LETTER TO THE EDITOR

Differential phenotype in Parkinson’s disease patients with severe versus mild GBA mutations

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Sir, We read with much interest the comprehensive study by Neumann et al. (2009), published in Brain, which further demonstrated the importance of GBA mutations as risk factors for Parkinson’s disease. GBA mutations are being divided into two groups according to the resulting Gaucher’s disease phenotype in homozygous or compound heterozygous individuals. Mild GBA mutations cause the adult Gaucher’s disease Type I with mild glucocerebrosidase deficiency, while severe GBA mutations (including null mutations), when inherited from both parents, result in the severe types of Gaucher’s disease, II or III (Beutler et al., 2005). We have previously demonstrated (Gan-Or et al., 2008) the differential effects of severe versus mild GBA mutations on the risk and age at onset (AAO) of Parkinson’s disease. Carriers of mild GBA mutations had a 2.2-fold higher risk to develop Parkinson’s disease and an average AAO of 57.9 years compared with non-carriers of GBA or LRRK2 G2019S mutations (average AAO of 60.7 years). However, carriers of severe GBA mutations had a 13.6-fold higher risk to develop Parkinson’s disease and an average AAO of 55.7 years. While carriers of mild GBA mutations had an average AAO of 62.6 (± 9.0 years), carriers of severe GBA mutations had an average AAO of 49.8 (± 10.9 years, P = 0.007, Student’s t-test, data were available for 19 patients). Calculating the odds ratio (OR) for each type of mutation separately was not possible since there were no carriers of severe GBA mutations among the control group, further demonstrating the higher risk of severe GBA mutations carriers to develop Parkinson’s disease. Interestingly, while Neumann et al. reported a high occurrence of cognitive symptoms in 50% of all GBA mutations carriers (15/30, data were not available for three patients with severe mutations), cognitive deficit occurred more frequently in 55.6% (10/18) of severe GBA mutations carriers, compared with 25% (2/8) in patients carrying mild GBA mutations. Altogether, these data support the observation that severe and mild GBA mutations carriage differentially affects the phenotype of Parkinson’s disease.

References