Bilateral Intracranial Vertebral Artery Disease in the New England Medical Center Posterior Circulation Registry

Hyun-Kil Shin, MD; Kyung-Moo Yoo, MD; Hui Meng Chang, MD; Louis R. Caplan, MD

Background: Previous studies of patients with bilateral intracranial vertebral artery (ICVA) disease were selective and retrospective.

Methods: We studied risk factors, vascular lesions, symptoms, signs, and outcomes in patients with bilateral ICVA disease among 430 patients in the New England Medical Center Posterior Circulation Registry.

Results: Forty-two patients had bilateral ICVA occlusive disease (18 had bilateral stenosis; 16, unilateral occlusion and contralateral stenosis; and 8, bilateral occlusion). The most common risk factors were hypertension (32/42 [76%]) and hyperlipidemia (22/42 [52%]). Sixteen patients (38%) had transient ischemic attacks (TIAs) only; 18 (43%), TIAs before stroke. Occlusive vascular disease also involved the basilar artery in 29 patients (69%), the extracranial vertebral arteries in 18 (43%), and the internal carotid arteries in 11 (26%). Only 6 patients had no other major vascular lesion. Cerebellar symptoms were common. Among 30 patients with infarction, 21 (70%) had proximal intracranial territory involvement, and 15 (50%) had distal territory involvement. The location of occlusive lesions in relation to posterior inferior cerebellar artery origins did not significantly influence prognosis. During follow-up, 31 patients had no symptoms or slight disability, 2 had progression, and 7 died. Among 7 patients with poor outcome, 6 also had basilar artery stenosis or occlusion and 5 had proximal and distal intracranial territory infarcts.

Conclusions: Most patients with bilateral ICVA occlusive disease have hypertension, other major occlusive lesions, and TIAs before stroke. Short- and long-term outcomes are usually favorable, but patients with bilateral ICVA and basilar artery–occlusive lesions often have poor outcomes.

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VERTEBROBASILAR ischemia has a variety of different vascular pathologic features at various locations, and has diverse clinical courses and outcomes. Newer diagnostic technology now makes it possible to localize and monitor occlusive vascular lesions within the posterior circulation.¹

For editorial comment see page 1329

We recently reviewed our experience with patients with occlusive lesions of the intracranial vertebral arteries (ICVAs).² Although bilateral ICVA disease is common, few studies have analyzed the clinical features in patients with these occlusive lesions.³⁴ Caplan⁵ described 9 patients with severe ICVA occlusive disease selected because of poor outcome. Bogousslavsky et al⁶ analyzed retrospectively the outcome in patients with bilateral ICVA disease who were included in the Extracranial to Intracranial Bypass Study. Other reports were necropsy based⁶ or included only patients treated with posterior circulation bypass surgery.⁷⁻¹²

We studied risk factors, vascular lesions, symptoms, signs, and outcome in patients with bilateral ICVA disease in the New England Medical Center Posterior Circulation Registry (hereafter referred to as the Registry), a prospective registry of patients with vertebrobasilar territory ischemia seen from January 1, 1986, to December 31, 1997. We sought to clarify the distribution of infarction and the clinical courses and outcomes and to correlate these with the severity and location of the ICVA disease. Because all patients were treated with antiplatelet aggregants and/or anticoagulants, we cannot comment on the effect of treatment in our series.

RESULTS

Forty-two Registry patients had bilateral ICVA-occlusive disease (28 men and 14 women; mean age, 64.1 years; range, 44-89 years; SD, 10.7 years). Thirty-seven pa-
SUBJECTS AND METHODS

SUBJECTS

We studied 42 patients with bilateral ICVA occlusive lesions collected from the 430 Registry patients with infarcts in the posterior circulation or definite posterior circulation transient ischemic attacks (TIAs). The Registry includes detailed clinical information about symptoms and signs, stroke risk factors, results of neurologic examination, hospital course, outcome, and results of neuroimaging, cardiac, and vascular studies. A detailed description of the Registry and the criteria for diagnosis of stroke mechanisms and vascular causes has been published.1

METHODS

All patients had vascular imaging studies, as seen in the following tabulation:

<table>
<thead>
<tr>
<th>Study</th>
<th>No. (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography</td>
<td>30 (71)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>38 (90)</td>
</tr>
<tr>
<td>Contrast angiography</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Magnetic resonance angiography</td>
<td>32 (76)</td>
</tr>
<tr>
<td>Extracranial duplex ultrasound</td>
<td>25 (56)</td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>29 (70)</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
<td>17 (40)</td>
</tr>
<tr>
<td>Cardiac rhythm monitoring</td>
<td>11 (26)</td>
</tr>
</tbody>
</table>

The only patient who did not have catheter angiography or magnetic resonance angiography had extracranial and transcranial ultrasound. All patients had brain imaging studies, computed tomography, or magnetic resonance imaging. Twenty-six patients (62%) had computed tomography and magnetic resonance imaging. Patients also routinely had cardiac evaluations. We excluded patients in whom cardiac embolism was the most likely stroke mechanism.

We reviewed the original imaging films when available. When films were no longer available, we relied on radiological reports and our original drawings and descriptions of the lesions. The ICVA lesions were divided by location into proximal, indicating disease at or just after distal penetration of the ICVA, including the first quarter of the artery; proximal to posterior inferior cerebellar artery (PICA), indicating disease located between the proximal quarter of the artery and PICA; distal to PICA, indicating disease located in the third quarter of the artery after the PICA origin; and vertebrobasilar junction, indicating disease located in the distal quarter of the ICVA.

We divided the posterior circulation territory into 3 levels illustrated in the Figure. Proximal intracranial posterior circulation territory included regions supplied by the ICVAs (medulla- and PICA-supplied region of the cerebellum). Middle intracranial posterior circulation territory included the region supplied by the basilar artery up to its superior cerebellar artery branches (pons- and anterior inferior cerebellar artery-supplied regions of the cerebellum). Distal intracranial posterior circulation territory included the regions supplied by the rostral basilar artery and its directly penetrating midbrain and thalamic branches, the superior cerebellar arteries, and the posterior cerebral arteries.3,14 Occlusion of the ICVA was inferred when there was total obstruction of flow in the ICVAs shown on results of catheter or magnetic resonance angiography. Stenosis refers to 50% or more luminal narrowing on results of angiography or magnetic resonance angiography.

We obtained follow-up data from 41 patients by telephone interview (8 [20%]), letter (8 [20%]), and outpatient visits (25 [61%]). One patient was unavailable for follow-up. We used a modified Rankin Scale to describe the patient’s condition.

RESULTS

Patients

Most patients also had severe occlusive vascular lesions (Table 2). Fifteen patients (36%) had symptoms aggravated by standing or antihypertensive treatment. Strokes were more common in patients with bilateral occlusive lesions proximal to PICA (9/12 [75%]) than when just 1 of the ICVAs was involved proximal to PICA (11/19 [58%]).

ICVA OCCLUSIVE LESIONS, OTHER VASCULAR LESIONS, AND COLLATERAL CIRCULATION

Eight patients had bilateral occlusions, 18 had bilateral stenosis, and 16 had unilateral occlusions and contralateral stenosis. The most common lesion was stenosis (52 of 84 arteries; 62%). Locations within the ICVAs were the proximal fourth (5, left ICVA; 10, right ICVA); the second fourth, proximal to PICA (12, left; 9, right); the third fourth, distal to PICA (16, left; 20, right); and the distal fourth (13, left; 17, right). The main cause of bilateral ICVA disease was atherothrombosis (40 patients; 95%); a few patients had vasospasm and dolichoectasia (1 patient each; 5%). Most patients also had severe occlusive vascular lesions at the following other sites: the basilar artery in 29 (69%), the extracranial vertebral arteries in 18 (43%), and the in-

RISK FACTORS

The most common risk factors were hypertension (32 patients [76%]), hyperlipidemia (22 [52%]), diabetes mellitus (15 [36%]), smoking (15 [36%]), coronary artery disease (15 [36%]), obesity (12 [28%]), and previous stroke (10 [24%]). Other risk factors, such as non–coronary-related cardiac disease, peripheral vascular disease, migraine, ethanol use, and recreational drug use, were found in less than 10% of patients. Table 1 compares the risk factors in patients with bilateral ICVA disease with those of Registry patients who had other occlusive lesions.

SYMPTOMS AND PRESENCE OF STROKE OR TIAs

Eight patients (19%) had strokes without TIAs, 18 patients (43%) had TIAs before stroke, and 16 patients (38%) had TIAs only. Among the patients with TIAs only, 14 had nonlocalized symptoms and 2 had localized symptoms (PICA and posterior cerebral artery territory). Most patients (33/34 [97%]) with TIAs, with or without stroke, had multiple episodes. Often, the same symptoms were repeated. Vertigo or dizziness, dysarthria, ataxia, diplopia, and headache were the most common symptoms (Table 2). Fifteen patients (36%) had symptoms aggravated by standing or antihypertensive treatment. Strokes were more common in patients with bilateral occlusive lesions proximal to PICA (9/12 [75%]) than when just 1 of the ICVAs was involved proximal to PICA (11/19 [58%]).
ternal carotid arteries in 11 (26%). Six patients (14%) had only bilateral ICVA disease. Most patients had good collaterals from the anterior circulation through the posterior communicating arteries, the posterior circulation through the cerebellar arteries, or both. We found no correlation between outcome and the origin of collateral circulation.

LOCATION OF INFARCTS WITHIN THE POSTERIOR CIRCULATION AND MECHANISMS OF STROKE

Table 3 shows the distribution of infarction within posterior circulation territories. Of 30 patients with infarction, 21 (70%) had isolated or multiple infarcts that included the proximal posterior circulation territory; 15 (50%), the distal posterior circulation territory; and 11 (37%), the middle posterior circulation territory. Among the patients with infarction, 16 (53%) had multiple territory infarcts. Posterior and distal infarcts (skipping the middle territory) was a common pattern, present in 9 (30%) patients. The most common mechanism of stroke and TIA was large-artery hemodynamic (38/42), and among patients with distal territory infarcts, 4 patients had presumed intra-arterial embolism as the stroke mechanism. Among the 30 patients with infarct, 15 (54%) had PICA territory cerebellar infarcts, and 3 (11%) had cerebellar border zone infarcts. Patients in whom PICA was not visualized using angiography usually had PICA cerebellar infarction (13 of 20 patients; 65%). Cerebellar infarcts in PICA territory and the border zone were less often present on the side with ICVA lesions distal to PICA.

OUTCOME AND FOLLOW-UP

Mean length of follow-up was 31.4 months (range, 1-118 months; SD, 30.8 months). One patient was unavailable for follow-up. Two patients had progression of disease and symptoms (increased modified Rankin Scale score by 2 levels), and 7 patients died during follow-up. Five
patients died of new stroke or complications of stroke; the other 2 patients died after subarachnoid hemorrhage and lung cancer. Table 4 shows the modified Rankin Scale scores at hospital discharge and last follow-up. The 2 patients with progression and the 5 with stroke-related death did not differ from the other patients with bilateral ICVA disease in relation to the presence of collateral circulation, the location and extent of infarction, or the severity of ICVA occlusive disease. Progression or stroke-related death was more common in patients with bilateral ICVA disease in relation to the presence of collateral circulation. Hypertension and hyperlipidemia were more frequent in patients with bilateral ICVA disease than in Registry patients with other vascular lesions or in patients with unilateral ICVA disease. Most patients with bilateral ICVA occlusive disease have extensive atherosclerosis, often including the basilar and extracranial carotid and vertebral arteries. The chronicity of the development of occlusive lesions usually allowed development of extensive collateral circulation. Collateral blood flow arises from the anterior circulation via the posterior communicating arteries, and within the posterior circulation through the long cerebellar arteries, the anterior spinal artery, and the leptomeningeal arteries.

VASCULAR LESIONS AND RISK FACTORS

Patients with bilateral ICVA disease usually have multiple-stroke risk factors and very often have other severe occlusive lesions within the anterior and posterior circulation. Hypertension and hyperlipidemia were more frequent in patients with bilateral ICVA disease than in Registry patients with other vascular lesions or in patients with unilateral ICVA disease. Most patients with bilateral ICVA occlusive disease have extensive atherosclerosis, often including the basilar and extracranial carotid and vertebral arteries. The chronicity of the development of occlusive lesions usually allowed development of extensive collateral circulation. Collateral blood flow arises from the anterior circulation via the posterior communicating arteries, and within the posterior circulation through the long cerebellar arteries, the anterior spinal artery, and the leptomeningeal arteries.

ISCHEMIA PATTERNS

The extensive intracranial occlusive posterior circulation lesions led to a tenuous circulatory equilibrium with resultant frequent episodes of reduced perfusion. The predominant temporal pattern in our patients with severe bilateral ICVA disease was TIAs, often multiple and stereotyped in individual patients. Transient ischemic attacks were noted by 81% of patients; 38% had only TIAs, whereas the others had TIAs before and after strokes. Thirty-three of the 34 patients with TIAs had multiple, stereotyped, usually brief, ischemic episodes. Symptoms that reflected vestibulocerebellar, motor, and cranial nerve abnormalities were most prominent during the origin of PICA. Narrowing often extends to the vertebrobasilar junction and into the proximal basilar artery. Bilateral ICVA atherosclerotic disease is common. To our knowledge, this is the first systematic, large, prospective study of patients with bilateral ICVA disease. The Registry was possible because of a large number of referrals of patients with vertebrobasilar disease, so that data from our 42 patients with bilateral ICVA disease may not reflect community- or nonreferral hospital–based experience.

Table 3. Stroke Localization in Patients With Infarcts*

<table>
<thead>
<tr>
<th>Territories</th>
<th>Bilateral ICVA† (n = 42)</th>
<th>Unilateral ICVA‡‡ (n = 46)</th>
<th>No Lesion Proximal PICA (n = 6)</th>
<th>Unilateral Lesion Proximal PICA (n = 19)</th>
<th>Bilateral Lesion Proximal PICA (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only proximal</td>
<td>7</td>
<td>16</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Only middle</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Only distal</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total proximal</td>
<td>21</td>
<td>28</td>
<td>1</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Total middle</td>
<td>11</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total distal</td>
<td>15</td>
<td>16</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Unknown or TIAs only</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

* ICVA indicates intracranial vertebral artery; PICA, posterior inferior cerebellar artery; and TIA, transient ischemic attack.
†P = .05 (x²) difference; other differences were not statistically significant (numbers small).
‡From the patients in the New England Medical Center Posterior Circulation Registry.

Table 4. Modified Rankin Scale Scores at Discharge and at Follow-up*

<table>
<thead>
<tr>
<th>Modified Rankin Scale</th>
<th>At Hospital Discharge</th>
<th>At Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (No symptoms)</td>
<td>14 (34)</td>
<td>13 (32)</td>
</tr>
<tr>
<td>1 (No significant disability)</td>
<td>11 (27)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>2 (Slight disability)</td>
<td>11 (27)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>3 (Moderate disability)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>4 (Moderate to severe disability)</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>5 (Severe disability)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>6 (Dead)</td>
<td>0</td>
<td>7 (17)</td>
</tr>
</tbody>
</table>

* One patient was unavailable for follow-up (n = 41).
TIAs. The pathogenesis of TIAs in patients with bilateral ICVA disease probably involves embolism and hypoperfusion. The presence of extensive hemodynamically significant occlusive lesions, the stereotypy and brevity of episodes, and provocation by changes in position and reduction in blood pressure led us to posit a hemodynamic, hypoperfusion mechanism for most TIAs in patients with bilateral severe ICVA disease.

Registry patients with unilateral ICVA disease were more likely to have acute-onset strokes without preceding TIAs than were patients with bilateral ICVA disease. Patients with unilateral ICVA disease often had distal territory posterior circulation infarcts presumably caused by intra-arterial embolism from the ICVA lesions. The most vulnerable regions for reduced perfusion in patients with ICVA disease are the lateral medulla, which is supplied by arteries that penetrate directly from the ICVA, and the PICA-supplied cerebellum. The main components of the vestibulocerebellar system, the vestibular nuclei and their connections with the vestibulocerebellar structures in the cerebellar vermis, lie directly within the core of ICVA supply, explaining the frequency of vertigo and ataxia during TIAs. Among cranial nerve-related symptoms, facial numbness, and oculomotor abnormalities were prominent because of the ICVA proximal basilar artery supply of the lower brainstem tegmentum.

**LOCATION OF INFARCTIONS**

Most patients with bilateral ICVA disease had posterior circulation infarcts (30/42 [71%]). Proximal and distal posterior circulation territory infarction was the most common distribution. As expected, when infarction was limited to 1 intracranial territory, the proximal territory that includes the medulla and PICA cerebellum was most often involved. This region is supplied directly by penetrating branches from the ICVA and the anterior spinal artery and PICA branches of the ICVs. Others have also noted the frequency of medullary and cerebellar infarcts in patients with ICVA occlusive disease. Although most patients had infarcts in more than 1 territory, the proximal territory was most frequently infarcted, followed by the distal territory. Distal territory ischemia and infarction is caused by intra-arterial embolism from the ICVs or hypoperfusion. Some patients had episodes of cortical blindness, often after sudden or prolonged standing, indicating hypoperfusion of the occipital cortex supplied by the posterior cerebral arteries. Registry patients with unilateral ICVA disease had more proximal and slightly less middle and distal territory involvement than those with bilateral ICVA disease.

Stenosis or occlusion of the extracranial vertebral arteries was a more frequent cause of proximal territory infarcts in Registry patients than was intrinsic ICVA disease. Although this finding may seem counterintuitive, it is explained by the fact that extracranial vertebral artery disease mostly causes infarcts by artery-to-artery embolism to the ICVA or to the distal basilar artery and its branches. Embolic occlusion of the ICVA probably more often causes local proximal territory infarcts than gradual occlusion of the ICVA with development of collateral flow that maintains perfusion of the proximal territory.

Because flow from the ICVs through PICA around the cerebellum through the other long circumferential cerebellar arteries (anterior inferior cerebellar arteries and the superior cerebellar arteries) forms such an important potential pathway, we explored whether the location of the ICVA lesions in reference to the origins of the PICAs influenced the clinical findings and outcomes. When flow through 1 or both PICAs is reduced because of ICVA obstruction proximal to or at the PICA origins, flow to the pons and midbrain is compromised. We posited that the location and distribution of posterior circulation infarction and patient outcomes might be influenced by whether neither, 1, or both ICVA lesions were located before the PICA branch origins. As predicted, the proximal intracranial territory was less often involved if the ICVA lesion was distal to PICA. The middle territory was more often involved when both ICVA lesions were distal to PICA, effectively causing reduced flow in...
the proximal basilar artery. Associated basilar artery disease and propagation of thrombus from an ICVA into the basilar artery also explained pontine infarction. Cerebellar infarcts were most common when the PICA branches on 1 or both sides were not seen on angiography. When stenosis of the ICVA was distal to PICA, cerebellar infarction was less common.

OUTCOMES

In 1983, Caplan3 described 9 patients with severe bilateral ICVA disease, and all had very bad outcomes (8 deaths and 1 locked-in state). This was a selected anecdotal series in which patients were chosen because of their poor outcomes. In contrast, Bogousslavsky et al9 described 10 patients with bilateral ICVA disease from among individuals undergoing evaluation for extracranial to intracranial anterior circulation bypass surgery. Muller-Kuppers et al9 reviewed the prognosis of all patients with ICVA disease in the Registry and reported a relatively poor prognosis in patients with distal territory infarction caused by intra-arterial embolism from their ICVA disease.

The outcomes in patients with bilateral ICVA disease in our series were relatively favorable, despite the severity and extent of the atherosclerotic lesions. Seven patients died, but only 5 (12%) died of stroke-related factors. During follow-up, 31 patients (75%) with bilateral ICVA disease had no symptoms or could care for their affairs without the need for assistance. Only 2 patients had progression of posterior circulation ischemia. Progression and stroke-related death did not correlate with the pattern of collateral circulation, the distribution of infarction, or the presence of stenosis vs occlusion of the ICVAs. Among those with poor outcomes, 6 (86%) also had severe basilar artery occlusive disease, and 5 (71%) had proximal and distal territory infarcts.

CONCLUSIONS

1. Most ICVA-occlusive lesions are atherostenotic. The most common location of stenosis is distal to PICA, especially near the vertebrobasilar junction.

2. Bilateral ICVA disease is common. Patients with bilateral ICVA occlusive disease have a very high frequency of atherostenosis in other extracranial and intracranial arteries.

3. The most common clinical pattern of ischemia is multiple, brief, stereotyped TIAs. However, posterior circulation infarcts develop in more than two thirds of patients.

4. The proximal, especially PICA-supplied cerebellum, and distal territories within the posterior circulation are infarcted most often.

5. Collateral circulation from anterior and posterior circulation sources is usually very well developed in patients with bilateral ICVA-occlusive disease.

6. The short- and long-term outcomes are usually favorable. However, patients who also have basilar artery-occlusive lesions, presumed embolism to the distal territory, or bilateral occlusive lesions proximal to PICA have a less favorable prognosis.

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REFERENCES