A Case of Fabry Disease Presenting with Young Stroke and Fever

Ling-Chih Wu, Chien-Ta Chiang, Kun-Feng Lee

Abtract

Although it is known that Fabry disease should be included in the differential diagnosis of young stroke and fever of unknown origin, it has not been reported in the literature of stroke with fever as the presentation of Fabry disease. This is relevant because stroke with fever may misguide the differential diagnosis. Here we present a young stroke patient with fever. DWI of brain MRI revealed acute multiple infarctions. Due to the fever, infectious and inflammatory origins such as infective endocarditis and autoimmune diseases were examined first. However, we could not identify the source of fever after fever workup. The fever did not respond to one week of acetaminophen and antibiotics, but responded promptly to steroid. Our patient is also a case of de novo mutation rather than being inherited that further complicates the diagnosis of this patient. Because of the rare combined presentation of stroke with fever, Fabry disease should also be considered in stroke with fever, even without family history of Fabry disease.

Key words: Fabry, stroke, fever, de novo, novel mutation

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INTRODUCTION

Fabry disease is a rare genetic disorder caused by deficiency of the enzyme α-galactosidase A (a-Gal A), which in turn leads to the buildup of a particular type of fat called globotriaosylceramide (Gb3, or GL-3) in the body. Fabry disease is inherited in an X-linked pattern, consequently this disorder occurs mostly in males, estimated 1 in 40,000 to 60,000 males. Females can also be affected. There can be difference in prevalence among different ethnic groups [1,2].

Due to the excessive deposition of Gb3 in the vascular endothelium of several organs and in epithelial and smooth muscle cells, Fabry disease is associated with clinical abnormalities of skin, eye, kidney, heart, brain, and peripheral nervous system.

Here we present a patient of de novo mutation at a novel mutation site with clinical presentation of stroke with fever and proteinuria; a case that has not yet being described in the literature.

CASE PRESENTATION

A 35-year-old man came to ER due to acute onset of weakness of right limbs and slurred speech for two days with a fluctuated course.

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He reported no history of any major systemic disease, except smoked 1 pack of cigarettes every day for decades. His job was making furnitures. The family history was reviewed and deemed non-contributory, since there is no young stroke of or other vascular disease in the family. The brain MRI of our patient at ER revealed multiple acute infarctions in bilateral hemispheres and in both anterior and posterior circulations. (Fig. 1) His body temperature was 37.4 degree Celsius at ER. Other laboratory findings revealed no leukocytosis, raised ESR to 54 mm/hr, normal renal function and proteinuria of 1.64 g/day. Heart echo conducted at ER showed no vegetation, nor thrombus inside the heart. EKG revealed no arrhythmia.

Aspirin and antibiotics by ceftriaxone were both prescribed from the beginning. However, daily nocturnal fever in between 37.5 to 38 degree Celsius associated with severe throbbing headache persisted after one week of antibiotics, aspirin and acetaminophen. For further survey of fever, we arranged blood culture, TB culture, autoimmune work-up that included ANA, C3, C4, anti Ro/La Ab, anti-Phospholipid Ab, anti-cardiolipin Ab, Ribosomal-P Ab, Chromatin Ab, Sm Ab, RNP Ab, Scl-70 Ab, anti-ds-DNA Ab, cANCA, pANCA, and atypical pANCA; and whole body CT to look for possible explanation of fever. All results were negative, except enlarged kidney from both abdominal CT and renal echo that revealed long axis of right kidney to 13.9 cm (normal 10.9cm) and 13.4cm in the left side (normal 11.2 cm) by sonography (Fig. 2)[3] without hydronephrosis or other structural abnormalities and raised IgA to 661 mg/dl (normal 82 to 453). Intravenous steroid, dexamethasone 5mg every 12 hours, was prescribed after one week of antibiotics as a therapeutic trial. Both fever and headache subsided promptly after two days of steroid prescription. IgA nephropathy was suspected due to raised IgA and proteinuria, and renal biopsy was also performed. However, pathologic report revealed no IgA on immunofluorescent study of the glomerulus. Fabry disease was now checked and revealed much reduced α-Galactosidase A of to 0.3 nmol/mg (normal 60.6±27.19) and increased lyso-Gb3 to 107.198 ng/mL (normal <0.8).

Renal biopsy was re-evaluated after we reached the

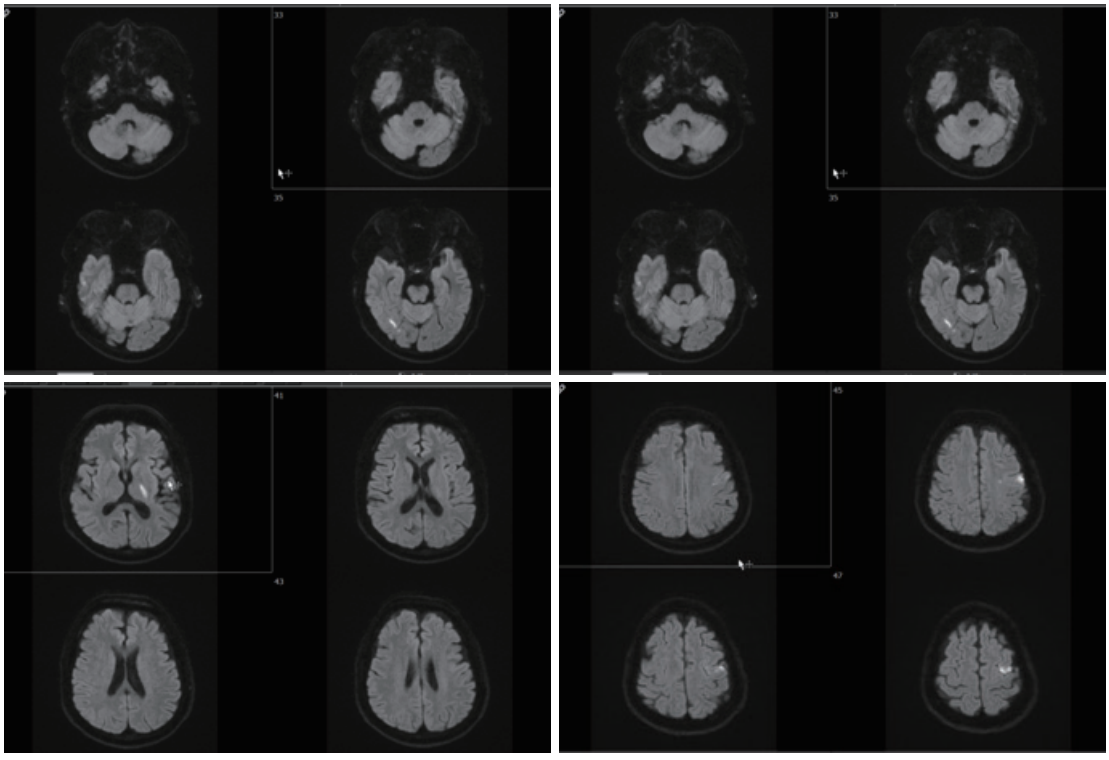

Figure 1. DWI of brain revealed multiple acute infarctions in bilateral hemispheres in both anterior and posterior circulation.

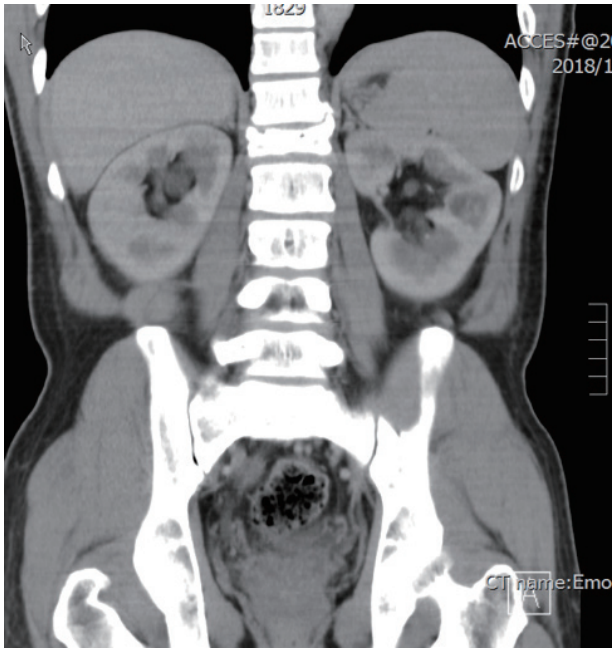

Figure 2. Enlarged kidneys without hydronephrosis, infiltrative or cystic like lesions.

diagnosis of Fabry disease. Still, our light microscopy failed to show definitive evidence that have been described of Fabry disease.

His mutation site is revealed to be a novel mutation in GLA (NM_000169.2:c.687del p. (Phe229Leufs*11)) . The latest version of HGMD Professional (2019.1) includes more than 900 GLA mutations causing Fabry disease[4] and the mutation site of our patient has not yet been included in HGMD database. This deletion of our patient occurs de novo rather than being inherited after screening his family.

Here we present a patient of de novo mutation at a novel mutation site with clinical presentation of combined young stroke with fever; a case that has not yet being described in the literature.

DISCUSSION

Fabry disease is a rare disease due to gene mutation on X chromosome. Some people call it a storage disorder for the mutation causes α galactosidase deficiency that results in Gb-3 accumulation inside the body. Fabry disease has a variety of clinical presentations; one of those symptoms is fever of unknown origin[5]. We did not suspect Fabry disease of our young stroke patient in the beginning due to (a) the combined fever with stroke, (b) the lack of related family history and (c) the absence of patient history of typical clinical symptoms of Fabry disease such as burning pain or neuralgia in limbs (acroparesthesia), anhydrosis, skin lesions (angiokeratoma), heat and cold intolerance, or repeated fever of unknown origin. The prompt response of fever with severe headache to steroid in our case may suggest an inflammatory pathogenesis of Fabry disease that lysosomal deposition of unmetabolized glycolipid substrates stimulates the activation of pathogenic cascades, including immunological processes, and particularly the activation of inflammation that may explain the raised ESR of our patient[6]. Another interesting finding of this patient is the enlarged kidneys. Enlarged kidneys are uncommon and are usually related to a few specific disorders such as infection, blockage, loss of function in the other kidney, polycystic disease, and infiltrative disease such as cancer and lymphoma[7]. We have not found in the literature of enlarged kidney in Fabry disease. Could it be the early stage of renal involvement and will become atrophied in the late stage? The enlarged-kidneys is one of the items we intend to follow up in our patient in the future.

Renal biopsy on light microscopy of our patient failed to show definitive evidence that have been described of Fabry disease[8], such as vacuolization of visceral glomerular epithelial cells (podocytes) and distal tubular epithelial cells, that is consistent with glycolipid accumulation showing the largest amount. On electron microscopy, deposits of Gb3 appear primarily within enlarged secondary lysosomes as lamellated membrane structures, called myeloid or zebra bodies[9]. These inclusions are considered a hallmark of glycolipid storage disease. In our case, the lack of findings by light microscopy highlights the importance of electron microscopy in the diagnosis of Fabry disease.

For Fabry disease is a disease that involves multiple organs with poor outcome if not treated before organ damage. Enzyme replacement therapy must be started early before irreversible damages such as heart failure, renal fibrosis or stroke. From this patient, we learn that a patient of Fabry disease doesn't have to have family history or other more typical findings such as pain, skin lesions or heart problems that may give a hint. I think it

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CONCLUSION

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CONSENT FOR PUBLICATION

We have the written consent from the patient, assisted by his mother due to his paralyzed right arm, for the publication of this case report.

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