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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-

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ate or splenic biopsy specimen, and on the basis of decreased glucocerebrosidase activity, developed a Parkinsonian syndrome: one non-Jewish patient from Italy, and five Ashkenazi Jewish patients from Israel. 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 undergone 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 extrapyramidal signs were intention tremors (in three patients), rigidity and bradykinesis (in all patients), expressionless facies (in two patients) and slurred or monotonous speech (in four patients). One patient had myoclonic jerks. Two patients had received psychiatric 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 symptoms, 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 population 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 previously 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 biochemically-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 neuropsychiatric 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 controlled by dopamine but who was unresponsive to all medications within two years. Turpin *et al.*[17] reported a Gaucher patient with Parkinson-like symptoms 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 without 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 I Gaucher disease is interesting in itself, the recent introduction of enzyme replacement therapy (alglucerase; Genzyme[21–23]), 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 studied[24] 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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References

1. Beutler E, Grabowski GA. Glucosylceramide lipidoses. In: Scriver CR, Beaudet AL, Sly WS, *et al.*, eds. *The Metabolic Basis of Inherited Disease*, 7th edn. New York, McGraw-Hill, 1995.
2. Knudson AG, Kaplan WD. Genetics of the sphingolipidoses. In: Aronson SM, Volk BW, eds. *Cerebral sphingolipidoses: a symposium on Tay-Sachs disease and allied disorders*. New York, Academic Press, 1962:395–411.
3. Horowitz M, Tzuri G, Eyal N, Berebi A, Kolodny EH, Brady RO, Barton NW, Abrahamov A, Zimran A. Prevalence of nine mutations among Jewish and non-Jewish Gaucher patients. *Am J Hum Genet* 1993; **53**:921–30.
4. Beutler E. Gaucher disease: new molecular approaches to diagnosis and treatment. *Science* 1992; **256**:794–9.
5. Zimran A, Sorge J, Gross E. Prediction of severity of Gaucher's disease by identification of mutations at DNA level. *Lancet* 1989; **2**:349–53.
6. Horowitz M, Wilder S, Horowitz Z, Reiner O, Gelbart T, Beutler E. The human glucocerebrosidase gene and pseudogene: structure and evolution. *Genomics* 1989; **4**:87–96.
7. Sidransky E, Sherer DM, Ginns EI. Gaucher disease in the neonate: A distinct Gaucher phenotype is analogous to a mouse model created by targeted disruption of the glucocerebrosidase gene. *Pediatr Res* 1992; **32**:494–8.
8. Svennerholm L, Dreborg S, Erikson A, Groth CG, Hillborg PO, Hakansson G, Nilsson O, Tibblin E. Gaucher disease of the Norbottnian (type III). Phenotypic manifestations. In: Desnick RJ, Gatt S, Grabowski GA, eds. *Gaucher Disease: A Century of Delineation and Research*. New York, Alan R Liss, 1982:67–94.
9. Patterson MC, Horowitz M, Abel RB, Currie JN, Yu K-T, Kaneski C, Higgins JJ, O'Neill RR, Fedio P, Pikus A, Brady RO, Barton NW. Isolated horizontal supranuclear gaze palsy as a marker of severe systemic involvement in Gaucher's disease. *Neurology* 1993; **43**:1993–7.
10. Davidson C. Disturbance in lipid metabolism and the central nervous system. *Mt Sinai J Med* 1942; **9**:389–406.
11. Groth C-G, Hagenfeldt L, Dreborg S, Lofstrom B, Ockerman PA, Samuelsson K, Svennerholm L, Werner B, Westberg G. Splenic transplantation in a case of Gaucher's disease. *Lancet* 1971; **31**:1260–4.
12. Miller JD, McCluer R, Kanfer JN. Gaucher's disease: Neurologic disorder in adult siblings. *Ann Intern Med* 1973; **78**:883–7.
13. King JO. Progressive myoclonic epilepsy due to Gaucher's disease in an adult. *J Neurol Neurosurg Psychiatr* 1975; **38**:849–53.
14. Neil JF, Glew RH, Peters SP. Familial psychosis and diverse neurologic abnormalities in adult-onset Gaucher's disease. *Arch Neurol* 1979; **36**:95–99.
15. Sack Jr GH. Clinical diversity in Gaucher's disease. *Johns Hopkins Med J* 1980; **146**:166–70.
16. McKeran RO, Bradbury P, Taylor D, Stern G. Neurological involvement in type 1 (adult) Gaucher's disease. *J Neurol Neurosurg Psychiatr* 1985; **48**:172–5.
17. Turpin JC, Dubois G, Brice A, Masson M, Nadaud MC, Boutry JM, Schram AW, Tager JM, Baumann N. Parkinsonian symptomatology in a patient with type 1 (adult) Gaucher's disease. In: Salvayre R, Douste-Blazy L, Gatt S, eds. *Lipid Storage Disorders. Biological and medical aspects*. New York, Plenum Publishing, 1987:103–4.
18. Soffer D, Yamanaka T, Wenger DA, Suzuki K, Suzuki K. Central nervous system involvement in adult-onset Gaucher's disease. *Acta Neuropathol (Berl)* 1980; **49**:1–6.
19. Chang-Lo M, Yam LT, Rubenstone AI. Gaucher's disease. Review of the literature and report of twelve new cases. *Am J Med Sci* 1967; **254**:303–15.
20. Lee RE. The pathology of Gaucher disease. In: Desnick RJ, Gatt S, Grabowski GA, eds. *Gaucher Disease: A Century of Delineation and Research*. New York, Alan R Liss, 1982:177–217.
21. Barton NW, Brady RO, Dambrosia JM, Bisceglie AM, Doppelt SH, Hill SC, Mankin HJ, Murray GJ, Parker RI, Argoff CE and collaborators. Replacement therapy for inherited enzyme deficiency: macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991; **324**:1464–70.
22. Pastores GM, Sibille AR, Grabowski GA. Enzyme therapy in Gaucher disease type 1: dosage, efficacy and adverse effects

in 33 patients treated for 6 to 24 months. *Blood* 1993; **82**:408–16.

23. Zimran A, Elstein D, Kannai R, Zevin S, Hadas-Halpren I, Levy-Lahad E, Cohen Y, Horowitz M, Abrahamov A. Low-dose enzyme replacement therapy for Gaucher's disease—effects of age, sex, genotype, and clinical features on response to treatment. *Am J Med* 1994; **97**:3–13.
24. Aker M, Zimran A, Abrahamov A, Horowitz M, Matzner Y. Abnormal neutrophil chemotaxis in Gaucher disease. *Br J Haematol* 1993; **83**:187–91.
25. Zimran A, Abrahamov A, Aker M, Matzner Y. Correction of neutrophil chemotaxis defect in patients with Gaucher disease by low dose enzyme replacement therapy. *Am J Hematol* 1993; **43**:69–71.