A Case of Adult-onset Pompe Disease with Cerebral Stroke and Left Ventricular Hypertrophy

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Background: Pompe disease is an autosomal recessive glycogen storage disorder caused by a deficiency of the lysosomal glycogen-hydrolyzing enzyme acid α-glucosidase. The adult-onset form, late-onset Pompe disease, has been characterized by glycogen accumulation, primarily in skeletal and smooth muscles, causing weakness of the proximal limb girdle and respiratory compromises. *Case Report:* A 59-year-old female was admitted to the hospital with acute cerebral stroke at the age of 57 years. Following her admission, conventional conservative stroke management followed by cerebral arterial clipping was performed. However, weakness of lower extremities, predominantly in the right side, and evening headache were persisting. After obtaining a careful past history, she noticed that she had a history of recurrent respiratory tract infection and she did not like any physical exercise in school. She also complained of gait disturbance since 32 years of age. She had also been suffering from systemic hypertension since 40 years of age. She had mild respiratory and swallowing difficulties. Her brain Magnetic Resonance (MR) revealed multiple infractions and white matter degeneration with irregular basilar arterial walls. A computed tomography (CT) scan of lower extremities showed diffuse fibrosis of the proximal muscles predominantly on the right thigh. Cardiac echocardiogram showed left ventricular hypertrophy. Electron microscopy of blood cells including lymphocytes and platelets and skin fibroblasts showed marked granular inclusions in lysosomes, suggesting glycogen accumulation. Her measured acid α-glucosidase activity was very low, 1.3 pmol hour^{-1} punch^{-1}, and we found a homozygous splice-site mutation c.546G>T in the *GAA* gene. *Conclusion:* Cerebral stoke as an initial finding for an adult-type Pompe disease is rare. Left ventricular hypertrophy is also rarely reported for adult onset of Pompe disease. This case will explore further ways to diagnose adult-onset Pompe disease.

Key Words: Late-onset Pompe disease—cerebral stroke—acid α-glucosidase—enzyme replacement therapy.

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Received April 16, 2018; revision received June 26, 2018; accepted June 30, 2018.

Conflict of interest: The authors declare that there were no conflicts of interest.

Informed consent: All the procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation in Japan. Informed consent was obtained from the patient and her family for the study.

Author contributions: M.A.H. conceived and designed the experiments, analyzed the data, and wrote the manuscript. T.M. performed laboratory experiments including acid α-glucosidase activity measurement and mutation analysis. K.A. was responsible for data management. Y.E. managed the case, collected the funds, performed critical revisions of the manuscript, and took full responsibility for the study.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.06.043

Pompe disease (acid maltase deficiency, glycogen storage disease type II, OMIM ID # 232300) is an autosomal recessive disorder caused by a deficiency of the lysosomal glycogen-hydrolyzing enzyme acid α-glucosidase (GAA OMIM ID # 606800),resultinginglycogenaccumulationprimarily in skeletal, cardiac, and smooth muscle.[1] The clinical spectrum of Pompe disease varies broadly, with significant differencesexistinginageofonset,rateofdiseaseprogression, andoverallclinicalphenotype.Themostseveretypeistheclassic infantile-onset disease, with prominent cardiomegaly, hypotonia, and death prior to 1-2 years of age.[2] Late-onset Pompe disease (LOPD) usually presents in adulthood, althoughcasescanpresentasearlyasthefirstyearoflife.Adults with LOPD typically present with difficulties in ambulation and respiratory involvement.[3] Other phenotypes, including lingualweaknesswithdysarthriaanddysphagia,osteoporosis, scoliosis, sleep apnea, and sensorineural hearing loss LOPD,havebeenreported.[4]CardiomegalyisararemanifestationofLOPD.[5]

Enzyme replacement therapy (ERT) for LOPD showed a significant beneficial effect, even in an advanced form of the disease,[6] improving the clinical severity. However, early diagnosis and early initiation of ERT were always highly recommended.[7]

Here, we present a case of adult-onset Pompe disease with cerebral stroke and left ventricular hypertrophy.

Materials and Methods

Patient's Clinical Summary

The patient is a 59-year-old Japanese female who was a child of non-consanguineous parents, with an uneventful birth and neonatal history. In her childhood, she had a history of recurrent respiratory tract infection that was not associated with any cardiac or respiratory illness. She did not like running and physical exercises in school. At the age of 32 years, she experienced some gait disturbance; however, physicians could not diagnose a cause for her gait disturbance. From the age of 40 years, she suffered from systemic hypertension and took antihypertensive drugs. At the age of 57 years (October 27, 2015), she had a sudden cerebral stroke and was admitted to the hospital. Following her hospital admission, she was diagnosed with subarachnoid hemorrhage and 3 mm aneurysm in the left middle cerebral artery by CT scan (Fig 3A) and taken care of with adult neurology. Both conservative and cerebral arterial clippings were performed immediately. After the cerebral arterial clipping, the arterial aneurysm and subarachnoid hemorrhage were dramatically improved. However, she meanwhile developed lower limb weakness and evening headache. She could stand up with support, and once she stood up, she could walk alone. She had mild respiratory and swallowing difficulties; no sleep apnea or regurgitation was noted. Her father was suffering from cardiac aneurism and arterial thrombosis and died at the age of 82 years from the consequences of his diseases. Her mother suffered from left ventricular hypertrophy and died at 62 years of age from carcinoma of the colon. She had one sister with psychiatric illness and two sons, 34 years and 32 years old, who were healthy (Fig 1). On examination, pulse and respiration rate were normal. Blood pressure was 140/90 mm hg. Generalized muscle wasting was noted; however, the proximal muscles of her lower limbs were more affected than distal. Scapular winging was not prominent. Muscle tone was diminished parallel; however, the right thigh was weaker than the left. Her gait was a waddling gait. Hearing, vision, and forced vital capacity were normal. Laboratory findings revealed elevated blood creatine phosphokinase (CPK) 327 mg/dL, ALT 44 mg/dL, AST 42 mg/dL, lactic dehydrogenase (LDH) 266 mg/dL, low-density lipoprotein (LDL) 162 mg/dL and LDL, with high-density lipoprotein (HDL) ratio 2.3. A chest X-ray showed a mildly flattened diaphragm; an echocardiogram

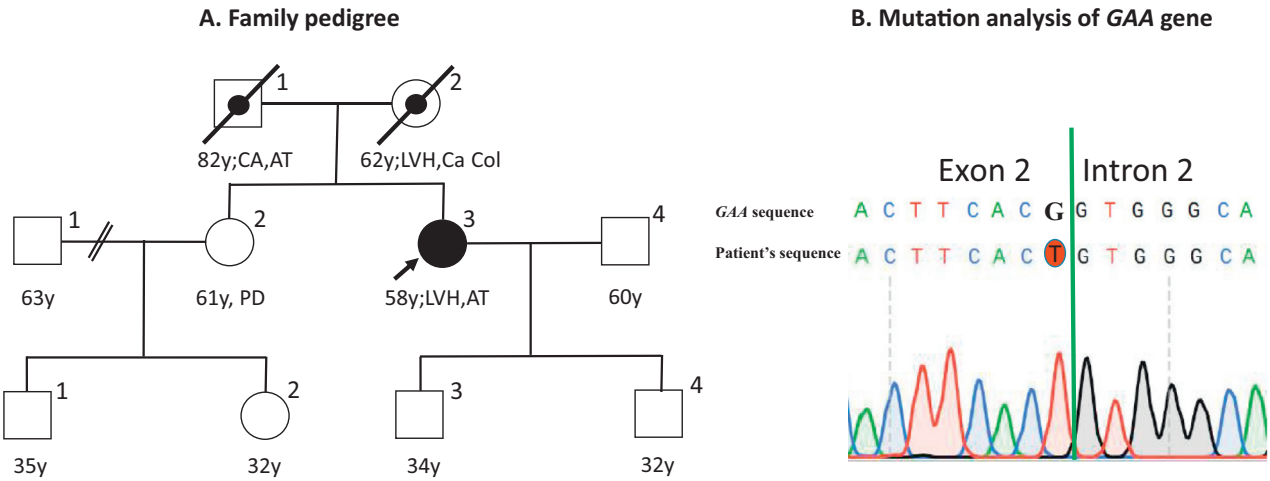

Figure 1. *A. Family pedigree of affected case: CA, cardiac aneurism; AT, arterial thrombosis; LVH, left ventricular hypertrophy; Ca Col, carcinoma of colon; PD, psychiatric disorder; y, years. B. Direct DNA sequencing of GAA gene. A single base nucleotide change c.546G>T in homozygous state, which did not affect the amino acid, causing splicing in the RNA level.*