Letter Regarding Brouns et al, Baptista et al, and Wozniak et al

To the Editor:

We congratulate the authors of the 3 recent studies addressing the prevalence of Fabry disease (FD) in stroke.1–3 Previous studies provided conflicting results with no practical conclusion.4,5 However, early diagnosis of FD could be crucial because enzyme replacement therapy may prevent severe disease manifestations.6 The 3 studies differ according to populations enrolled.1–3 Two studies considered ischemic or hemorrhagic strokes,1,2 although the relation between FD and hemorrhagic stroke is unclear. Moreover, these 2 studies included patients regardless of stroke etiology, which may have led to underestimation of FD. The other study considered cryptogenic ischemic strokes only, but there was no definition for cryptogenic stroke.3 Women were investigated in 2 studies only.1,2 The studies also differed according to the method used for FD diagnosis. Screening for FD reliably can be performed by α-galactosidase A analysis in men, whereas gene mutation analysis is required in women. Although 2 studies used this approach,1,3 the PORTYSTROKE study measured enzyme activity only in patients with identified gene mutation.2 However, the pathological role of some polymorphisms (eg, D313Y, which is associated with a pseudodeficient plasmatic activity) is uncertain.

Interestingly, despite these differences, the results of the 3 studies are consistent: the prevalence of FD among stroke patients is low. Thus, using all available studies and excluding patients with D313Y mutation, the combined prevalence is 1.34% (95% CI, 0.21–3.42) in men and 1.45% (95% CI, 0.65–2.57) in women (Figure).7,8 Heterogeneity across studies is mainly accounted for by the Rolfs et al4 study, which reported a high prevalence of enzymatic deficiency but no information on mutation analyses.

The main practical implication of these findings is that the yield of screening for FD is low and that systematic screening in young stroke patients is not justified. However, the diagnosis of FD must not be missed because it has implications for the patient and family. Recent data of a FD registry found that 50% of men and 38% of women had a history of stroke before the diagnosis of FD was established.9 Moreover, stroke preceded cardiac and renal manifestations in ~70% of cases, suggesting that stroke is...
commonly the first manifestation of FD. If the true prevalence of FD is $\approx 1\%$ in young stroke patients, then we may speculate that FD is currently underdiagnosed in practice.

None of the 3 recent studies was designed to identify which patients should be screened. Curiously, no study reported on family history data of patients identified as having FD. Therefore, pending further studies that would help identify patients at high risk for FD, we believe that screening for FD should be restricted to patients with family history compatible with FD. These arguments can be easily retrieved through a detailed interrogation and simple tests, considering that neomutations are rare in FD.

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