Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small vessel disease caused by highly stereotyped mutations in NOTCH3. This genetic abnormality is responsible for characteristic alterations of vascular smooth muscle cells all along the arterial tree. Despite this, the clinical manifestations of the disease are confined to the central nervous system and include mainly migraine with aura, recurrent subcortical infarcts, mood disturbances, and dementia. Interestingly, silent retinal microvascular circulatory changes have been reported in CADASIL patients as well as high frequency of myocardial infarction in a single series of Dutch patients, suggesting that ischemic heart disease may be part of the manifestations of CADASIL. However, classical cardiovascular risk factors were frequently present in these patients, which may interfere with the results.

Herein we report the results of a case-control study that we conducted to determine the frequency of cardiac abnormalities on a 12-lead resting ECG in CADASIL patients without classical cardiovascular risk factors.

Patients
We analyzed clinical and ECG data of 23 CADASIL patients (11 women; mean±SD age: 55.1±11 years; range 39 to 75) who participated in a case-control study of skin microvascular reactivity. Patients were included if they had a characteristic NOTCH3 mutation, had no past history of cardiovascular diseases including coronary heart disease, hypertension or diabetes mellitus, heavy past
or current tobacco smoking, were not severely demented, and if they gave their written informed consent. Because it was extremely difficult to recruit CADASIL patients without hypercholesterolemia in addition to the other selection criteria, we included those with treated hypercholesterolemia or low-density lipoprotein (LDL) cholesterol >4.2 mmol/L (n = 9). However, LDL cholesterol level was considered in the statistical analysis by splitting the patients into 2 subgroups of patients with hypercholesterolemia (if treated hypercholesterolemia or LDL cholesterol >4.2 mmol/L) or without hypercholesterolemia.

**Controls**

CADASIL patients were compared with 23 age- and sex-matched healthy subjects free of any known cerebrovascular or cardiovascular diseases, including any previous history of coronary heart disease, hypertension, diabetes mellitus, hypercholesterolemia, or tobacco use on the basis of the medical history and a careful medical examination before inclusion (11 women; mean ± SD age; 54.7 ± 9.5 years; range 40 to 74).

A regional ethic committee approved the study (CCPPRB/40-01/ Pitié-Salpêtrière), and all participants signed an informed consent. Each participant had at inclusion a complete physical and neurological examination and a fasting blood examination, including serum total cholesterol, LDL, and high-density lipoprotein (HDL) cholesterol, triglycerides, and homocysteine. The systolic and diastolic blood pressures were measured after resting for 10 minutes in a sitting position.

**Electrocardiogram**

A resting supine 12-lead ECG was recorded at inclusion in each participant at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The ECGs were later, blindly analyzed by 2 reviewers including a board-certified cardiologist (P.H.). Prespecified signs of myocardial infarction or myocardial ischemia, conduction disturbances, and arrhythmias were looked for. Pathological Q waves suggesting myocardial infarction were defined as a first negative deflexion exceeding 0.04-s duration and a depth exceeding 33% of the following R wave, provided the R wave itself was <5 mm in 2 consecutive derivations. Signs suggesting myocardial ischemia were defined as the presence of ST segment depression >1 mm and abnormal T-wave inversion in 2 consecutive leads. Conduction and rhythm analyses were also conducted. Complete right or left bundle branch block was considered when QRS complex duration exceeded 120 ms. Other conduction disturbances such as atrioventricular block or incomplete right or left bundle branch block were systematically assessed as well as cardiac rhythm abnormalities including sinus bradycardia or tachycardia, extrasystolic beats, atrial fibrillation, or flutter.

Electrocardiographic signs of left ventricular hypertrophy defined as the joint occurrence of isolated high R waves in combination with either ST depression or T-wave morphology change in lateral leads were recorded. The Sokolow index was calculated as the sum of the largest R wave of the V5 or V6 derivation plus S wave in V1. Values ≥35 mm were considered as pathological in favor of left ventricular hypertrophy.

QT-corrected interval was calculated according to Bazett’s formula (QTc=QT divided by √ interval between 2 R waves).

**Statistical Analysis**

The data analysis was computed using the JMP statistical software (Abacus Concepts). Descriptive statistics were obtained for the main clinical features and ECG data in each of the studied groups. Comparisons between groups were tested using the χ² or Student t tests. P values <0.05 were considered statistically significant.

**Results**

The patient and control baseline characteristics including demographics, risk factors and concomitant medications are shown in Table 1. No significant differences were found between CADASIL patients and controls for sex, age, systolic and diastolic blood pressure, pulse pressure, LDL and HDL cholesterol, serum homocysteine, and glucose (Table 1). The triglycerides level was significantly higher in CADASIL patients compared with controls (Table 1).

Nine of 23 CADASIL patients had treated or untreated hypercholesterolemia and formed the hypercholesterolemic group. Hypercholesterolemic patients were significantly older than those with normal cholesterol (mean ± SD; 61 ± 10 versus 51 ± 10 years; P = 0.04). They also had higher systolic blood pressure (mean ± SD; 78 ± 8 versus 71 ± 6 mm Hg; P = 0.04).

Among the CADASIL patients, 18 had a previous ischemic stroke, 9 had migraine with aura, 12 had mood disturbances, 5 were demented according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria, and 2 had epileptic seizures. Four of 23 patients were functionally dependent (modified Rankin score >3 and Barthel index <75). The use of antiplatelets and statines were more frequent in CADASIL patients than in controls (Table 1).

The heart rate was significantly higher in CADASIL patients than in controls (mean ± SD; 70 ± 11 bpm versus 56 ± 7 SD bpm; P < 0.001; Table 2). The difference remained significant in each group of CADASIL patients (either hypercholesterolemic [mean ± SD; 69 ± 9 bpm versus 55 ± 6 bpm; P = 0.017] or normocholesterolemic [mean ± SD; 71 ± 12 bpm versus 56 ± 8 bpm; P = 0.009]). There were no differences in other conduction parameters such as P-R interval, P waves, QRS duration, Q-T, and corrected QT intervals between patients and controls. There was a slight difference in Sokolow index between the 2 groups, but it remains in the normal range in both groups (mean ± SD; 15.4 ± 6.76 mm in CADASIL patients versus 18.9 ± 5.07 mm in controls; P = 0.04). No subjects, either cases or controls,
TABLE 2. ECG Parameters in the CADASIL and the Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CADASIL Patients (n=23)</th>
<th>Matched Controls (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean heart rate ± SD, bpm</td>
<td>70 ± 11</td>
<td>56 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean P-R interval ± SD, s</td>
<td>0.155 ± 0.28</td>
<td>0.146 ± 0.28</td>
<td>0.50</td>
</tr>
<tr>
<td>P wave, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.08</td>
<td>18 (78)</td>
<td>18 (78)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;0.08</td>
<td>5 (22)</td>
<td>5 (22)</td>
<td>1.00</td>
</tr>
<tr>
<td>QRS complex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.08</td>
<td>16 (61)</td>
<td>17 (74)</td>
<td>0.49</td>
</tr>
<tr>
<td>&gt;0.08</td>
<td>9 (39)</td>
<td>6 (26)</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean QRS amplitude ± SD, mV</td>
<td>0.93 ± 2.9</td>
<td>0.97 ± 2.5</td>
<td>0.63</td>
</tr>
<tr>
<td>Mean Q-T interval ± SD, s</td>
<td>0.39 ± 0.07</td>
<td>0.42 ± 0.06</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean QT corrected interval ± SD</td>
<td>0.37 ± 0.08</td>
<td>0.44 ± 0.07</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean Sokolov index ± SD, mm</td>
<td>15.4 ± 6.76</td>
<td>18.9 ± 5.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Incomplete RBBB, n (%)</td>
<td>6 (26)</td>
<td>5 (22)</td>
<td>0.33</td>
</tr>
<tr>
<td>Incomplete LBBB, n (%)</td>
<td>3 (13)</td>
<td>1 (4)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

RBBB indicates right bundle branch block; LBBB, left bundle branch block.

had ECG signs of myocardial infarction. Incomplete right bundle branch block was found in 6 patients and in 5 controls, whereas incomplete left bundle branch block was found in 3 patients and in 1 control (Table 2).

Discussion

In this case-control study, 12-lead resting ECG parameters did not differ between CADASIL patients and their age- and sex-matched healthy controls except for a significantly higher heart rate and a significantly lower Sokolow index in CADASIL patients. However, the values of the heart rate in both patients and controls correspond to those reported in general population and the Sokolow index was as well in the normal range in both groups.9,10 The significantly higher heart rate in this group of CADASIL patients may be the consequence of a recruitment bias because the majority of controls were recruited from healthy volunteers with regular physical activities, which was not the case of the CADASIL patients. It is to note that in a recently reported study, there was no difference in heart rate between transgenic mice expressing a CADASIL mutant Notch3 in vascular smooth muscle cells and wild-type mice.11

Contrary to previous case reports, we found no evidence for increased rate of electrical myocardial infarction or ischemia in CADASIL patients. However, there are several limitations in our study. First, the ECG may be not powerful enough to detect moderate or mild myocardial ischemia. Further studies including myocardial single-photon emission computed tomography or echocardiography may be useful to detect any myocardial ischemic damage in CADASIL patients. Second, because we excluded severely demented patients, we cannot exclude that at very late stage of CADASIL, alteration of myocardial small arteries attributable to NOTCH3 mutations may lead to ischemic heart disease. Finally, we excluded patients with classical cardiovascular risk factors except for hypercholesterolemia. These factors may play a role on myocardial ischemic consequences of small vessels alteration because of CADASIL mutations. Smoking has been associated with an increased risk of stroke in CADASIL, whereas other cardiovascular risk factor including hyperhomocysteinemia were not associated with the severity of the clinical phenotype of stroke and dementia or the extent of white matter abnormalities on MRI in a cohort of CADASIL patients.12 Further prospective longitudinal cohort studies will be needed to better understand the issue of the role of classical vascular risk factors in the ischemic consequences of NOTCH3 mutations both in the cerebral tissue and the myocardium.

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