Letter by Dichgans et al Regarding Article, “Peripheral Artery Disease as a Manifestation of Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Practical Implications”

To the Editor:

We read with interest the report from Briceno et al.1 Although we agree that the clinical presentation of their patient represents some diagnostic challenges, we question the author’s conclusion that their patient suffered from cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and express our concern that some of the authors’ considerations are potentially hazardous.

We feel the clinical presentation speaks against cerebral small vessel disease, which is among the core features of CADASIL and always present in mutation carriers beyond age 20 years. The MRIs demonstrate extensive bilateral signal hyperintensities involving both the cortical grey matter and the subcortical white matter predominantly in watershed regions. This pattern is seen with cardiac insufficiency, large artery disease, severe hypotension, and other conditions, but not with cerebral small vessel disease. Having followed >600 patients from multiple families with CADASIL we did not come across a single case of clinically manifest small vessel peripheral arterial disease.2 3 (unpublished observations) and the literature also gives no indication in this direction. Thus, one might ask why the authors considered a diagnosis of CADASIL. The presence of dementia is well explained by the visible brain lesions, and the family history presented is not suited to guide diagnosis.

Diagnostic confirmation was based solely on ultrastructural examination of dermal vessels. However, the electron micrograph findings shown in their report by no means resemble the granular osmiophilic materials that are typically seen in Notch3 mutation carriers. Instead the sample exhibits debris of unknown origin, which is not adjacent to the plasma membrane of smooth muscle cells and lacks the characteristic fine granular structure of granular osmiophilic materials. In fact, the debris shown in the electron micrograph is very similar to the material provided in Figure 3c of Tikka et al,4 which was cited by the authors and which gives an example of fallacious deposits not diagnostic of CADASIL. More importantly, there is no mention on molecular genetic testing, which is mandatory, especially in cases with an atypical clinical presentation. We would therefore conclude their patient likely suffered from a condition other than CADASIL.

The authors miss to inform whether their patient had diabetes mellitus as the most common cause of dry gangrene, and there is no mention of other potential causes such as vasculitis, paraneoplasia, or sickle cell disease, which, although uncommon in white individuals, may cause both dry gangrene and bilateral watershed infarcts.

We have difficulties following the author’s interpretation that the arteriogram of their patient shows severe peripheral small vessel disease. The respective image shows an early phase of the arteriogram, which in our opinion is not suited to document small vessel disease. Moreover, the vascular changes in CADASIL cannot be visualized by this modality. Of note, we strongly discourage performing conventional angiography in patients with a suspicion of CADASIL, because these patients carry a high risk of developing angiographic complications.5 Vascular reactivity tests as suggested by the authors have no established utility in diagnosing CADASIL. However, we agree that this is an important area that deserves further investigation.

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Disclosures

None.

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References


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