Association Between Carotid Bulb Diaphragm and Ischemic Stroke in Young Afro-Caribbean Patients

A Population-Based Case–Control Study

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Background and Purpose—Carotid bulb diaphragm (CBD) has been described in young carotid ischemic stroke (CIS) patients, especially in blacks. However, the prevalence of CBD in CIS patients is unknown, and whether CBD is a risk factor for CIS remains unclear. We assessed the association between CBD and incident CIS in a population-based study.

Methods—We selected all young (<55 years) CIS patients from a 1-year population-based cohort study in the Afro-Caribbean population of Martinique in 2012. All patients had a comprehensive work-up including a computed tomographic angiography. We calculated CIS associated with ipsilateral CBD incidence with 95% confidence intervals using Poisson distribution. We then selected age- and sex-matched controls among young (<55 years) Afro-Caribbean stroke-free patients admitted for a road crash who routinely had computed tomographic angiography. Odds ratio (ORs) were calculated by conditional logistic regression adjusted for hypertension, dyslipidemia, diabetes and smoking.

Results—CIS associated with ipsilateral CBD incidence was 3.8 per 100,000 person-years (95% confidence interval, 1.4–6.1). Prevalence of ipsilateral CBD was 23% in all CIS and 37% in undetermined CIS patients. When restricted to undetermined CIS, CBD prevalence was 24 times higher than that in controls (adjusted OR, 24.1; 95% confidence interval, 1.8–325.6).

Conclusions—CBD is associated with an increased risk of ipsilateral CIS in young Afro-Caribbean population.

Key Words: angiography • case–control study • cohort study • diaphragm • stroke
Definition of CBD

CBD was defined by the classic aspect on CTA, that is, a thin intraluminal filling defect along the posterior wall of the carotid bulb, on oblique sagittal section and seen as a septum on axial slices (Figure 1A). All CTA were ascertained by 2 experienced neurologists (J.J. and S.O.) with a third blinded review by a radiologist with specific interest in stroke (S.J.). To avoid misclassifications with atherosclerotic lesions, presence of calcifications or evidence of atherosclerosis on cervical or cerebral arteries ruled out the diagnosis of CBD. Similarly, CTA with characteristics compatible with CBD but including features of carotid dissection (filling occlusion above the carotid bulb and artery enlargement) were not considered as CBD.

Statistical Analysis

CIS associated with CBD incidence per 100 000 person-years, with 95% confidence intervals (95% CIs), were calculated using Poisson distribution. Odds ratio (ORs) and 95% CIs for the prevalence of CBD were calculated in cases compared with controls using conditional logistic regression with adjustment for hypertension, diabetes mellitus, dyslipidemia, and smoking to control for known potential confounders.

Incidence of CIS Associated With CBD

In the ERMANCIA-II study, 544 incident strokes occurred, including 439 IS (81%), of which 69 (16%) were in young patients (Figure 2). Among the 43 (62%) CIS in young patients, 27 (63%) remained undetermined after a comprehensive work-up.

Ten out of the 43 young CIS patients had an ipsilateral CBD, of which 2 patients had a bilateral CBD. In these 10 patients, the cause of CIS remained undetermined after the comprehensive work up. Prevalence of CBD associated with undetermined CIS was estimated to be 37% (95% CI, 19–55). None of the patients with CBD had concomitant spontaneous carotid dissection or bulbar calcifications. Five patients had a surgical resection of the CBD confirming an intimal hyperplasia in all cases. These 10 patients with CBD had been previously described in the original CBD cohort.

Results

Figure 1. Carotid bulb diaphragm with typical pattern on computed tomographic angiography sagittal view (A) and corresponding macroscopic specimen (B). The white arrows show the diaphragm on both images. Histological results are not presented here but showed intimal hyperplasia.

The incidence of CIS with ipsilateral CBD was 3.8 per 100 000 person-years (95% CI, 1.4–6.1). 3.2 in men (95% CI, 0.1–6.4) and 4.3 in women (95% CI, 0.9–7.7).

Case–Control Study

Two hundred and sixty-eight stroke-free patients were admitted for a road crash and had a cervical CTA in 2013 to 2014. After exclusion of patients aged >55 years (n=44), patients with low quality of CTA (n=16) and those with a traumatic carotid dissection (n=5), 203 patients were eligible. We finally selected 43 age- and sex-matched controls (Figure 2).

The main characteristics of cases and controls are described in Table. CIS patients were more likely to have CBD(10, 23.3%) than controls (3, 7%; P=0.035). In all CIS patients, CBD was associated with a nonstatistically significant higher risk of CIS (unadjusted OR=3.33; 95% CI, 0.92–12.11; P=0.0674). After adjustment for hypertension, diabetes mellitus, dyslipidemia, and smoking, CBD was associated with a 9 times higher risk of CIS (adjusted OR=9.45; 95% CI, 1.71–52.21; P=0.009).

Looking at the 27 patients with undetermined CIS and their 27 corresponding controls, the prevalence of CBD was significantly higher in cases (10, 37%) than that in controls (2, 7%; P=0.009). CBD was strongly associated with CIS (unadjusted OR=5.00; 95% CI, 1.10–22.82; P=0.038), and the association remained after adjustment for hypertension, diabetes mellitus, dyslipidemia, and smoking (adjusted OR=24.06; 95% CI, 1.78–325.63; P=0.016).

No disagreements between reviewers were identified for the diagnosis of CBD.

Discussion

This is the first study to date reporting the incidence of CIS associated with CBD and investigating their relation. In our young Afro-Caribbean population, incidence of CIS associated with CBD reaches 3.8 per 100 000 person-years; CBD is associated with an increased risk of ipsilateral CIS and may account for one third of former undetermined CIS.

We found a higher prevalence of CBD in young Afro-Caribbean CIS patients than in a previous large case series (23% versus 1.2%) conducted on a hospital-based registry in consecutive Canadian CIS patients of all ages. Differences in methodology and population characteristics may explain discrepancies in findings because prevalence of CBD is thought to be increased in black compared with white populations.

CBD-related CIS may be mediated by an embolic mechanism, with stasis of blood flow in the CBD, increasing the thrombogenicity and the risk of artery-to-artery embolism. CBD could represent the predominant form of fibromuscular dysplasia in blacks, whereas typical medial FMD with string of beads appears as the prevalent lesion in whites.

The significance and the magnitude of the association between CBD and CIS were increased after adjustment for hypertension, diabetes mellitus, dyslipidemia, and smoking, which confirms the confounding role of these factors. The
strength of this association supports causality and makes unlikely the risk of chance finding. However, the exact magnitude of the effect of CBD on the risk of CIS and comparisons between unadjusted and adjusted odds must be interpreted cautiously considering the small sample size of our cohort leading to wide 95% CIs.

The small number of publications on CIS associated with CBD may suggest that CBD remains underdiagnosed. Early diagnosis of CBD seems crucial not only to establish the probable cause of CIS but also to prevent the risk of recurrence. In our previous cohort, 20% of patients with CIS associated with CBD had a recurrent CIS within 1 year after the index stroke despite antiplatelet therapy.1

The strengths of our study include the prospective design and the population-based nature of the cohort study with multiple overlapping sources of case ascertainment, which minimize the selection biases. CTA for the diagnosis of CBD were performed in the same center in cases and controls and were blindly reviewed, minimizing the risk of differential misclassification biases. Our study has limitations. We restricted our analysis to young patients to avoid misclassification of CBD with atherosclerotic lesions, which prevented us from exploring the effect of age on the prevalence of CBD. CBD diagnosis was not performed with the gold-standard conventional angiography but with systematic CTA. However, the high agreement in the assessment of CBD with CTA, and the histological confirmation in patients who underwent a carotid surgery suggests that CTA ensure accurate CBD diagnosis. Eventually, we were unable to increase the statistical power of the case–control study by increasing the number of controls because of the small number of women in the road crash population.

In summary, CBD is associated with an increased risk of ipsilateral CIS in young Afro-Caribbean population. Further follow-up studies are required to assess which effective strategies (anticoagulant drugs, surgical removal of CBD, or stent-procedures) should be proposed.

Table. Baseline Characteristics and CBD Distribution of the Cases and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=43)</th>
<th>Controls (n=43)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>46.70 (7.1)</td>
<td>45.91 (7.8)</td>
<td>…</td>
</tr>
<tr>
<td>Median age (IQR), y</td>
<td>48 (10)</td>
<td>47 (12)</td>
<td>…</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>9 (20.9)</td>
<td>2 (4.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (14)</td>
<td>2 (4.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (37.2)</td>
<td>7 (16.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Tobacco</td>
<td>11 (26.6)</td>
<td>5 (11.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>CBD</td>
<td>10 (23.3)</td>
<td>3 (7)</td>
<td>0.035</td>
</tr>
<tr>
<td>Unilateral CBD</td>
<td>8 (18.6)</td>
<td>3 (7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bilateral CBD</td>
<td>2 (4.7)</td>
<td>0</td>
<td>0.15</td>
</tr>
<tr>
<td>Ipsilateral to stroke CBD</td>
<td>10 (23.3)</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

Numbers are n (%) unless otherwise indicated. CBD indicates carotid bulb diaphragm; and IQR, interquartile range.

Disclosures

None.

References


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