4)		

Table 2.

		ET+ (11 patients)	ET-PD (9 patients)
Motor signs	Bradykinesia	//	9
	Resting tremor	11	9
	Rigidity	4	5
	Postural instability	//	//
Non-motor symptoms	Hyposmia	1	2
	Constipation	2	3
	Mood disturbances	4	3
	REM behavioral disorders	1	5

Table 3.

	PD (n=74)	ET- (n=36)	ET+ (n=11)	ET-PD (n=9)	Controls (n=48)
SN+ right side	14,88 mm ² (±13,60)	5,91 mm ² (±9,24)	9,84 mm ² (±13,79)	15,88 mm ² (±16,96)	3,57 mm ² (±4,44)
SN+ left side	13,71 mm ² (±14,19)	6,31 mm ² (±10,26)	14,34 mm ² (±14,63)	9,12 mm ² (±12,39)	3,45 mm ² (±5,21)
SN+ mean value	14,53 mm ² (±11,49)	6,11 mm ² (±8,26)	12,09 mm ² (±10,03)	14,29 mm ² (±14,61)	3,51 mm ² (±3,47)
SN+ maximum value	19,02 mm ² (±14,27)	9,15 mm ² (±11,26)	20,05 mm ² (±13,78)	20,13 mm ² (±13,51)	5,62 mm ² (±5,40)



