

White Matter Damage in Parkinson's Disease Patients With Glucocerebrosidase Gene Mutations: A Study Using Diffusion Tensor Imaging

Federica Agosta¹, Kristina Davidovic¹, Nikola Kresojevic², Lidia Sarro¹, Marina Svetel², Iva Stankovic², Giancarlo Comi³, Vladimir S. Kostic², and Massimo Filippi¹

¹Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, Italy,

²Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Yugoslavia, ³Department of Neurology, San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy, Italy

Introduction. Glucocerebrosidase (GBA) gene mutations represent a significant risk factor for the development of Parkinson's Disease (PD) and other Lewy body disorders. The mechanisms underlying the association between GBA mutations and PD are still not known (1). GBA mutation carriers with PD frequently have an earlier age of onset and increased likelihood to present cognitive symptoms compared with non-carriers (2). Diffusion tensor imaging (DTI) allows an in vivo assessment of white matter (WM) damage.

Objective. Aim of this study was to investigate the pattern of brain WM damage in patients with PD carrying mutations in the gene encoding GBA compared with healthy controls and PD patients without GBA mutation, but at similar disease stage.

Methods. Among 360 PD patients screened for mutations of the GBA gene, 19 (5.3%) heterozygous mutation carriers were identified. Eleven of them (mean age 66 years, mean age at onset 54 years, median Hoehn and Yahr [HY] stage score 3.0), found to be heterozygous for N370S (six cases), D409H (three cases), D380V (one case), and E388K (one case) GBA mutations, were enrolled in this study. Eleven PD patients without GBA mutations (mean age 65 years, mean age at onset 55 years, median HY stage score 3.0) and 11 healthy controls (mean age 65 years) were also studied. DTI scans were obtained from all subjects. Tract-based spatial statistics was used to perform a brain voxel-wise analysis of mean diffusivity (MD) and fractional anisotropy (FA).

Results. DTI showed that GBA mutation PD carriers had statistically significant increased MD of the corpus callosum and decreased FA of the corpus callosum and cingulum bilaterally, when compared to controls ($p < 0.05$) (Figures 1 and 2)

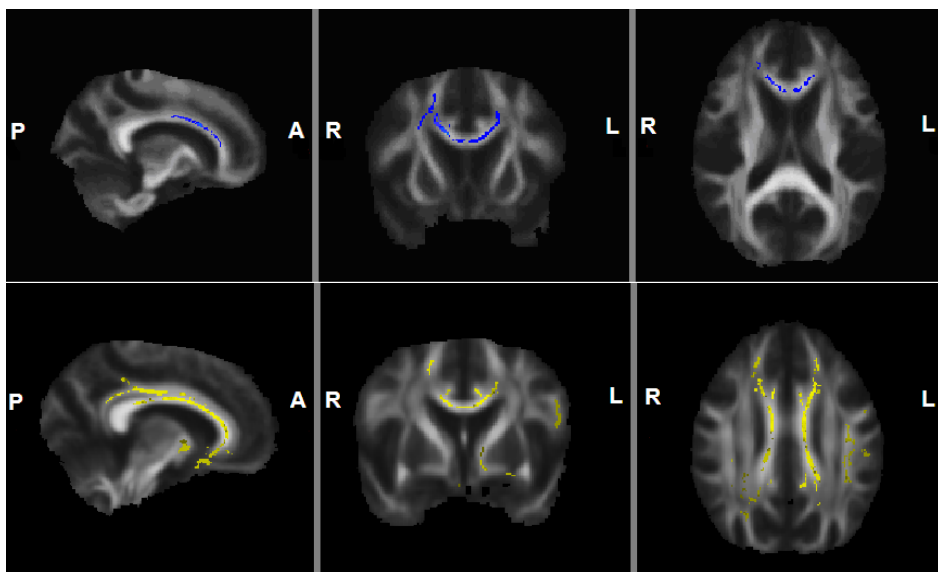


Figure 1.

Increased MD in GBA mutation PD carriers compared with healthy controls ($p < 0.05$, Family-wise error corrected). P=posterior, A=anterior, R= right, L= left.

Figure 2.

Decreased FA in GBA mutation PD carriers compared with healthy controls ($p < 0.05$, Family-wise error corrected). P=posterior, A=anterior, R= right, L= left

When compared to controls, PD patients without GBA mutations did not show any significant DT MRI abnormality.

Conclusions. PD patients carrying GBA mutations show WM abnormalities involving the corpus callosum and the cingulum. Future research will clarify whether WM damage in these patients may have an impact on the clinical phenotype, in particular on the development of cognitive impairment.

References. [1] Westbroek et al., Trends in Molecular Medicine 2011;17:485-493; [2] Neumann et al., Brain 2009; 132:1783-1794