□ CASE REPORT □

Parkinsonism in Type I Gaucher's Disease

Kaori Itokawa¹, Naotoshi Tamura¹, Nobutaka Kawai², Kunio Shimazu¹ and Kenji Ishii³

Abstract

The majority of patients with type I Gaucher's disease never develop neurological signs or symptoms. However, several case reports of Parkinson's disease associated with type I Gaucher's disease have been published, suggesting a genetic link between the two diseases. Hence, detailed clinical investigations are required when the two diseases occur simultaneously, in order to determine whether this is coincidental or whether a true association is present. We present a Japanese man in whom parkinsonism was associated with type I Gaucher's disease. Findings of brain positron tomography (PET) and metaiodobenzylguanidine (MIBG) cardiac scintigraphy are presented.

Key words: Gaucher's disease, parkinsonism, metaiodobenzylguanidine myocardial SPECT, fluorodeoxy-glucose PET, levodopa

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Case Report

A 42-year-old man with type I Gaucher's disease was admitted to our hospital with an 8-month history of poor mobility of the right leg. His intelligence seemed normal; he was working in computer engineering with no reported difficulties. Gaucher's disease had been diagnosed at the age of 31, based on the following typical findings; hepatosplenomegaly, Gaucher cells on bone marrow biopsy, reduction in β -glucosidase activity, and L444P/R463C mutation of the glucocerebrosidase gene on genetic analysis. Enzyme replacement therapy had been started at the age of 34, and signs of Gaucher's disease, including anemia and hepatosplenomegaly, were absent at the present admission. On neurological examination, cogwheel-type rigidity was evident in the right upper and lower limbs, and poor arm swing was noted on walking, but tremor was absent. Mental function was normal. However, his speech was limited and monotonous, and facial expression was masked. Finger tapping was slow on the right side but retropulsion was absent. Deep tendon reflexes were normal and pathological reflexes were absent. Dysidiadochokinesis was absent. Brain MRI failed to demonstrate any lesions. PET using [F-18] fluorodeoxyglucose (FDG) as a tracer showed hypometabolism in

the frontal and parietal cortices, although metabolism in the striatum was well preserved (Fig. 1). [I-123] MIBG myocardial SPECT revealed persistent low uptake in the inferoposterior area on early phase and complete absence of MIBG uptake in this area on delayed phase. [Tc-99m] tetrofosmin SPECT revealed low uptake in the septum and inferior areas (Fig. 2), suggesting that the reduced MIBG uptake in these areas was due to old myocardial infarction. However, ECG was normal, and the patient denied any history of apparent myocardial infarction. Levodopa-carbidopa therapy was commenced at an initial dose of 100 mg daily and subsequently increased to 200 mg daily, following which his gait disturbance and hand immobility were resolved.

Discussion

In their case report of Parkinson's disease associated with type I Gaucher's disease, Tayebi et al (1) described a crossover between the glucocerebrosidase gene (GBA) and metaxin gene. The metaxin gene is involved in mitochondrial function, which may be altered in Parkinson's disease. Aharon-Peretz et al (2) reported that 31.3% of cases with Parkinson's disease exhibit genetic susceptibility. These studies suggest a common genetic basis for both Gaucher's disease and Parkinson's disease. To date, no anomaly in the

¹ Department of Neurology, Saitama Medical University, Saitama, ² Department of Hematology, Saitama Medical University, Saitama and ³ Position Medical Center, Tokyo Metropolitan Institute of Gerontology, Tokyo

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Correspondence to Dr. Kaori Itokawa, Department of Neurology, Saitama Medical School, 38 Moro Hongo, Moroyama-cho, Iruma-gun, Saitama 350-0495

Figure 1. [F-18] FDG PET shows hypometabolism in the frontal and parietal cortices, but metabolism in the striatum is well preserved.

Figure 2. MIBG myocardial SPECT shows persistent low uptake in the infero-posterior area (a); however, [Tc-99m] tetrofosmin SPECT also reveals low uptake in the septum and inferior areas (b), suggesting that reduced MIBG uptake is due to cardiac infarction rather than sympathetic denervation. H/M ratio is 1.84.

GBA/metaxin gene has been identified in any form of hereditary parkinsonism, but we do not consider the co-existence of Gaucher's disease and Parkinson's disease to be a mere chance association.

However, the clinical features of Parkinson's disease in type I Gaucher's disease differ somewhat from those of typical Parkinson's disease (1-7). In most published cases,

the age at onset of parkinsonism was younger than that seen in typical Parkinson's disease, resting tremor was not evident, and the effect of levodopa was relatively poor. However, further clinical investigations were not described in these articles. In the present case, parkinsonism responded well to levodopa therapy, and [F-18] fluorodeoxyglucose (FDG) PET revealed that function of the striatum, a post-synaptic structure of the nigro-striatal dopaminergic pathway, was well preserved. These findings are identical to those of idiopathic Parkinson's disease.

However, onset as early as the 5th decade of life, absence of resting tremor, and relative preservation of myocardial MIBG uptake are not typical features of idiopathic Parkinson's disease. In particular, MIBG myocardial scintigraphy has been established as a useful tool to distinguish idiopathic Parkinson's disease from other parkinsonian syndromes such as multiple system atrophy and progressive supranuclear palsy. Myocardial uptake of MIBG is completely absent, indicating cardiac sympathetic denervation, in the majority of cases of idiopathic Parkinson's disease, even in the earlier stages, while it is well-preserved in other parkinsonian syndromes (8-11). In the present case, apart from a partial defect of MIBG uptake probably due to old myocardial infarction, MIBG scintigraphy did not indicate a reduced uptake. Normal uptake of MIBG in the present case may represent a lack of Levy body pathology, since MIBG uptake is also preserved in autosomal recessive juvenile parkinsonism with PARK2 anomaly (10).

It is noteworthy that the clinical features of parkinsonism in Gaucher's disease differ distinctly from those of typical Parkinson's disease. While we do not consider the co-existence of Gaucher's disease and Parkinson's disease to represent a mere chance association, it is noteworthy that the clinical features of such cases differ distinctly from those of typical Parkinson's disease. Gaucher's disease-related parkinsonism may account for a small number of cases of Parkinson's disease.

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