Occurrence of Parkinson’s syndrome in type I Gaucher disease

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Summary

Gaucher disease, the most prevalent glycolipid storage disorder, is classically subdivided into types according to the presence or absence of neurological involvement. Type I has hitherto been considered non-neuronopathic. We present six cases and a review of the literature of Parkinsonian symptoms in type I Gaucher disease patients. The hallmark of this atypical Parkinsonian syndrome is a relatively severe clinical course with early appearance of neurological signs in the 4th to 6th decade of life, aggressive progression of the signs and refractoriness to conventional anti-Parkinson therapy. We discuss the implications of these findings in the light of enzyme replacement therapy for Gaucher disease.

Introduction

Gaucher disease, the most prevalent sphingolipid storage disorder, is a defect of glucocerebrosidase activity due to mutations in the gene encoding the lysosomal enzyme glucocerebrosidase, with consequent accumulation of the glycolipid glucocerebroside in the cells of the monocyte-macrophage system.¹ The disease has three clinical forms, distinguished by the presence and aggressivity of neurological complications.² Type I, the non-neuronopathic form, is the most common, with an ethnic predilection among Ashkenazi Jews.³,⁴ Presentation in type I is variable, with onset of symptoms noted in infants as well as in the elderly; the course of the disease is also variable with sudden accelerations at all ages. Even among family members with the same genotype, the severity of the disease may differ. Clinical heterogeneity is most characteristic of type I, and many patients with this type remain virtually asymptomatic and are only diagnosed during evaluation for an unrelated disorder or because of family screening of a symptomatic relative.⁵ The presence of the single most common mutation, N370S (1226G) on one allele appears to be protective of development of a neuronopathic form, and indeed the genotype N370S/N370S is the most common among type I patients.³,⁶

Type II Gaucher disease (infantile, acute neuronopathic) and type III (juvenile, subacute neuronopathic) are rare and panethnic. In type II, the neurological signs become evident during the first months of life, including oculomotor apraxia, strabismus, hypertonia and retroflexion of the head. These contribute to death (of aspiration pneumonia in most cases) before the age of 2 years.⁷ Type III disease is characterized by similar but less fulminant symptoms, including horizontal supranuclear gaze palsy, myoclonic epilepsy, dementia, ataxia or spasticity, and is usually fatal before early adulthood.⁸,⁹

Methods

Patients

Six patients, all of whom had been diagnosed with Gaucher disease on the basis of bone-marrow aspir-
Jewish extraction was 47.5 ± 4.76 years. We have
there were three males and three females; mean age
at diagnosis was 32 (range 15–45) years. Most
suffered from anaemia and/or thrombocytopenia, and
moderate hepatosplenomegaly, and three had under-
gone splenectomy. Four of six patients complained
of bone pains or other skeletal involvement.

Mean age at onset of Parkinsonian symptoms was
48.8 (range 41–55) years. The common extrapyram-
idal signs were intention tremors (in three patients),
rigidity and bradykinesia (in all patients), expres-
sionless facies (in two patients) and slurred or mono-
tonous speech (in four patients). One patient had
myoclonic jerks. Two patients had received psychiat-
ric treatment for depressive or psychotic episodes.
The course of the neurological manifestations was
well-recorded in four patients, one patient refused
all medical care and was lost to follow-up, and
another patient died during initial evaluation. Of the
four patients with documented clinical histories, four
had neurological symptoms and signs that were
refractory to Levodopa or other anti-Parkinsonian
medications. Two patients underwent stereotactic
thalamotomy for relief of their neurological symp-
toms, with only partial responses.

**Statistical analyses**

The age of onset of Parkinsonian symptoms in the
Gaucher patients in this study who were of Ashkenazi
Jewish extraction was 47.5 ± 4.76 years. We have
compared this group to 41 randomly assigned
Ashkenazi Jewish patients with the clinical diagnosis
of Parkinson disease, who underwent an enzymic
assay, and in whom Gaucher disease was excluded.

The age of onset of symptoms in the group of patients
with Parkinson disease was 61.4 ± 10.24 years. The
Student’s t-test for two groups revealed this to be
significant: \( p = 0.002 \); as did the non-parametric
U-test (Mann-Whitney): \( p = 0.005 \). The age of onset
of Parkinsonian symptoms in Ashkenazi Jewish
Gaucher patients is thus significantly earlier than in
patients with Parkinson’s disease in the same popula-
tion without Gaucher disease.

**Discussion**

Anecdotal reports of adult patients with type I
Gaucher disease but with neurological symptoms,
such as seizures, psychosis or mental illness and
deterioration have previously been considered late-
onset type III disease or unrelated concurrence of
symptoms.\(^{10–18}\) Neurological symptoms in what has
been regarded as the non-neuronopathic form of
Gaucher disease have however been reported previ-
ously in the literature. Among the earliest is a case
in 1942 by Davidson\(^{10}\) of a 26-year-old male with
clinically assessed type I Gaucher disease who
subsequently developed facial immobility. Groth
et al.\(^{11}\) described a 24-year-old male who presented
with tremor, muscle atrophy, epilepsy and mental
retardation, but who was consequently assumed to
have type III disease. Another case reported by Miller
et al.\(^{12}\) of adult, non-Jewish siblings with biochem-
ically-ascertained Gaucher disease, had presented
with a neurological disorder in the fourth decade of
life, characterized by seizures, mental deterioration
and oculomotor disturbances which was concluded
to be not unlike CNS impairment of type III Gaucher
disease. King\(^{13}\) outlined a 20-year history of
myoclonic epilepsy and mental deterioration in a
38-year-old man with type I Gaucher disease. Neil
et al.\(^{14}\) reported a mother and two adult children,
the latter of whom were diagnosed by bone-marrow
aspirate as having Gaucher disease at ages 21 and
20 years, respectively. All three demonstrated neuro-
psychiatric abnormalities including psychosis,
depression, mental deterioration and confusion; the
mother and daughter were both diagnosed as having
Parkinson syndrome. In a series of four patients,
Sack\(^{15}\) emphasized the variegated clinical picture of
type I Gaucher disease, including one patient with
‘atypical Parkinson syndrome’. McKeran et al.\(^{16}\)
discussed the case of tapetoretinal degeneration in a
woman with moderate Gaucher disease for 38 years,
whose extrapyramidal symptoms were initially con-
trolled by dopamine but who was unresponsive to
all medications within two years. Turpin et al.\(^{17}\)
reported a Gaucher patient with Parkinson-like symp-
toms which they considered to be causally related.

The nature of the putative association between
Gaucher disease and extrapyramidal symptoms
remains to be elucidated. It appears, however, that
there is no overt relationship between the presence
of CNS symptoms and pathological findings in the
brain. In most instances where Gaucher’s cells have
been identified in the brains of patients with type I
disease, the cells were observed in the perivascular
space\(^{18}\) and in sheets in the meninges.\(^{19}\) However,
those pathological findings occurred in patients with-
out neurological symptoms. Conversely, in one of
our patients, post-mortem examination of the brain
and meninges was unremarkable, and no cellular
infiltration with Gaucher cells was observed. The
absence of Gaucher’s cells in the nervous system
was also noted in some cases of neuronopathic
Gaucher disease,\(^{20}\) thus it is clearly not a requirement
for the diagnosis of neurological complications of
Gaucher disease.
While the possibility of late development of neurological complications in patients with type 1 Gaucher disease is interesting in itself, the recent introduction of enzyme replacement therapy (algulcerase; Genzyme21-23), adds a practical consideration to dealing with these disabling late manifestations of the disease. We speculate that Gaucher patients, including those with mild disease but who develop Parkinsonism, could benefit from treatment with enzyme replacement therapy, which may indirectly affect the emergence or deterioration of the extrapyramidal disorder. A physiological correlate of this hypothetical relationship has been described: defective neutrophil migration has been demonstrated in approximately one third of untreated Gaucher patients studied24 and correction of this chemotactic defect was documented during the course of enzyme replacement therapy.25 It is possible that by correcting the biochemical defect, late sequelae of the disease may be averted.

Until more information is available regarding the contribution of enzyme replacement therapy to the natural clinical course of the disease, we suggest that patients with early onset of post-synaptic extrapyramidal syndrome that responds poorly to conventional anti-Parkinson medication, should be evaluated for Gaucher disease.

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