Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and primary angiitis of the central nervous system (PACNS) share several clinical and radiological features. However, digital subtraction angiogram (DSA) is generally reported as normal in CADASIL, whereas lumen irregularities in distal cerebral arteries indicate PACNS.

Objective: To describe a potential pitfall of DSA interpretation, which led to the tentative diagnosis of PACNS in a CADASIL patient.

Patient and Methods: Single case observation.

Results: A 47-year-old man sustained recurrent subcortical infarcts. He had mild hypercholesterolemia and migraine. His family history was unremarkable. The underlying cause of stroke could not be elucidated. Transcranial Doppler sonography revealed decreased intracranial blood flow velocities compatible with CADASIL. Lumen irregularities of several peripheral intracranial arteries were seen on DSA, which suggested PACNS. CADASIL was confirmed by results from skin biopsy and genetic testing.

Conclusions: First, in patients with CADASIL, DSA can show segmental lumen irregularities in distal cerebral arteries suggestive of PACNS. Second, the potential role of transcranial Doppler sonography to distinguish CADASIL from PACNS deserves further testing.
plantar response was present on both sides. Percutaneous reflexes were brisk.

Findings from computed tomography (not shown) and MRI (Figure 1) revealed multiple chronic subcortical lesions bilaterally and an acute ischemic lesion in the right internal capsule. Findings from Doppler and duplex sonography of the extracranial arteries were normal; no atherosclerosis was recorded. Transesophageal echocardiography and 24-hour electrocardiograph monitoring revealed no abnormalities. There was no patent foramen ovale. Cerebrospinal fluid examination results showed a slightly elevated protein level (0.069 g/dL [reference, <0.048 g/dL]) but were otherwise normal. Laboratory testing did not indicate systemic vasculitis, coagulopathy, or sarcoidosis. Hematocrit levels were normal (41% [reference, 38%-52%]). The only vascular risk factor present was moderate hypercholesterolemia (266 mg/dL [6.9 mmol/L]). Cerebral DSA revealed segmental narrowing of several peripheral arterial branches within the territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery bilaterally and a mild dilatation of proximal portions of major cerebral arteries (Figure 2). Findings on DSA (most notably the peripheral irregularities) were considered indicative of PACNS. Accordingly, the patient was treated with prednisone (1 mg/kg body weight) and oral cyclophosphamide (150 mg/d). Findings from TCD revealed low mean flow velocities in the major intracranial arteries (Table), as recently reported in CADASIL patients.8 A skin biopsy was performed, which showed granular osmiophilic material within the basal lamina of vascular smooth muscle cells in small subcutaneous arterioles. Genetic testing (Laboratoire Cytogenetique, E. Tournier-Lasserve, MD, Hôpital Lariboisiere, Paris, France) revealed a mutation of the notch 3 gene with a nucleotide substitution (CGC→TGC) at position 475 on exon 4. CADASIL was diagnosed, and the immunosuppressive therapy was stopped. Within the next 3 months, the patient recovered only slowly with persistent severe left-sided hemiparesis.

**COMMENT**

From his mid-thirties on, our patient had recurrent subcortical brain infarcts without evidence of an underlying atherothrombotic or embolic disease, of a coagulopathy, or of systemic vasculitis. Investigation results were negative until DSA showed focal lumen irregularities with multiple stenosis of distal intracranial arteries. In the clinical context of an unremarkable family history, as yet unexplained recurrent subcortical strokes, and (slightly) abnormal cerebrospinal fluid findings (increased protein), these DSA findings suggested PACNS.6 However, clinical signs and symptoms of PACNS are unspecific. In addition, angiographic findings in PACNS have a sensitivity of 80% and a specificity of only 30%,5 indicating a moderate diagnostic yield. Of interest, brain tissue has a sensitivity of only 53% and a specificity of 87%.5 Despite the limited diagnostic utility of both methods, the diagnosis of PACNS in most cases essentially relies on angiographic or biopsy findings.6 Differential diagnosis of PACNS includes systemic vasculitis, central nervous system infection (eg, human immunodeficiency virus, syphilis), lymphoma, demyelinating disease, drug use (eg, cocaine or amphetamine), sarcoidosis, and rare vasculopathies such as fibromuscular dysplasia and moyamoya disease.5,6 However, none of these diseases was confirmed in our patient.

A recent case report illustrates the difficulties in distinguishing CADASIL from PACNS owing to similar clinical presentation and MRI appearance. Although it has been reported that most CADASIL patients have normal DSA results,8 this patient, like ours, showed multifocal segmental intracranial stenosis, which first suggested PACNS. A positive history of stroke at mid-adulthood in several first-degree relatives provided the clue to CADASIL in this patient, whereas our patient lacks a positive family history of stroke or dementia.

Concerning CADASIL and DSA findings in the literature, at an international CADASIL workshop it was reported7 that cerebral angiography was performed in at least one affected member in all studied [ie, eight] families. It was essentially normal except in the family from . . . with dolichocephaloma-arteries, and in one . . . with angiographic aspect suggestive of fibromuscular dysplasia. . . . they most likely were associated conditions.

In their article about the clinical spectrum of CADASIL, Chabriat et al7 reported that 14 of 45 symptomatic
family members underwent DSA. Findings were normal in 13 patients, while 1 patient had “a narrowing of some small branches of the anterior, middle, and posterior cerebral arteries.” No further clinical data (eg, presence of migraine) on the patients with abnormal DSA findings were given.

In our patient, TCD findings revealed decreased mean flow velocities in both MCA and ACA. These findings are in accordance with the results of a recent TCD study in CADASIL patients that focused on carbon dioxide reactivity but also reported in detail on mean flow velocities; the 29 CADASIL patients in the study showed significantly lower MCA mean flow velocities than the 29 age-matched controls. Low MCA mean flow velocities are unspecific, and primary causes include increasing age and high blood viscosity. Both factors were not applicable in our patient because (1) his mean blood flow velocities were low (ie, <2 SDs of the mean) compared with age-matched normal values, and (2) his hematocrit level was normal. Low mean flow velocities can be present in other forms of subcortical vascular encephalopathy, most notably in Binswanger disease, which, however, was not present in our patient. Of interest, Mohr stated that “Binswanger’s famous case, no less, may have been CADASIL,” and that “CADASIL may join granulomatous arteritis of the central nervous system [PACNS] to suggest that the brain vasculature has biological properties somewhat different from other vascular beds.”

In contrast to CADASIL patients (with low MCA mean flow velocities), in all PACNS case studies that include TCD investigations, all 5 patients had increased MCA mean flow velocities. These observational data support the assumption that TCD might be helpful in choosing which further invasive diagnostic tests should be applied (ie, skin biopsy vs DSA) in patients with signs of a subcortical leukoencephalopathy of unclear origin. An algorithm for the distinction of both entities would have clinical implications. First, DSA encompasses an increased complication rate in CADASIL. Second, immunosuppressive therapy is indicated only in PACNS. However, functional TCD variables such as carbon dioxide reactivity were assessed neither in our study nor in the mentioned TCD reports in PACNS. Furthermore, this is only a single case observation. Therefore, a detailed discussion about a possible future role of TCD in CADASIL and PACNS is beyond the limitations of this case report and has to await further studies.

Our finding of low MCA and ACA blood flow velocities in CADASIL is in agreement with hemodynamic studies in CADASIL using MRI, positron emission tomography, or single-photon emission computed tomography. All these methods showed reduced cerebral blood flow and cerebral blood volume, especially in white matter. In addition, carbon dioxide–induced vasoreactivity was reduced in CADASIL patients. Low mean flow velocity of MCA and ACA as well as low cerebral blood flow, low cerebral blood volume, and impaired vasoreactivity all point to a dilatation of the major intracranial arteries in CADASIL. Vasodilatation of the proximal arterial segments might be interpreted as an attempt to compensate for the lumen reduction in distal arterial branches as visualized by DSA in our patient. Distal lumen reduction of small perforating arteries may reflect vascular smooth muscle cell dysfunction or vessel destruction and replacement by extracellular matrix with superimposed subendothelial fibrous proliferation. The fact that histological alterations in CADASIL are predominantly found in smaller arteries and arterioles might explain our DSA result of stenosis involving the distal arterial branches rather than the major cerebral arteries. However, it remains unclear why, in general, DSA findings in CADASIL have been reported to be normal.

Transcranial Doppler Sonography of a Patient With CADASIL

<table>
<thead>
<tr>
<th>Arterial Segment (Insonation Depth)</th>
<th>Mean Flow Velocity, cm/s</th>
<th>Pulsatility Index†</th>
<th>Patient Normal ± SD‡</th>
<th>Patient Normal ± SD‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-M1 (50 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>30§</td>
<td>57 ± 11</td>
<td>1.25</td>
<td>0.90 ± 0.24</td>
</tr>
<tr>
<td>Left</td>
<td>31§</td>
<td>1.36</td>
<td>0.94 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>ICA-C1 (62 mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>30</td>
<td>39 ± 9</td>
<td>1.40</td>
<td>. . .</td>
</tr>
<tr>
<td>Left</td>
<td>27</td>
<td>1.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA-A1 (70 mm)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Right</td>
<td>25§</td>
<td>48 ± 7</td>
<td>0.89</td>
<td>0.88 ± 0.23</td>
</tr>
<tr>
<td>Left</td>
<td>23§</td>
<td>1.27</td>
<td>0.88 ± 0.20</td>
<td></td>
</tr>
</tbody>
</table>

*CADASIL indicates cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MCA-M1, middle cerebral artery, main stem; ICA-C1, internal carotid artery, segment prior to bifurcation in MCA; and ACA-A1, anterior cerebral artery segment prior to anterior communicating artery.

†Peak systolic flow velocity minus diastolic flow velocity divided by mean flow velocity.
‡Age-matched normal values ± SDs.4
§≥2 SDs below normal values.

Figure 2. Digital subtraction angiogram (DSA) of a patient with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Selective DSA (oblique view, magnified) of the left internal carotid artery shows multifocal vessel narrowing in the peripheral anterior cerebral artery territories (small arrows). In addition, mild segmental arterial dilation can be seen in the proximal middle cerebral artery (large arrow).
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REFERENCES