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A rapidly progressive PSP-FTD like phenotype in a carrier of the GBA L444P mutation

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Introduction: Heterozygous GBA mutations increase the risk of PD, LBD and worsen the severity in other neurodegenerative disorder different from the alpha-synucleinopathies.Previous studies failed to report a significant association between tauopathies and GBA mutations [1].

Objective: To describe the phenotype of a patient with a FTD like-phenotype carrying a severe GBA pathogenic variant.

Methods: Phenotypic data were repeatedly collected along three years.

Results: A 58-year-old right-handed man came at our attention for a progressive language disorder. Family history was negative.The examination revealed photophobia,vertical and horizontal hypometric saccades with higher latency,mild dysphagia, and speach apraxia.Postural instability,parkinsonism,pyramidal and cerebellar signs were absent.The electromyography performed on the face and limbs was normal.The neuropsychological evaluation revealed a primary progressive aphasia associated to executive/attention difficulties. A PET-FGD scan showed a frontal widespread hypometabolism without cortical or midbrain atrophy.CSF biomarkers levels were normal.The course of the disease was remarkably aggressive.After 36 months the patient developed a frontal dementia,anartria, severe dysphagia without hypertonia or balance disturbances.Eight months later he developed diffuse myoclonus and died for pneumonia.Genetic analysis excluded C9ORF72 pathologic expansions.The Exome Sequencing failed to detect pathogenic variants in genes associated to fronto temporal dementia and revealed the L444P heterozygous mutation in the GBA gene.

Conclusions: We present a rapidly progressive PSP-FTD phenotype, mainly characterized by pseudobulbar involvement in a carrier of a severe GBA pathogenic variant. To the best of our knowledge,this mutation has been found only in one other case of PSP-like phenotype, mainly characterized by falls [2]. Recent evidence suggests that GBA mutations may influence the cognitive status of patients with ALS [3]. Several genes causing ALS and FTD, are related to lysosomal function and protein degradation.Moreover, mutations in genes that encode proteins important for endosome-lysosome function also occur in other age-dependent neurodegenerative diseases, including Alzheimer's and Parkinson's disease.A more understanding of the features of lysosome dysfunction in neurodegeneration will help guide the development of disease-modifiyng therapies.

References:

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