A Patient with the GLA p.E66Q Mutation Exhibiting Vascular Parkinsonism and Bilateral Pulvinar Lesions

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Abstract

A 76-year-old man was admitted to our hospital due to gait difficulty. Brain imaging indicated bilateral pulvinar lesions and moderate white matter lesions. The serum α-galactosidase A levels were measured for the differential diagnosis of bilateral pulvinar lesions and were found to be abnormally low. Therefore, the patient was suspected to have variant Fabry disease. A GLA mutation analysis showed the p.E66Q mutation, which is speculated to be a functional polymorphism rather than a disease-causing mutation of Fabry disease. Enzyme replacement therapy did not result in a marked improvement, however, the disease progression stopped.

Key words: pulvinar sign, Fabry disease, vascular parkinsonism

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Introduction

Recently, pulvinar lesions (pulvinar sign) have been recognized as a characteristic finding in patients with Fabry disease (1, 2). We herein report a patient with the pulvinar sign and low, but residual α-galactosidase A (α-Gal A) levels. The genetic analysis revealed a GLA p.E66Q mutation, which is considered to be a functional polymorphism. We additionally discuss the pathophysiology of pulvinar lesions and their relationship to the p.E66Q mutation.

Case Report

A 76-year-old man was admitted to our department for an examination of a slowly progressive gait disturbance that he first noticed 2 years previously. He had developed an intracranial hemorrhage at 64 years of age and ischemic stroke at 72 years of age and had received cilostazol (200 mg/day). Thereafter, the patient exhibited no apparent signs of motor deficit. He was aware of mild cardiomegaly for more than 30 years, which did not require treatment. Moreover, he was diagnosed with diabetes mellitus, hypertension, and dyslipidemia, for which he was treated with oral hypoglycemic and antihypertensive drugs. His parents had no histories of specific disease and both died at an advanced age. He had one brother, five sisters, and two children. His brother had diabetes and one of his sisters had a history of stroke. Other than these conditions, the patient had no specific family history of any disease.

On admission, he presented with a mild cognitive impairment, reduced motivation, and lower-body parkinsonism, which was defined as a shuffling gait with small steps without laterality, and preserved agility in the upper extremities. There were no specific general findings, such as skin or corneal lesions. The patient did not have either neuropathic or limb pain.

A blood test showed mild diabetes (HbA1C: 6.8%) but no dyslipidemia (low-density lipoprotein cholesterol, 88 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; triglycerides, 146 mg/dL). The renal function was within the normal limits (blood urea nitrogen, 14.7 mg/dL; creatinine, 0.9 mg/dL). The serum calcium level was 9.0 mg/dL, and the phosphorus level was 3.2 mg/dL. The cerebrospinal fluid cell count was 0/mm³ and the protein level was 52 mg/dL. Echocardiography showed mild left ventricular hypertrophy.

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Brain computed tomography (CT) showed high-density lesions in the bilateral pulvinar areas (Figure A). The bilateral pulvinar lesions showed a high intensity on T1-weighted magnetic resonance imaging (MRI) (Figure B). Brain MRI also revealed moderate white matter lesions and diffuse mild atrophy of the brain (Figure C). Brain magnetic resonance angiography showed diffuse mild sclerotic changes and the basilar artery was slightly enlarged and tortuous (Figure D).

The serum α-Gal A level, which was examined for the differential diagnosis of bilateral pulvinar lesions, was 0.027 U/L (measured by Mitsubishi Chemical Medience, Tokyo, Japan; reference value 0.074-0.457). A GLA mutation analysis indicated the p.E66Q mutation in exon 2.

The patient was suspected to have variant Fabry disease according to the findings of the low serum α-Gal A level, cardiomegaly, and the pulvinar sign. Although levodopa-benserazide (300 mg/day) therapy was administered, no improvement was observed in the patient. Enzyme replacement therapy (ERT) [agalasidase alfa (genetic recombination), 0.2 mg/kg, once every 2 weeks] was initiated to control the progression of the symptoms.

The patient showed no adverse reactions to this treatment. During a 1-year follow-up, his gait disturbance did not progress, despite the progression before the initiation of therapy, and his motivation improved.

Discussion

Bilateral pulvinar lesions are occasionally observed in several other disorders, such as Creutzfeldt-Jakob disease, fungal meningitis, cerebrovascular disease, epilepsy, and paraneoplastic limbic encephalitis. However, these disorders were unlikely in the differential diagnosis of the present patient according to his medical history and clinical data. Recently, bilateral T1 hyperintense lesions (pulvinar sign) in Fabry disease patients have been reported and are considered to be a characteristic finding for Fabry disease (1, 2). However, a small number of cases with the pulvinar sign which were not related to Fabry disease have also been reported (3, 4).

The pathogenesis of the pulvinar lesions of Fabry disease remains unclear. No histopathological studies have been performed on the pulvinar lesions, however, the pathogenesis is...
assumed to be tissue mineralization, such as calcium or other metallic deposition, as shown by radiology (1). Fellgiebel et al. reported that basilar arterial dilatation is a characteristic central nervous system change in Fabry disease (5). Because the thalamus is in the area of posterior circulation, basilar arterial dilatation and the development of the pulvinar lesion may be related. The basilar artery in the present case appeared to be slightly dilated, but not enlarged, similar to the case reported by Fellgiebel et al (5). Fellgiebel et al. showed dilatation by an absolute value, and this value is thought to vary by ethnic differences (5).

In previous reports, the pulvinar sign was observed in the patients whose diagnosis of Fabry disease was already established. Therefore, the diagnostic value of the pulvinar sign in Fabry disease has not yet been verified. In the present patient, the pulvinar sign was the initial clue that led to the measurement of the α-Gal A level, which we found to be low.

Fabry disease is an X-linked lysosomal storage disorder caused by α-Gal A deficiency. The patients with Fabry disease typically present with neuropathic pain, telangiectasias, and angiokeratomas. There are variants of Fabry disease, however, the symptoms are confined to the heart or kidney and are characterized by residual α-Gal A enzyme activity (6, 7). The present patient showed an abnormally low α-Gal A level but still had residual α-Gal A activity. The typical symptoms were absent, although mild cardiomegaly was observed. Considering the low α-Gal A level and the pulvinar sign, the present patient was suspected to show the common pathophysiology of Fabry disease.

The GLA p.E66Q mutation is not considered to be a disease-causing mutation of Fabry disease, but rather a functional polymorphism (8, 9). Nakamura et al. reported that the p.E66Q mutation was associated with a high risk of cerebral small-vessel occlusion in elderly Japanese men (10), and the present case presented with moderate white matter lesions, similar to the report of Nakamura et al. Additionally, Takanashi et al. reported that all the patients with pulvinar lesions had white matter lesions (2). Therefore, the combination of pulvinar lesions and white matter lesions in Fabry disease may have a common pathophysiology. Conversely, Nakamura et al. did not observe any pulvinar lesions in their study (10). Therefore, it is difficult to determine a direct relationship between the p.E66Q mutation and the pulvinar lesion. The activity of α-Gal A in the patients with the p.E66Q mutation has been previously reported to be lower than that in the patients with the wild-type allele (6, 8, 11, 12). However, the histopathological changes in Fabry disease have yet not been observed in patients with the p.E66Q mutation (9). Therefore, such patients are not thought to require ERT if they only have the p.E66Q mutation. It is necessary to investigate whether or not the small-vessel injury seen in the population having the p.E66Q mutation is the result of a lower α-Gal A activity. Recently, Maruyama et al. reported that, using a highly sensitive technique, plasma globotriaosylphosphoglycerine-a hallmark of Fabry disease-can be detected in the patients with the p.E66Q mutation (13). Their report highlights the need to continue investigations and discussions on the pathogenicity of the p.E66Q mutation.

The present patient exhibited lower-body dominant, symmetrical parkinsonism, with a poor response to levodopa. Brain MRI showed no specific signs of degenerative Parkinson’s syndrome, but demonstrated moderate white matter lesions. Vascular parkinsonism has been reported to be more closely associated with white matter lesions than with basal ganglia lesions (14). Other causes of gait disturbance, such as lumbar spondylosis, were not observed in the present patient. Therefore, we diagnosed the patient with vascular parkinsonism. If the formation of the white matter lesions accompanied by the pulvinar lesions is due to the low α-Gal A activity, ERT may reduce the progression of the symptoms, such as parkinsonism or cognitive impairment.

Although the present patient could not be definitively diagnosed with Fabry disease due to the lack of histopathological and genetic evidence, attention to the pulvinar sign on MRI and CT may help identify the patients with low α-Gal A activity, even without a family history or typical symptoms. Additionally, ERT for such patients may inhibit the progression of functional deterioration, such as parkinsonism. However, no evidence currently exists to support the use of ERT in elderly people with residual α-Gal A activity. Further studies are required to evaluate the pathognomonic significance of the pulvinar sign and determine the efficacy of ERT for such patients.

The authors state that they have no Conflict of Interest (COI).

References
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