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LETTER TO THE EDITORS

Long-term follow-up of subthalamic nucleus stimulation in glucocerebrosidase-associated Parkinson's disease

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Dear Sirs,

Heterozygous mutations in the gene encoding the lysosomal enzyme beta-glucocerebrosidase (*GBA*) are associated with an increased susceptibility to Parkinson's disease (PD) and dementia with Lewy body disease [1, 2] and some cases with phenotypes similar to multiple system atrophy were reported [3]. *GBA* mutation carriers generally present with an earlier age at onset and particularly severe motor [2, 5] and non-motor [6] genotype-phenotype relations probably reflecting the more pronounced neocortical Lewy body-type pathology in *GBA*-associated PD [4]. Therefore, these were predicted to show an unfavorable therapeutic outcome from Deep-brain stimulation of the subthalamic nucleus (STN-DBS). Here, we provide the first quantitative data on the therapeutic outcomes of *GBA*-associated PD in response to L-Dopa and STN-DBS in a series of three cases followed for up to 10 years.

Ninety-eight PD patients treated with STN-DBS at the Department of Neurology of the Tübingen University between 1999 and 2011 were screened for the two most common *GBA* mutations (N370S and L444P) after written informed consent in accordance to the local ethics committee. Three GBA mutation carriers were identified (one N370S, two L444P; Table 1) and compared to two non-mutation carriers with Idiopathic Parkinson's disease (iPD) matched for 'age', 'gender', and 'disease duration at DBS implant'. The mutation carrier status was unknown to the raters until final 2010 when genetic testing was performed. Postoperative imaging confirmed correct electrode placement and no surgical complications were reported.

All patients underwent regular standardized clinical follow-up assessments before and after surgery on therapeutic efficacy of L-Dopa and STN-DBS on Unified Parkinson's disease rating scale (UPDRS) III motor scores (1) 'OnMedication-OnStimulation', (2) 'OffMedication-OffStimulation', (3) 'OffMedication-OnStimulation', and (4) 'OnMedication-OffStimulation' including subscores for 'segmental' (items 20–26) and 'axial' motor symptoms (items 27–31). Motor fluctuations were monitored with UPDRS IV scores. Dopaminergic medication was expressed as L-Dopa equivalent dosage. Moreover, retrospective analyses of non-motor symptoms based on consecutive assessments of the Mini Mental State Examination, neuropsychological testings, Beck's Depression Inventory,

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Table 1 Clinical characteristics of the *GBA* carriers and the non-mutation carriers with iPD

Patient	Genotype	Sex	AaO (years)	Duration of disease (at DBS implant) (years)	Follow-up range (years)
GBA1	*N370S*	F	54	21 (11)	10
iPD1a		F	52	14 (9)	6
iPD1b		F	56	16 (12)	4
GBA2	*L444P*	F	48	27 (21)	7
iPD2a		F	42	31 (25)	8
iPD2b		F	45	31 (25)	6
GBA-3	*L444P*	F	47	25 (20)	6
iPD3a		F	52	19 (15)	6
iPD3b		F	49	26 (21)	6

F female, *AaO* age at onset

deglutition (logopaedic and videofluoroscopic examinations) and patient's records were performed and assigned to major domains: (1) 'neuropsychiatry' (items: anxiety, depression, hallucination), (2) 'cognition', (3) 'sleep', and (4) 'autonomic and gastrointestinal symptoms' (items: urge incontinence, constipation, orthostase, hypersalivation, dysphagia). The dichotomic data of each domain ('present' or 'not present') was assigned to time intervals of two consecutive years, respectively. At the final follow-up, specific assessments of gait and balance were performed (CAPSIT-PD, Freezing of Gait Questionnaire (FOG-Q) [7], Berg Balance Scale) and the Non-Motor Symptoms Scale (NMSS), and Non-Motor Symptoms Questionnaire (NMSQ) were assessed [8].

Motor fluctuations and dyskinesias were well controlled after surgery (UPDRS IV) in both groups and the L-Dopa equivalent dosage was substantially reduced (Supplemental Fig. 1). All *GBA* carriers showed a stable motor outcome after surgery relative to the best total UPDRS III ('OnMedication-OnStimulation'). In both groups, segmental and axial symptoms were improved in the first 4 years after surgery, however, 4 to 6 years from STN-DBS there was only sparse therapeutic response of axial motor symptoms on both L-Dopa and STN-DBS in the *GBA* carriers (Fig. 1, Supplemental Table 1).

At the final follow-up examination, freezing of gait presented in both groups and particularly severe in patients GBA1 and GBA2 and in four out of six patients with iPD according to individual FOG-Q scores with sparse response on STN-DBS. Balance impairment was particularly severe in all *GBA* carriers. Both groups exhibited severe non-motor symptoms (Supplemental Table 2).

Our long-term observations revealed depressive symptoms in all *GBA* carriers and iPD (Supplemental Table 3). Two *GBA* carriers and four iPD were diagnosed with (in part transient) both anxiety disorders and hallucinatory behavior. All *GBA* carriers but only two out of six iPD patients presented with cognitive impairments. One iPD

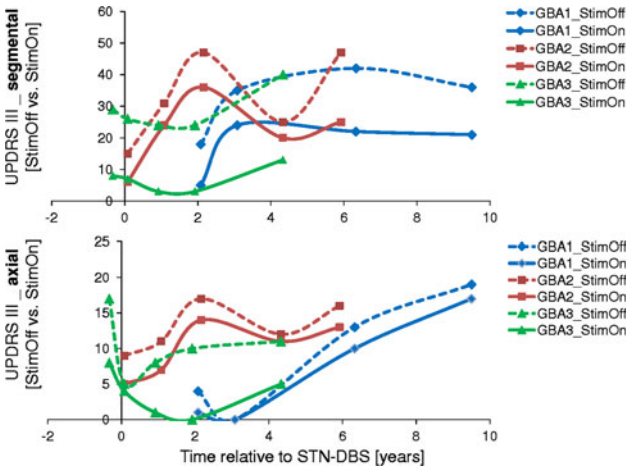

Fig. 1 Differential therapeutic response of segmental and axial motor symptoms in *GBA*-associated PD. Comprehensive follow-up data of *GBA* carriers on **a** 'segmental' (UPDRS III items 20–26) and **b** 'axial' motor symptoms (UPDRS III items 27–31). *Dotted lines* indicate the motor scores 'OffMedication-OffStimulation', *constant lines* 'OffMedication-OnStimulation'. Axial symptoms show constant worsening with sparse therapeutic response in the long term. *X-axis* time relative to the onset of subthalamic nucleus stimulation (years); *y-axis* UPDRS III motor subscores

patient (iPD1a) presented with pseudo-dementia due to depression, however recovered over time under antidepressive treatment. All patients—irrespective of the genetic status—presented with sleep disturbances.

Urge incontinence, constipation, hypersalivation, and dysphagia were regularly observed in both groups. GBA1 presented with severe liquid aspiration unresponsive to both optimized stimulation and L-Dopa challenge after 21 years of disease. Orthostatic dysregulation appeared more pronounced in the *GBA* carriers.

Our case series provides the first comprehensive data on the therapeutic efficacy of long-term STN-DBS and L-Dopa in PD due to heterozygous *GBA* mutations and points to a favorable outcome with sustained control of motor fluctuations and stable reduction of the dopaminergic

medication. Whereas both segmental and axial symptoms were well controlled initially, we observed a substantial increase of axial motor impairment in the long term with declining therapeutic response in *GBA* carriers. In contrast to iPD patients, all *GBA* carriers developed a significant cognitive impairment that paralleled the axial motor decline and therefore might relate to the more severe neocortical Lewy body pathology in *GBA*-associated PD[4] and the particularly severe neurodegeneration in non-dopaminergic systems [9].

Indeed, the preoperative screening for neuropsychiatric and cognitive disorders might have introduced a selection bias to our cohort, potentially under-representing *GBA* carriers with earlier or more severe cognitive and neuropsychiatric symptoms. However, the percentage of 3.1% of identified *GBA* mutation carriers in our cohort is consistent with previous epidemiological findings in non-Ashkenazi patients with PD and therefore argues against significant selection.

Based on this first longitudinal data in *GBA* mutation carriers, we assume a more severe axial motor impairment in the long term as a major unmet therapeutic need. Indeed, an increasing number of studies on STN-DBS address gait disturbances in PD [10, 11]. Therefore, larger clinico-genetic studies based on this first outcome data could define *GBA* as a genetic predictor in PD and translate into concepts for personalized medicine, i.e., by fixing the optimal time point or neuroanatomic target for invasive therapeutic interventions.

Conflicts of interest None.

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