Posterior Cortical Hypometabolism in Two Siblings with *GBA1* Mutations: Divergent phenotypes

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INTRODUCTION

Heterozygous mutations in the ***GBA1* gene** are the main genetic risk factor for **Parkinson's disease (PD).** We describe two siblings, both carriers of a severe *GBA1* variant, showing similar brain **FDG-PET hypometabolism** but markedly different clinical and biochemical profiles.

OBJECTIVES

To compare the profiles of **two *GBA1* carriers** and explore the potential dissociation between PET findings and clinical severity.

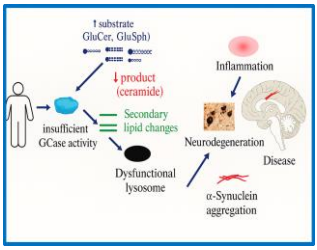

Figure 1: This illustration shows how mutations Mutations in *GBA1* reduce GCase activity, leading to lipid buildup, lysosomal dysfunction, and α-synuclein aggregation, contributing to Parkinson's disease.

Evaluation	GBA-PD	GBA-nonPD
Scolarità	17	17
MoCA	23,52	25,52
TMT A	28	28
TMT B	122	75
TMT B-A	94	47
ROCF copy	29	34
ROCF recall	9,75	15
Degraded figure test (Judgment)	0	1
Superimposed figure test	48,94	71
Cognitive Profile (0=normal 1≤MCI 2=PDD)	1	0

Table 1: Neuropsychological assessment in the two siblings.

METHODS

Two *GBA1* (*GBA1* p.H255Q) siblings (one affected and one asymptomatic) underwent a comprehensive clinical evaluation, including MDS-UPDRS, NMSS, SCOPA-AUT, PDQ-39 and a detailed neuropsychological battery. Both participants underwent FDG-PET imaging, along with biochemical analyses of glucocerebrosidase (GCase) activity and monomeric alpha- synuclein levels in peripheral blood mononuclear cells (PBMCs).

RESULTS

The **proband,** a 59-year-old man, developed PD at age 52, preceded **by prodromal symptoms (RBD, constipation, hyposmia) starting about a decade earlier.** He exhibited mild-to-moderate bradykinesia (left-predominant), minimal rigidity, mild gait disturbances with minimal freezing and postural instability, and mild left-sided tremor (MDS-UPDRS-III: 52). Cognitive testing revealed **multi-domain deficits consistent with PD-MCI** [1][2]. He also showed a significant non-motor symptom burden (NMSS: 75; SCOPA-AUT: 29) and reduced quality of life (PDQ-39: 53).

His **56-year-old sister** presented only minimal left-predominant bradykinesia and slight arm swing reduction during gait (**MDS-UPDRS-III: 9**), with no cognitive impairment and minimal non-motor symptoms.
Both had similar education, occupation, and lifestyle.
Despite marked clinical differences, **FDG-PET revealed comparable bilateral parieto-occipital hypometabolism** in both, suggesting early cortical involvement in *GBA1* carriers [3]. GCase activity was similar, but the **proband** had substantially **higher monomeric alpha-synuclein levels** in PBMCs (382.04 vs. 127.15 ng/mg).

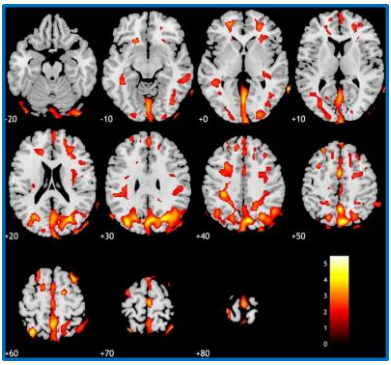

Figure 2: FDG-PET hypometabolism pattern of a GBA-PD subject (age 59y, sex: M) carrying a severe GBA1 variant. The hypometabolism pattern was obtained by means of SPM single-subject procedure comparing patient's scan with a dataset of 125 healthy controls, correcting for age ($p<0.05$, $k = 100$ voxels).

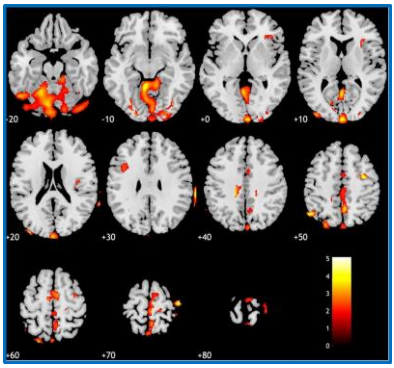

Figure 3: FDG-PET hypometabolism pattern of the unaffected carrier (age 56y, sex: F). The hypometabolism pattern was obtained by means of SPM single-subject procedure comparing patient's scan with a dataset of 125 healthy controls, correcting for age ($p<0.05$, $k = 100$ voxels).

CONCLUSION

Despite shared genetics, imaging patterns, and environmental exposures, the stark clinical divergence between the siblings points to the role of unknown modifiers influencing the onset and progression of GBA-PD.
Identifying these factors is essential to refine risk prediction, guide monitoring, and develop personalized therapeutic strategies for GBA1 mutation carriers.

References

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