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GLA mutation as a risk factor for later life small vessel ischemic disease

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Nakamura and colleagues report in this issue of the Journal a study of Fabry disease in 475 male ischemic stroke patients seen at fifteen clinics in the Nagano prefecture of Japan [1]. Every patient was screened for low alpha galactosidase activity, and patients with low activity levels underwent confirmatory testing. Patients with confirmed low levels had direct DNA sequencing of their entire alpha galactosidase A (GLA) gene. Five of the 10 patients with confirmed low alpha galactosidase A activity levels had the p.E66Q point mutation. This mutation rate among patients with ischemic stroke was significantly higher than the base rate seen in 5051 newborns screened for inborn errors in the Kumamoto prefecture. Thus, assuming that the Kumamoto population adequately substitutes for the Nagano population, investigators concluded that the p.E66Q mutation increased the risk of ischemic stroke by more than three fold.

The cases may not be fully representative of the stroke population in Nagano. The investigative team accrued 475 male patients in four years and four months thorough an impressive collaboration with 15 neurology clinics. However, the proportion of patients with stroke receiving care outside of the participating clinics is unknown. Many stroke patients in the catchment area are managed by neurosurgeons, who may be more likely to care for more severe cases than neurologists. Additionally, participants were included only if they could provide informed consent. This too can bias toward accrual of patients with milder strokes. These factors may explain why more than half the cases had small vessel stroke.

One of the challenges facing clinicians seeking to diagnose Fabry disease is that the disease tends to present heterogeneously within and across families. Fabry disease may be even more challenging to diagnose in older patients because they tend to suffer from conditions like neuropathic pain and small vessel stroke, which commonly occur in the general population. Fabry disease is often considered as a cause of stroke in the young, but the mean age of patients with ischemic stroke and the p.E66Q mutation described by Nakamura was 69.6 years, certainly not a distinguishing characteristic when the mean age of the overall ischemic stroke population was 69.7 years. Physicians should consider having a low threshold for testing for Fabry disease.

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Fabry disease is one of the inherited causes of cerebral small vessel disease, along with CADASIL, CARASIL, and *TREX1* and *COL4A1* mutation-associated conditions [2]. Nakamura and colleagues have shown that p.E66Q can cause the full spectrum of small vessel cerebrovascular disease: microbleeds, symptomatic ganglionic bleeds, leukoaraosis, and lacunar infarcts. Multifocal leukoaraosis has also been seen in a family with the GLA D313Y mutation [3].

Agalsidase alpha and agalsidase beta are commercially available options for treating Fabry disease, but they have limitations. Long-term enzyme replacement therapy does not arrest the disease process. Patients can still develop white matter lesions [4] and strokes [5]. In fact, a recent systematic review of 6 trials involving 223 participants concluded that the evidence supporting use of enzyme replacement is not compelling [6]. As a lysosomal storage disease, Fabry may be a potential target for molecular chaperone therapy. The concept is that a substrate analog competitive inhibitor, the chaperone, forms a stable complex with the diseasecausing mutant misfolded enzyme, e.g., mutant alpha galactosidase A, and that this complex dissociates once transported to the acidic environment of the lysosome [7]. The molecular chaperone migalastat hydrochloride has shown promise as a genotype-specific treatment for Fabry disease [8]. Gene therapy also holds promise as establishment of even modest levels of enzyme activity may be clinically effective [9].

Antiplatelet therapy is generally recommended for secondary stroke prevention in patients presenting with small vessel strokes; however, this practice may not be safe and effective in patients with small vessel disease due to Fabry disease. Nakamura and colleagues show that symptomatic and asymptomatic hemorrhages are not rare in older patients with Fabry disease. A randomized trial may be the only way to resolve the management question of antiplatelet use in the setting of competing risks of infarction and hemorrhage. Because Fabry disease causes a nephropathy, the blood pressure goal for patients should be < 130/80 mm Hg [10]. Because Fabry nephropathy causes proteinuria, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are preferred antihypertensive treatments, with a therapeutic goal of achieving a urinary protein < 500 mg/day [11]. In addition to theoretically protecting the kidneys, tight blood pressure control may also help slow the progression of cerebral small vessel disease.

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