P156

Genetics isn't enough: clinical and biochemical profile of GBA and non-GBA related Parkinson's disease in twins and non-twins brother

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Introduction: GBA mutations lead to impaired lysosomal-mediated autophagy leading to a-synuclein accumulation and synucleopathies development. However, not every individual carrying a variant in GBA gene develop Parkinson Disease (PD) due to incomplete penetrance of these variants. Investigate lysosomal dysfunction in GBA carriers compared to non-mutated PD individuals will help to identify risk factors that could contribute to disease development.

Objective: To characterize genetic, clinical, biochemical profile of GBA monozygotic sisters clinically discordant for PD and two non-twins PD brothers discordant for GBA mutations.

Methods: Genetic and clinical characterization were performed and lysosomal alterations (GCase, LAMP1, LIMP2, Saposin C) and alpha-synuclein levels were analyzed in peripheral blood lymphocytes.

Results: Two 66 years old monozygotic sisters had a heterozygous GBA N370S mutation (mild variant); one of them with an history of depression and anxiety developed at age of 56 bradykinesia and rigidity on the right upper limb with an initial good response to levodopa. After 6 years she developed motor fluctuations, cognitive decline and moderate psychotic symptoms requiring advance therapy intervention (duodopa infusion gel). Her sister had a normal neurological exam without parkinsonian symptoms.
The non-twins brothers both developed PD at age of 40 and 54 years and genetic analysis revealed a heterozygous GBA L444P mutation only in the latest. The GBA-PD carrier although developed PD later than the non-mutated brother had a more rapid and severe motor progression requiring STN-DBS implant after 6 years from onset. On the contrary, the non-mutated brother showed a milder non-motor and cognitive phenotype than GBA-PD brother, although the longer disease duration.

Conclusions: To the best of our knowledge no environmental factors or other genetic mutations were found in these subjects that could explain the different phenotypes. Biochemical investigation is currently ongoing to deeper explore the role of lysosomal dysfunction on clinical heterogeneity.