Characteristics of Cerebral Microbleeds in Patients with Fabry Disease

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Background and Purpose: Fabry disease (FD) is an X-linked lysosomal storage disorder frequently associated with the central nervous system manifestations. Although white matter hyperintensity (WMH) on MRI has been previously reported, little is known about cerebral microbleeds (CMBs) in patients with FD. Our aim is to investigate the clinical characteristics of CMBs in patients with FD. *Methods:* All patients with FD were diagnosed by enzyme activity and/or gene analysis at Jikei University Hospital. We retrospectively enrolled consecutive patients with FD who underwent MRI study, including fluid-attenuated inversion recovery and susceptibility-weighted imaging, between July 2008 and September 2013. After categorizing the patients into CMB-positive and CMB-negative groups, we compared the clinical characteristics between the 2 groups. *Results:* We enrolled 54 patients (males, 24; median age 39 years, interquartile range; 29-50 years). The CMB-positive group included 16 (30%) patients. The number of males was significantly higher in the CMB-positive group than in the CMB-negative group (75% versus 32%, $P = .003$). The prevalence rates of chronic kidney disease (CKD) (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) and WMH were higher in the CMB-positive group than in the CMB-negative group (CKD: 44% versus 13%, $P = .013$; WMH: 88% versus 58%, $P = .035$). No significant differences in the number of vascular risk factors were observed between the 2 groups. *Conclusions:* The distinct characteristics of FD patients with CMBs were male sex, presence of CKD, and WMH. These factors may play an important role in the mechanism of hemorrhagic stroke in FD. **Key Words:** Fabry disease—cerebral microbleeds—chronic kidney disease—susceptibility-weighted imaging—white matter hyperintensity.

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Introduction

Fabry disease (FD) is an X-linked recessive lysosomal storage disorder that is caused by deficiency in the activity of alpha-galactosidase A. Systemic glycosphingolipid deposits occur with a predilection for vascular endothelial and smooth muscle cells, myocardium, renal epithelium, cornea, and the central nervous system, causing renal and cardiac failure, painful acroparesthesias, angiokeratomas, hypohydrosis, corneal opacity (verticillata), and stroke.[1,2] Stroke is a common manifestation of FD and has been identified in approximately 25% of patients.[3-6] FD also has been recognized as rare but one of the causes of juvenile stroke. A previous large cohort study indicated that FD occurs in .5% of juvenile stroke patients.[7-10] Therefore, brain magnetic resonance imaging (MRI) studies in patients with FD would allow a better understanding of the natural course and may lead to earlier treatment.

The most prominent structural imaging findings of brain MRI in FD are white matter hyperintensity (WMH) on T2-weighted imaging, dilatation of large vessels (dolichoectasia) on magnetic resonance angiography, and the pulvinar sign as seen on T1-weighted imaging.[11] In contrast, little is known about cerebral microbleeds (CMBs) in patients with FD. Our aim is to investigate the clinical characteristics of CMBs in patients with FD.

Materials and Methods

Patients

All patients with FD are diagnosed by an alpha-galactosidase assay and/or gene analysis in the Department of Pediatrics at Jikei University Hospital, Japan. We retrospectively enrolled consecutive patients with FD who underwent an MRI study, including fluid-attenuated inversion recovery (FLAIR) and susceptibility-weighted imaging (SWI) between July 2008 and September 2013. After categorizing the patients into the CMB-positive group or the CMB-negative group, we compared the clinical characteristics, including the presence of WMH, between the 2 groups.

Imaging

MRI was performed with the use of echo-planar imaging on a 1.5-T magnet (MAGNETOM Avanto; Siemens, Munich, Germany). The imaging protocol consisted of a FLAIR sequence (repetition time, 9000 milliseconds; echo time, 92 milliseconds; field of view, 210 × 210 mm; acquisition matrix, 256 × 256; section thickness, 5.0 mm with a .5-mm intersection gap); SWI (repetition time, 49 milliseconds; echo time, 40 milliseconds; field of view, 230 × 230 mm; acquisition matrix, 173 × 256; section thickness, 2.0 mm with a .5-mm intersection gap). The severity of WMH in the FLAIR images was scored as described by Fazekas et al[12] into grades of 0, absent; 1, punctate; 2, early confluent; and 3, confluent. Scoring above grade 1 was regarded as WMH-positive (Fig 1, A). CMBs were defined as small, rounded or circular, well-defined hypointense lesions within brain parenchyma with clear margins ranging from 2 to 10 mm in size on SWI (Fig 1, B). We evaluated the numbers and the locations of CMBs using the Microbleed Anatomical Rating Scale.[13] CMBs were into classified, deep, infratentorial, and lobar categories. Deep regions included the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter. Infratentorial regions included the brain stem and cerebellum. The lobar region included the cortical and subcortical regions.[13]

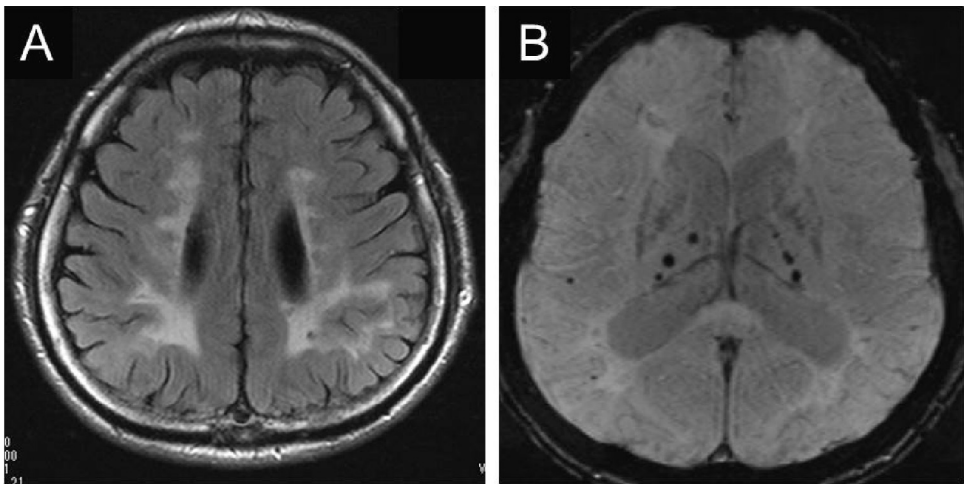

Figure 1. *MRI scans of a 49-year-old male patient with Fabry disease. (A) FLAIR shows WMH. (B) SWI shows multiple hypointense lesions in the bilateral thalamus. Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging; WMH, white matter hyperintensity.*