A Twelve-Year Follow-Up Study on a Case of Early-Onset Parkinsonism Preceding Clinical Manifestation of Gaucher Disease

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Abstract Mutations in the glucocerebrosidase gene (*GBA1*) cause Gaucher disease (GD) and are the most common genetic risk factor for the development of Parkinson's disease (PD). Here, we present a 12-year follow-up study of a male with GD and PD (diagnosed 24 years ago), which PD preceded the clinical manifestation

of GD by 12 years. The patient is a compound heterozygote for mutations c.115 + 1G > A and c.1226A > G (IVS2 + 1/N370S) in the *GBA1* gene. Imiglucerase had a beneficial effect on GD, but not on PD. Treatment with L-dopa and other PD drugs showed temporary efficacy but 2 years later significant wearing-off phenomenon and dyskinesias appeared. Unilateral pallidotomy was performed with transient benefit. Cognitive decline appeared later and developed in to akinetic mutism. A lumbar puncture was performed to characterize the biochemical profile of cerebrospinal fluid (CSF). Analyses of monoamine metabolites levels in the CSF, determined by reverse-phase high-performance liquid chromatography, revealed remarkably low levels of all studied monoamine metabolites (HVA, DOPAC, 5-HIAA, MHPG). These data indicate that PD associated with *GBA1* mutations may not only affect dopaminergic neurons, but also noradrenergic and serotonergic neurons. Of note, normal levels of P-tau, total tau and β -amyloid (1–42) were detected on ELISA assay. Thus, the cognitive decline, akinetic mutism and moderate cortical atrophy found on the CT scan were not paralleled by any changes of dementia markers in CSF. This single case study extends the follow-up period and adds novel CSF information; however additional data on other patients with both PD and GD may help put our observations in its ultimate proper context.

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Abbreviations

ADL Activities of daily living
CSF Cerebrospinal fluid

DBS	Deep brain stimulation
ERT	Enzyme replacement therapy
GBA	Glucocerebrosidase
GD	Gaucher disease
GD1	Gaucher disease type 1
LSD	Lysosomal storage disorder
PD	Parkinson's disease
P-tau	Phosphorylated tau protein (181P)
RBD	REM-sleep behavioral disorder
Tau	Total tau protein
UPDRS	Unified Parkinson's disease rating scale

Introduction

Gaucher disease, the most common LSD, is caused by deficient activity of the lysosomal enzyme, glucocerebrosidase (glucosylceramidase, E.C.3.2.1.45), arising from autosomal recessive mutations in the *GBA1* gene (1q21) (Hruska et al. 2008). Recent studies have shown that *GBA1* mutations are the most common genetic risk factor for Parkinson's disease (Bultron et al. 2010; Neumann et al. 2009; Sidransky et al. 2009). One of the early reports on association between parkinsonism and GD1 was published by our group in 1999, describing a Polish patient who developed parkinsonism preceding clinical manifestation of GD by about 12 years (Machaczka et al. 1999). Here, we provide an update on the patients' current status, 12 years after the initial report and 24 years after the onset of parkinsonism. To our knowledge, this is the longest published follow-up of early-onset PD associated with *GBA1* mutations. Furthermore, we provide data on GD biomarkers in blood and cerebrospinal fluid namely analyses of monoamine metabolites, total tau protein, phosphorylated tau protein (181P) and β -amyloid (1–42).

Material and Methods

Patient and Previous Clinical Outcome

A 63-year-old right-handed non-Jewish Caucasian male with no family history of movement disorders developed a shuffling gait, rigidity, bradykinesia and resting tremor confined to the left side of his body at the age of 39 (in 1986). Shortly after, symptoms resembling RBD have been reported. L-dopa therapy started 2 years later in 1988 with initially beneficial effect. Bilateral symptoms were evident in 1992. In 1997, the patient developed notorious wearing-off and disabling dyskinesias. Then also thrombocytopenia and splenomegaly were noticed and further investigations disclosed Gaucher disease type 1 with the heterozygous

mutations c.115 + 1G > A (IVS2 + 1) and c.1226A > G (N370S) in the *GBA1* gene (Machaczka et al. 1999). Enzyme replacement therapy with imiglucerase was started in 1999, 40 U/kg (2,600 U, later reduced to 1,200 U) every other week. The treatment has led to prompt normalization of spleen size and thrombocytopenia.

At the age of 54, the patient became wheelchair bound due to severe akinesia and stiffness despite treatment with 1,000 mg L-dopa/day. This deterioration motivated a right-sided posteroventrolateral pallidotomy in 2001, which resulted in significant improvement that lasted for 3 years (Sobstyl et al. 2009). The patient became ambulatory and L-dopa was reduced to 300 mg/day; he was able to perform all ADL independently. Before pallidotomy his mini mental test score was 27/30 but a neuropsychological evaluation was not performed.

Methods

In 2010, the patient's symptoms were reported by his wife and confirmed by revision of chart notes. Detailed neurological examination and lumbar puncture (performed at the level L3–4) were performed. The biochemical profile of CSF was characterized by measurements of monoamine metabolites by reverse phase high-performance liquid chromatography, as previously described (Weikop et al. 2007). P-tau, tau and β -amyloid (1–42) were measured using ELISA assay by Innogenetics N.V., Ghent, Belgium (Mattsson et al. 2009). The patient's clinical condition made it impossible to perform new imaging examinations, but we report the results of CT scan of his brain taken in 2009.

The study was approved by the Regional Ethical Review Board in Krakow, Poland (KBET/62/B/2010).

Results

Outcome After Pallidotomy

Four years after pallidotomy (in 2005) antecollis and frequent falls were reported. One year later increasing memory loss was noticed. He became again wheel chair-bound in 2007 and decided then to discontinue both ERT (due to deterioration of general and neurological status) and L-dopa (due to loss of response and occurrence of benign visual hallucinations). He has since progressed into a state of akinetic mutism. Currently, he requires complete assistance with all ADLs. Pronounced daytime sleepiness and a new pattern of breathing apnea resembling Cheyne-Stokes breathing have developed in 2010. He is still able to swallow and drink, but has gradually lost his weight from 80 to 50 kg. Symptom fluctuations are denied.

On clinical examination in February 2010, the patient is confined to a wheel chair, somnolent and in a state of akinetic mutism but reacts to simpler commands. Clinical examinations yielded a total UPDRS score of 101 (9 + 41 + 45 + 6); a Hoehn and Yahr score of 5; and a Schwab and England score of 10%. He is unable to stand up with support; while sitting, his feet are in a supine position without signs of resting tremor or myoclonus. Rigidity and *Gegenhaltung* in the forearms and legs are present bilaterally. Marked axial neck dystonia with antecollis, an intermittent startle reaction and a limited range of horizontal and especially vertical ocular pursuit are found. Of the primitive reflexes, only grasping reaction is evident. Bilateral plantar signs are present but tendon reflexes are otherwise normal. L-dopa test was performed (with 100 mg) but did not yield any improvement 1 h after drug intake.

Biochemical and Radiological Results

Significant decreases of monoamine metabolites (HVA, DOPAC, 5-HIAA, MHPG) were found in the CSF (Table 1). In contrast, normal levels of P-tau, tau and β -amyloid (1–42) were found in the CSF. Analyses of GD biomarkers in blood are summarized in Table 1.

A CT scan of the brain, taken approximately 1 year earlier, showed status post right-sided pallidotomy, mild-to-

moderate bilateral subcortical atrophy, and moderate bilateral cortical atrophy of the frontal and temporal lobes with enlargement of the subarachnoidal spaces (Fig. 1).

Discussion

Recent studies indicate that both GD patients and single *GBA1* mutation carriers face an increased risk for PD (Bultron et al. 2010; Neumann et al. 2009; Sidransky et al. 2009). Common *GBA1* mutations such as c.1226A > G (N370S) and c.1448T > C (L444P) have been reported as the most frequent among PD patients of non-Jewish ancestry (Neumann et al. 2009; Sidransky et al. 2009). An open question remains whether the presence of the heterozygous *GBA1* gene mutation c.115 + 1G > A (IVS2 + 1) in the reported patient, uncommonly seen among GD patients and *GBA1* mutations carriers suffering from PD, influenced the reported course of PD.

The parkinsonian phenotypes reported among *GBA1* mutation carriers are variable and their response to L-dopa treatment has yielded conflicting reports (Toft et al. 2006; Velayati et al. 2010). Visual hallucinations and varying degrees of cognitive decline have been described among individuals with parkinsonism associated with *GBA1* mutations (Neumann et al. 2009). Interestingly, some

Table 1 Laboratory data on Gaucher disease biomarkers in blood and monoamine metabolites and dementia proteins in cerebrospinal fluid

Variable		Results (units)	Control ranges
Gaucher disease biomarkers measured in peripheral blood	Hemoglobin	133 (g/L)	120–180
	Platelets	63 ($\times 10^9$ /L)	150–450
	Chitotriosidase	2,010 (nkat/L) ^a	<40
	CCL18	2,070 (μ g/L)	<100
	Glucocerebroside (RBC)	9.6 (μ mol/L)	1.8–6.0
	Glucocerebroside (plasma)	13.9 (μ mol/L)	4.7–9.7
Monoamine metabolites and dementia proteins measured in cerebrospinal fluid	HVA	18.7 (nmol/L)	140–360
	DOPAC	8.9 (nmol/L)	20–50
	5-HIAA	29.6 (nmol/L)	70–180
	MHPG	1.6 (nmol/L)	35–60
	HVA _{corr}	6.6	40–170
	5-HIAA _{corr}	21.4	50–170
	MHPG _{corr}	3.3	65–140
	P-tau (181P)	31 ng/L	<80
	Total tau	128 ng/L	<400
	β -amyloid (1–42)	624 ng/L	>450

CCL18 chemokine (C–C motif) ligand 18 (pulmonary and activation-regulated), *RBC* red blood cells, *HVA* homovanillic acid, *DOPAC* 3,4-dihydroxyphenylacetic acid, *5-HIAA* 5-hydroxyindole-3-acetic acid, *MHPG* 3-methoxy-4-hydroxyphenylethylenglycol

^a The patient is a heterozygote for polymorphism in chitotriosidase gene and the theoretical activity of the chitotriosidase is doubled (4,020 nkat/L). The activity of chitotriosidase is expressed in the international unit (SI) as nkat/L. 1 nkat/L = 3.6 nmol/mL/h

Fig. 1 Horizontal CT scan of brain showing status post right-sided pallidotomy and mild-to-moderate bilateral subcortical atrophy as well as moderate bilateral cortical atrophy in frontal and temporal lobes with associated increases of subarachnoid spaces. *R* – right hemisphere; *L* – left hemisphere

patients with parkinsonism associated with *GBA1* mutations had partial (Neudorfer et al. 1996) or excellent (Toft et al. 2006) responses to neurosurgical treatment by means of thalamotomy or DBS of the subthalamic nucleus. In accordance with previous studies (Neumann et al. 2009; Tayebi et al. 2003), optimal ERT did not influence the course of PD in our patient. The relatively early loss of L-dopa responsiveness in this case was interpreted as atypical parkinsonism in previous reports; however, the patient did not display autonomic dysfunction, apraxia, early falls or ataxia during the course of the disease. Moreover, in contrast to the present case, survival is significantly reduced in atypical parkinsonism.

Recent studies have demonstrated the presence of Lewy bodies in the brains of patients with PD associated with *GBA1* mutations (Neumann et al. 2009). Lewy bodies consist of α -synuclein inclusions associated with other proteins. Glucosylceramide has been found in α -synuclein inclusions in the brains of individuals with parkinsonism associated with *GBA1* mutations and less frequently in individuals without *GBA1* mutations (Goker-Alpan et al. 2010).

The role of tau in PD associated with *GBA* mutations has been less studied than that of α -synuclein. Several atypical forms of parkinsonism including progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia show increased levels of P-tau, tau and/or altered splicing of this protein (Eller and Williams 2009). Our patient demonstrated normal concentrations of P-tau and tau in his CSF. In contrast to previous case study

(Alonso-Canovas et al. 2010), reporting lowered β -amyloid (1–42) levels in CSF, our patient showed normal CSF concentrations of β -amyloid (1–42). Thus, the cognitive decline, akinetic mutism, and moderate cortical atrophy found in the reported patient are not paralleled by any changes of dementia markers in CSF. These findings are in contrast with those found in Niemann–Pick disease type C (neuronopathic LSD), where tau and β -amyloid (1–42) levels in CSF are increased (Mattsson et al. 2011). Further CSF analyses revealed that our patient had remarkably low levels of all studied monoamine metabolites. These data indicate that parkinsonism associated with *GBA1* mutations may not only affect dopaminergic neurons, but also noradrenergic and serotonergic neurons.

Both the gain- and loss-of-function of *GBA* have been proposed as mechanisms of disease leading to possible ceramide accumulation (Bras et al. 2008), disturbances in lysosomal functioning/trafficking in microglia and/or neurons, due to a membrane imbalance of recycled glucosylceramide as well as enhanced α -synuclein aggregation (Goldin 2010). One possibility is that mutated *GBA* may act as a “second hit” in some individuals genetically predisposed to develop PD. Further studies on how *GBA1* mutations predispose to Lewy bodies pathology, neuronal vulnerability and parkinsonism are needed. This report extends current knowledge on PD associated with *GBA1* mutations and suggests that parkinsonian symptoms in such cases can develop over many years and be treated relatively successfully.

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Synopsis

The article reports the longest follow-up of Parkinson’s disease associated with Gaucher disease and provides the clinical and biochemical data on this association.

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