Recurrence Cerebrovascular Complications under Enzyme Replacement Therapy in a Patient with Fabry Disease on Peritoneal Dialysis

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Abstract:
Fabry disease is an X-linked lysosomal storage disorder due to mutations in the alpha-galactosidase A (GLA) gene, which leads to the accumulation of globotriaosylceramide in various organs. In Fabry disease with end-stage renal disease (ESRD), cerebrovascular events are lethal, even with enzyme replacement therapy (ERT). However, the utility of biomarkers to evaluate the ERT response is unclear. We herein report a case of recurrent cerebrovascular complications under ERT in a Fabry disease patient, progressing to ESRD on peritoneal dialysis. Further studies are warranted, but Fabry disease patients with ESRD receiving ERT might need careful long-term follow-up in cases with cerebrovascular manifestations.

Key words: Fabry disease, peritoneal dialysis, renal replacement therapy, enzyme replacement therapy, end-stage renal disease

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Introduction

Fabry disease is a rare X-linked lysosomal storage disorder due to mutations in the alpha-galactosidase A (GLA) gene causing complete or partial deficiency of the enzyme GLA. Subsequently, various metabolites, mainly in the form of globotriaosylceramide (GL-3), slowly accumulate in several cell types and body fluids, leading to life-threatening renal, cardiac, and cerebrovascular complications, during the third to fifth decades of life (1).

In Fabry disease, cerebrovascular manifestations, such as stroke and cerebral bleeding, are frequent and severe (2). However, the efficacy of enzyme replacement therapy (ERT) for reducing cerebrovascular mortality in Fabry disease patients with end-stage renal disease (ESRD) undergoing dialysis therapy has not been shown (3). Furthermore, no specific guidelines have addressed monitoring during ERT, and the utility of biomarkers such as GL-3 in the monitoring of the response to ERT has not been clearly demonstrated, although recent studies have mentioned the possible utility of plasma globotriaosylphosphoglycerine (Lyso-Gb3) (4-10). However, biomarkers for predicting lethal events have yet to be identified, especially in Fabry disease patients with ESRD under ERT.

We herein report a case of recurrent cerebrovascular complications under ERT in a patient with Fabry disease on peritoneal dialysis for 10 years. Further studies are necessary, but Fabry disease patients with ESRD receiving ERT might need continuous careful long-term monitoring in case of unexpected cerebrovascular complications.

Case Report

A 45-year-old man with classic Fabry disease started peritoneal dialysis due to ESRD. At 40 years old, he had been

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referred to our department with proteinuria, anhidrosis, acroparesthesia, and a dark-red rash on the scrotum and inner thigh. He had two cousins with Fabry disease who were on hemodialysis. We conducted a skin biopsy, which showed angokeratoma. Electrocardiography showed left ventricular hypertrophy (data not shown). He also displayed neurological, renal, and dermatological manifestations as well as cardiac manifestations. His GLA activity was low in neurological, renal, and dermatological manifestations as well as cardiac manifestations. His GLA activity was low in the peripheral leukocytes, at 0.26 nmol/2 h/mL (healthy control: 98.6±27.3 nmol/2 h/mL). These results confirmed a diagnosis of classic Fabry disease. Regarding his genotype, he was hemizygous for the C.195-1 G>T splicing variant. However, genetic analyses were not performed in his relatives.

With marketing approval having been obtained in Japan, agalsidase beta was started at a dose of 1.0 mg/kg every two weeks when the patient was 42 years old, according to the recommendations from the manufacturer. At 45 years old, the renal function gradually decreased, progressing to ESRD. The patient selected peritoneal dialysis as a renal replacement therapy, as admission to the hemodialysis clinic three times a week was deemed difficult due to his full-time employment.

A physical examination at the initiation of peritoneal dialysis therapy showed the following: height, 162 cm; weight, 51.8 kg; body temperature, 36.8 °C; blood pressure, 118/71 mmHg; and heart rate, 64 beats/min in sinus rhythm. Clinical laboratory findings were as follows: white blood cells, 3,600/μL; hemoglobin, 11.4 g/dL; platelets, 13.5×10^4/μL; C-reactive protein, 0.2 mg/dL; blood urea nitrogen, 74.0 mg/dL; triglyceride, 98 mg/dL; low-density lipoprotein cholesterol 86 mg/dL; urinary red blood cells, 1-3 per high-power field; and urinary protein, 1.8 g/day (Table). Peritoneal dialysis was started on a regimen comprising 1.5% dextrose (total, 3.3 L/day, 3 bag exchanges, Dianeal-N PD-4 1.5%; Baxter, Tokyo, Japan).

Three months after starting peritoneal dialysis, the patient suddenly developed dysarthria. Magnetic resonance imaging (MRI) showed signal hyperintensity in the left cerebral white matter, suggesting acute cerebellar infarction (Fig. 1a). Rehabilitation relieved the dysarthria. At 46 years old, he experienced rapid paralysis of the right upper and lower extremities. Computed tomography (CT) showed hyperintensity in the left putamen (Fig. 1b), interpreted as cerebellar hemorrhaging. Rehabilitation again led to improvements in his paralysis. Unfortunately, at 48 years old, the dose of agalsidase beta had to be almost halved due to a supply disruption when the manufacturing plant was shut down to clean up an instance of viral contamination. During this 1.5-year period of dose reduction in agalsidase beta, he only presented with palpitations once, an instance that was diagnosed as paroxysmal atrial fibrillation. However, after treatment with disopyramide and cardioversion, sinus rhythm was restored. Furthermore, his echocardiographic parameters were fairly constant, while the brain natriuretic peptide (BNP) level was slightly increased between 45 and 50 years old (Fig. 2). Of note, after resuming the prescribed dose of agalsidase beta following the 1.5-year dose-reduction period, no new active events were observed for another 4 years.

However, at 53 years old, he experienced sudden paralysis of the left upper and lower extremities. CT showed a hyperintense lesion in the right thalamus (Fig. 1c). He was then transferred to a rehabilitation hospital and abruptly died at 55 years old. The cause of death was unclear. His blood pressure values and lipid blood levels were within normal ranges; however, he had received minor doses of angiotensin receptor blocker, β-blocker, and spironolactone for cardiac stress during our 10-year observation period (11). The plasma D-dimer level had remained <0.50 μg/mL during his recurrent cerebrovascular complications. We did not measure the value of antiphospholipid antibody, congenital protein S, protein C, or antithrombin. However, anti-nuclear antibody and complement values were normal. Furthermore, T2-weighted MRI showed an enlarged basilar artery (5.94 mm, reference range: 3.30±0.59 mm), suggesting that Fabry disease was the etiology of stroke (Fig. 3). The basilar artery diameter was defined as the average of three measuring points: rostral, intermediate, and caudal (12, 13). These findings further supported the notion that the cause of his stroke was Fabry disease.

His clinical course is shown in Fig. 4.

### Discussion

This case involved a patient on peritoneal dialysis for 10

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**Table. Laboratory Data at the Initiation of PD.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (/μL)</td>
<td>5,000</td>
<td>3,300-8,400</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>64.4</td>
<td>39.8-70.0</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>3.4</td>
<td>0.0-5.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.3</td>
<td>11.0-14.7</td>
</tr>
<tr>
<td>Platelets (x10^4/μL)</td>
<td>17.5</td>
<td>13.0-34.0</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>19.0</td>
<td>8.0-20.0</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5</td>
<td>0.2-0.8</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m2)</td>
<td>53.0</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Total serum protein (g/dL)</td>
<td>6.5</td>
<td>6.7-8.3</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.1</td>
<td>3.9-4.9</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139</td>
<td>135-145</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>101</td>
<td>98-102</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.9</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>16</td>
<td>13-33</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>13</td>
<td>2-27</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.1</td>
<td>0.0-0.3</td>
</tr>
<tr>
<td>Urinary red blood cells (/HPF)</td>
<td>1-3</td>
<td>&lt;1-4</td>
</tr>
<tr>
<td>Urinary protein (g/day)</td>
<td>2.0</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>Alpha-galactosidase A activity (nM)</td>
<td>0.26</td>
<td>&lt;6.4</td>
</tr>
</tbody>
</table>

years with classic Fabry disease who suffered recurrent cerebrovascular complications despite ERT.

Compared to cases without ESRD, Fabry disease patients with ESRD show a higher incidence of serious cerebrovascular events (14). The prognosis of Fabry disease patients with ESRD is therefore poor, despite the development of ERT (14, 15). Clinically, ERT prevents development of the complications of classic Fabry disease in a dose-dependent manner (16). Antonio et al. showed that during two years of follow-up, dialysis patients treated with ERT did not develop
cerebrovascular manifestations (17). However, in Fabry disease with ESRD, particularly over the long term, the efficacy of ERT to reduce cerebrovascular events is still unclear (3).

Despite recently published studies having shown that regular observation of plasma Lyso-Gb3 is useful for monitoring Fabry patients during ERT (4-10), effective biomarkers for predicting life-threatening manifestations have yet to be identified, especially in patients with Fabry disease progressing into ESRD under ERT. Some studies have shown that the plasma GL-3 levels were higher in classic male Fabry patients than in control patients (8-10). Furthermore, other studies have observed a reduction in the plasma GL-3 levels after ERT treatment (7, 9). However, in Fabry patients with ESRD under ERT, the optimal GL-3 levels for predicting Fabry disease manifestations are unclear (18). In the present case, plasma GL-3 levels were not increased at the onset of cerebrovascular events during ERT. While we only measured the plasma GL-3 levels in our own case, we speculate that the level of plasma GL-3 might not correlate with cerebrovascular events.

In conclusion, we encountered a case of recurrent cerebrovascular complications under ERT in a patient with Fabry disease on peritoneal dialysis for 10 years. Further studies are warranted, but Fabry patients with ESRD receiving ERT might need to receive continuous, careful, long-term follow-up, in case of unexpected cerebrovascular manifestations.

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

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Authors’ contributions

RM and MM were responsible for the manuscript idea, interpretation of data, and writing of this paper. RM, YS, HS, KY, TI, SM, MM, and YI attended to the patient. MM took part in composing the manuscript and providing advice on the concept. All authors were involved in drafting, reviewing, and approving the final manuscript.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Written informed consent for the publication of this report was obtained from the patient.

References


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