

Cryptogenic Stroke and Fabry Disease

a report by

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Although the incidence of ischaemic stroke increases with age, stroke in children and young adults is not uncommon.¹ The average population-based annual incidence rate for ischaemic stroke (cases per 100,000 per year) has been reported as about 11.3 among those aged 15 to 49 years.^{2,3} For at least 20–40% of the stroke cases in young adults no specific causes are found (so-called cryptogenic stroke), even if the patients are examined extensively and very carefully for causes like Moyamoya syndrome, dissection, infection, haemoglobinopathies, coagulopathies, migraine, CADASIL, V. zoster infection, hyperhomo-cysteinemia, oral contraceptives, heart failures etc.^{4,5} With technical and medical advances this proportion may be as low as 18%.⁶

The definition of cryptogenic strokes is ambiguous because it can include the mechanism and risk factors. This high percentage of unclarified etiologies of stroke in young adults demands the investigation of even apparently rare diseases, like Fabry disease.

Fabry disease is an X-linked inborn error of glycosphingolipid catabolism resulting from deficiency of the lysosomal hydroxylase, alpha galactosidase A (AGLA).⁷ In humans, the disease is characterised by the systemic accumulation of the glycosphingolipid substrate, ceramide trihexoside (CTH) and ceramide dihexoside in tissue. Clinical manifestations of Fabry disease include chronic pain, kidney impairment, skin lesions, ocular opacities, vascular deterioration, stroke and cardiac deficiencies leading to premature mortality.⁸ Recently, enzyme replacement therapy (ERT) has become available.⁷

Death usually occurs in adult life from renal, cardiac, or cerebrovascular complications of vascular disease. Heterozygote females are either asymptomatic or exhibit fewer signs and symptoms of disease, although there are continually more reports describing females with symptoms similar to the males.⁹ In the central nervous system (CNS), diffuse storage occurs in the vascular endothelium, with more localised involvement of central neurons

together with the dorsal root and autonomic ganglia in the peripheral nervous system. The incidence of stroke together with vessel ectasia is about 40% in hemizygous males;¹⁰ mainly younger subjects seem to be affected. The most frequent cerebrovascular symptoms in Fabry patients are hemiparesis, vertigo/dizziness, diplopia, nystagmus and ataxia of gait in the hemizygote group; and memory loss, dizziness, ataxia, hemiparesis, loss of consciousness and hemisensory symptoms in the heterozygote group.¹¹ The cerebrovascular manifestations consist of large-vessel ectasia, large-vessel occlusive disease, and small-vessel disease; the vascular diathesis is reported to have a vertebrobasilar circulation distribution, although the reason for this is unclear. positron emission tomography (PET) investigations suggest a chronic alteration of the nitric oxide (NO) pathway in Fabry disease.¹² On the other hand, there exists an increased endothelium-mediated vascular reactivity, where the increased vessel response to acetylcholine with and without NG-monomethyl-L-arginine (L-NNMA) suggests altered functionality of non-NO endothelium-dependent vasodilatory pathways. Vessel wall alterations with narrowing of cerebral resistance vessels are likely to comprise cerebral blood flow (CBF) velocity and to contribute to the early and increased incidence of stroke. Hyperintensity in the pulvinar on T1-weighted magnetic resonance imaging (MRI) images seems to be a common finding in Fabry disease, which probably reflects the presence of calcification.¹³ Increased cerebral blood flow in the posterior circulation, particularly in the thalamus, suggests that the dystrophic calcification is secondary to cerebral hyperperfusion and selective vulnerability of the pulvinar and adjacent thalamic structures.

In a recent publication the author and co-workers analysed 721 (432 male, 289 female) consecutive unrelated young patients (18–55 years of age) who had had an apparently unexplained acute cerebrovascular event (CVE), a cryptogenic stroke.¹¹ Biologically significant mutations within the AGLA gene were found in 28 patients (21 male, 7 female), which proves the diagnosis of Fabry disease. The mean age of onset of symptomatic cerebrovascular disease was 38.4 ± 13.0



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years in the group of the male stroke patients and 40.3 ± 13.1 years in the female group compared with the non-Fabry cohort with a mean age of 47.9 years. The most important result of this study is the high frequency of Fabry disease in a cohort of stroke patients with cryptogenic stroke aged between 18 and 55 years: the number of newly diagnosed Fabry patients corresponds to 4.9% and 2.4% of the male and female groups of stroke patients, respectively. This is about one-third of the frequency of valvular heart disease in such a group (mean 5.9% from a meta-analysis for young patients aged between 15 and 45 years)⁴ or dissection (mean 5.8%) and comparable with the frequency of, for example, Sneddon's syndrome or antiphospholipid syndrome (2.3–4.1%).

Up to now no clear data exist about the frequency of Fabry disease in young stroke patients. From the Fabry Outcome Survey (FOS), an international database of the natural history of Fabry disease and the effects of ERT with agalsidase alpha, it is now known that the most frequently reported signs and symptoms in proven cases of Fabry disease are neurological, and are reported for the majority of both male (84%) and female (79%) patients.¹⁴ The frequency of stroke, transient ischaemic attacks (TIA) and prolonged reversible ischaemic neurological deficit is higher in women than in men, with 12% of male and 27% of female patients reporting these incidents.

The neuropathology in Fabry disease is characterised by vascular and neuronal glycosphingolipid accumulation. The vascular change in Fabry disease is considered to be responsible for increased regional cerebral blood flow (rCBF) documented in PET scans, especially in the posterior circulation. Several studies have reported an increased number of lacunar, predominantly periventricular, infarctions, as well as small cortical infarcts.¹⁵ The swollen vascular endothelial cells, often accompanied by endothelial cell proliferation, encroach upon the lumen of involved vessels and might lead to focal increase of intraluminal pressure, dilatation and angiectasis of small cerebral arteries. Grewal described eight Fabry patients with CVE which involved in all cases the deep or penetrating arteries similar to those arteries which cause lacunar strokes.¹⁶ Beside the small vessels being involved in the pathogenesis large vessels are also pathologically changed in Fabry disease. Moore and co-workers investigated, in the course of a randomised double-blind placebo-controlled six-month ERT trial with agalsidase alpha, the functional blood flow response of the brain, the cerebral vasoactivity and PET in Fabry patients.¹²

They demonstrated that Fabry patients had a significantly greater increase in rCBF and that the

time for recovery of the cerebral vasculature following acetazolamide was prolonged in Fabry patients as well. ERT with agalsidase alpha was able to reverse the exaggerated cerebrovascular response.¹²

The reason for the predilection of the vertebrobasilar system in stroke in Fabry disease is not clear, as it seems reasonable to presume that the endothelial changes in the scope of Fabry disease should affect the cerebral arteries in a uniform manner. Mitsias and Levine reported in their careful neuropathologic analysis of cerebrovascular complications in 12 hemizygotic and three heterozygotic Fabry patients a prevalence of thickened vessels of the circle of Willis with narrowing of the lumina in about one third of the cases, moderate atheroma of the major cerebral vessels or intracellular deposits in arteries and arterioles in about 15%.¹⁷ A massive dilatation of the basilar was seen in one case.

Cardiac involvement in Fabry disease is frequent due to structural and functional changes of the myocardium, the conduction system, and the valves. A progressive intracellular accumulation of Gb3 leads to an increase in ventricular wall thickness, mitral valve prolapse and electrocardiogram abnormalities.¹⁸ Little is known about onset of cardiac involvement in Fabry disease in relation to brain manifestations. About one fourth of our patients with Fabry disease and stroke reveal cardiac abnormalities, like ST-segment and T-wave abnormalities, atrioventricular conduction delay or hypertrophic cardiomyopathy (HCM). Especially for the latter, it is important to be excluded Fabry disease in the diagnostic approach since Fabry may account for up to 12% of females with late onset HCM and to 6% in males.

Summarizing the potential mechanisms of cerebral ischaemia in patients with Fabry disease, the intracranial arterial dolichoectasia due to glycosphingolipid deposition in vascular smooth muscle, the progressive occlusion of small arteries or arterioles secondary to deposition of glycosphingolipid, endothelial and leukocyte activation, reduced cerebral blood flow velocity and impaired cerebral autoregulation, seem to be the most important aspects in the role of Fabry disease in stroke. Other potential mechanisms, like cardiogenic embolism and impaired autonomic function, might play a less important role for cerebral ischaemia, compared with the cerebrovascular changes induced by the enzymopathy.

It is evident that acute stroke in young patients especially in Fabry disease is a multifactorial process. Fabry disease must be considered in all cases of unexplained stroke in young patients, especially in cases with the combination of infarction in the

vertebrobasilar artery system and proteinuria. Although there has been no clear evidence up to now of the long-term benefit of enzyme replacement treatment especially in young patients with stroke, several studies have shown that ERT does have an effect on resting cerebral blood flow abnormalities.⁸ Therefore it might be important to treat stroke patients as early as possible with ERT. However, specific trials determining the efficacy and optimal dosing in patients with established cerebrovascular disease are required together with consideration of when it might be too late to benefit from ERT. Until effective therapy becomes a reality, primary and secondary prevention of strokes

is critical in Fabry disease. Besides antiplatelet agents other treatable risk factors should be appropriately addressed with statins, angiotensin-converting-enzyme inhibitors, or angiotensin receptor blockers.

Importantly, as ERT has demonstrated long-term beneficial effect on renal function,^{19,20} significant improvement in cardiac involvements,²¹ neuropathic pain²² and quality of life,²¹ this treatment should be considered for all patients diagnosed with the condition. The newly acquired quantitative link between Fabry disease and stroke should hopefully lead to improved understanding and treatment of both conditions. ■

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