Letter by Benbir et al Regarding Article, “The Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Scale. A Screening Tool to Select Patients for NOTCH3 Gene Analysis”

To the Editor:

The need for pregenetic screening tools was discussed in a recent study published in Stroke by Pescini et al., and the Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) scale was introduced comprising mainly clinical and radiological findings. MRI is the most relevant tool for monitoring cerebral pathology in CADASIL, with very high sensitivity. Although definitive diagnosis could be made by demonstrating highly stereotyped mutations on NOTCH3 gene, genetic analysis is costly and time-consuming because it is a long gene with mutations located at any point. In addition, there is a growing body of literature reporting a considerable number of patients with clinical and neuroimaging features suggestive of CADASIL but with negative NOTCH3 mutation. Because there is currently no understanding of correlation between clinical and neuroimaging features, in addition to wide variability in clinical phenotypes throughout the world, the use of a simple and enough accurate screening tool for clinicians to select patients with high suspicion of CADASIL before genetic testing is considerably important from practical point of view.

Of our 23 patients, NOTCH3 mutation was demonstrated in 10 patients, whereas no mutation was found in 13 patients. In comparison with risk factors, sex, age at disease onset, history of migraine (with/without aura), recurrent stroke and family history of stroke were not found significantly different. Of radiological data, besides from temporal pole involvement, being more common in patients with positive NOTCH3 mutation ($P=0.001$), involvement of temporal or periventricular white matter or extreme capsule did not show significant difference. CADASIL scale constituted by Pescini et al. was applied to our study population. The mean score of CADASIL scale was 14.0+3.4 points (between 9 and 19 points) in NOTCH3-positive patients and 10.8+2.1 points (between 6 and 16 points) in NOTCH3-negative patients. The mean score of CADASIL scale was significantly higher in patients with mutation ($P=0.031$), compatible with authors’ results.

Although different attempts of diagnostic strategies for CADASIL have previously been made, they could not reach wide acceptance. The need for pregenetic screening attributable to a significant number of negative pathogenic mutations in patients with clinical and radiological features suggestive of CADASIL has led many researches to build different criteria. Because clinical suspicion of CADASIL displays variability according to different combinations of clinical and neuroimaging features, accurate selection of patients is crucial to limit the number of NOTCH3-negative patients, and to explore other genes involved in causing CADASIL-like hereditary strokes. As a limitation in our center, we could not perform whole-genome analysis because of costly and time-consuming analysis. Two of our patients had novel mutations c.194G>T (p.C65F) on exon 2, which was considered as causative mutation because other mutations involving the same codon were previously associated with CADASIL.

This worldwide prevalent disease has a large spectrum of phenotypic and genotypic characteristics, for which a more comprehensive and systematic approach is requisite for accurate and feasible diagnosis. Thus, not only NOTCH3-negative CADASIL patients, but also NOTCH3-positive patients with atypical clinical features for CADASIL, would better be delineated. On this context, we believe this newly described CADASIL scale would provide a better selection of patients and increase the feasibility of genetic testing.

Disclosures

None.

Gulcin Benbir, MD
Birsen Ince, MD
Aksel Siva, MD
Department of Neurology
Cerrahpasas Faculty of Medicine
Istanbul University
Istanbul, Turkey

Oya Uyguner, MD
Department of Medical Genetics
Istanbul Faculty of Medicine
Istanbul University
Istanbul, Turkey

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Gulcin Benbir, Birsen Ince, Aksel Siva and Oya Uyguner

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