Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary small vessels disease determined by mutations in the Notch3 gene. Main clinical manifestations include recurrent strokes, dementia, and migraine with aura (MA). The reasons for the extreme variability in presentation and clinical progression are still not understood. Recently, right-to-left shunt (RLS) attributable to patent foramen ovale (PFO) was detected by Transcranial Doppler (TCD) with gaseous contrast in a family with CADASIL, presenting with MA.

The aim of the present study was to establish the prevalence of RLS in a larger population of CADASIL patients and to investigate a possible correlation between RLS, clinical picture, and cerebral MRI lesion load.

Materials and Methods

Patients

Twenty-three consecutive CADASIL patients with positive genetic test were recruited for the study. Demographic and clinical data, including age, sex, presence of TIA/stroke, MA, cognitive impairment and behavioral dysfunction and the concomitant history of hypertension, smoking, hypercholesterolaemia, diabetes mellitus, and hyperhomocystinemia were recorded. The local medical ethics committee approved the study. Informed consent was obtained from all participants.

Methods

Twenty-three CADASIL patients underwent Transcranial Doppler with gaseous contrast to assess RLS. Correlations between RLS, clinical features, and MRI lesion volume (LV) were determined.

Results

Large RLS was diagnosed in 47% of patients. No significant clinical or MRI differences were found between patients with and without RLS.

Conclusion

We found a high prevalence of RLS in our group of CADASIL patients. This may not be a coincidence, but can be rather related to the role of the Notch receptor family in the development of cardiovascular system. (Stroke. 2008; 39:2155-2157.)

Key Words: right-to-left shunt ■ patent foramen ovale ■ Transcranial Doppler ■ CADASIL.
Table 1. Main Clinical and Demographic Characteristics (Overall CADASIL Population; n=23)

<table>
<thead>
<tr>
<th>Main Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD (range)</td>
<td>49±11 (27 to 73)</td>
</tr>
<tr>
<td>Sex</td>
<td>15 males 8 females</td>
</tr>
<tr>
<td>Arterial hypertension (95% CI)</td>
<td>7/23 30% (16 to 51)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia (95% CI)</td>
<td>4/23 17% (7 to 37)</td>
</tr>
<tr>
<td>Past or current smoker (95% CI)</td>
<td>6/23 26% (13 to 46)</td>
</tr>
<tr>
<td>Asymptomatic patients (95% CI)</td>
<td>4/23 17% (7 to 37)</td>
</tr>
<tr>
<td>TIA/stroke (95% CI)</td>
<td>15/23 65% (45 to 81)</td>
</tr>
<tr>
<td>Migraine (95% CI)</td>
<td>7/23 30% (16 to 51)</td>
</tr>
<tr>
<td>Cognitive impairment (95% CI)</td>
<td>9/23 39% (22 to 59)</td>
</tr>
<tr>
<td>Behavioural dysfunction (95% CI)</td>
<td>14/23 61% (41 to 78)</td>
</tr>
</tbody>
</table>

Statistical Analysis

Data are expressed as mean and standard deviation (SD). The Mann Whitney Wilcoxon test has been used to compare the quantitative variables between RLS positive and RLS negative patients. For the nonquantitative variables the odd ratios has been used, and the significance has been based on the normal approximation. A probability value lower than 0.05 has been considered statistically significant.

Results

The main clinical characteristics of the study population are summarized in Table 1.

Fifteen patients had experienced at least 1 cerebrovascular event (65%). Migraine was recorded in 7 patients (30%). Brain MRI examination performed in 22/23 CADASIL patients showed a T2-W LV of 55.1 ± 50.8 cm³ and a T1-W LV of 58.0 ± 53.6 cm³. All CADASIL patients had MRI WM lesions.

TCD assessment of RLS was performed in 21 patients. From 2 of 23 there was no acoustic window. RLS was diagnosed in 15 out of 21 patients (71%). Overall, patients with and without RLS showed overlapping demographic, clinical, and MRI characteristics (Table 2). Eight patients had level (3) and 2 level (4) of RLS (47%). No significant differences on clinical phenotype or the amount of MRI changes were found between RLS-positive and RLS-negative patients (Table 2).

Discussion

Our results are the first evidence of a high prevalence of large RLS in relatively large group of CADASIL patients. This is twice more than what we found in cerebrovascular non-CADASIL patients in our laboratory (data not shown). This finding is probably attributable to PFO, a hemodynamically silent interatrial communication reported to occur in about 25% of the general population. This cardiac septal defect is associated with several pathological conditions such as “cryptogenic” ischemic stroke, usually occurring in subjects under 55 years of age. The prevalence of PFO with large RLS in stroke ranges from 40% to 56%. In addition, a high prevalence of RLS (41%) and PFO (48%) has been recorded in patients with MA and in some families common dominant inheritance has been proposed for PFO and MA.

Ischemic strokes and MA are the most common clinical manifestations of CADASIL, a dominantly inherited monogenic disease attributable to Notch3 gene mutations.

In our study, the high prevalence of RLS in CADASIL patients might not be a coincidence but may rather suggest a common genetic origin of CADASIL and the cardiac septal defect. Indeed, Notch signaling regulates cell differentiation during cardiovascular system development. In adults, Notch3 is expressed exclusively in vascular smooth muscle cells (VSMCs). Gradual degeneration of VSMCs leads to progressive wall thickening and luminal narrowing in small penetrating arteries. Reduced cerebral blood flow finally causes lacunar infarcts and leukoencephalopathy leading to motor deficits and subcortical vascular dementia. Moreover, Notch3 mutations may have a role in abnormal development of the endocardial cushion, as suggested by experimental work showing that Notch3 is also expressed in heart precursors during embryogenesis and that the Notch pathway is...
crucial role in regulating atrioventricular morphogenesis, including cardiac valves and septa.8

The possible influence of other genetic or environmental factors in the occurrence of RLS cannot be ruled out and should be evaluated by studying nonmutation carriers of the same families.

Despite the high incidence of RLS in our CADASIL population, this hemodynamic defect was not correlated with clinical severity or MRI lesion load. Many factors, which probably include subjective (genetic) variability in response to injury as well as the ability to activate mechanisms of adaptation to compensate damage, concur in the full clinical picture of this complex disease. Larger studies are probably necessary to provide definite insights into the prevalence and role of cardiac shunts in modulating clinical phenotype in CADASIL.

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Disclosures

None.

References


Right-to-Left Shunt in CADASIL Patients: Prevalence and Correlation With Clinical and MRI Findings
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