Intracranial Bleeding in Patients With Vertebrobasilar Dolichoectasia

Stefano G. Passero, MD; Benedetta Calchetti, MD; Sabina Bartalini, MD

Background and Purpose—Intracranial bleeding in patients with vertebrobasilar dolichoectasia (VBD) is considered uncommon, but there are no precise data to support this opinion. The purpose of this study was to examine the incidence and characteristics of intracranial hemorrhage in patients with VBD and to evaluate factors that may promote bleeding.

Methods—We conducted a prospective study of 156 consecutive VDB patients followed-up for an average 9.35 years. The association of demographic, clinical, and imaging features with occurrence of intracranial bleeding was evaluated by multivariate analysis. Survival analysis was used to evaluate rates of incidence.

Results—32 hemorrhagic strokes were observed in 28 patients either as a diagnostic event (n=10) or during follow-up (n=22). Of the 32 hemorrhagic events, 6 were subarachnoid hemorrhage and 26 intraparenchymal hemorrhage. Multivariate analysis found an association between intracranial bleeding and maximum diameter of the basilar artery (OR, 4.29; P=0.009), degree of lateral displacement of the basilar artery (OR, 4.53; P=0.004), hypertension (OR, 4.74; P=0.024), use of antiplatelet or anticoagulant agents (OR, 3.07; P=0.033), and female sex (OR 6.33; P=0.001). The cumulative proportion of survivors free of hemorrhagic stroke was 88.6 at 5 years and 84.4 at 10 years.

Conclusions—Our study showed that intracranial bleeding in patients with VBD is not as uncommon as usually believed. Its occurrence is associated with the degree of ectasia and elongation of the basilar artery and may be favored by hypertension and use of antiplatelet or anticoagulant agents. (Stroke. 2005;36:1421-1425.)

Key Words: aneurysm ■ hemorrhage ■ stroke ■ subarachnoid hemorrhage ■ vertebrobasilar stroke

Clinical expression of vertebrobasilar dolichoectasia (VBD) is variable and includes compression of cranial nerves or brain stem,1–5 obstructive hydrocephalus,3,6 and ischemia in vertebrobasilar arterial territory.7–13 However, pathological changes in the arterial wall, consisting primarily in defects in the internal elastic lamina with thinning of the media secondary to smooth muscle atrophy,14–16 may predispose patients to intracranial bleeding of various kinds. Knowledge of hemorrhagic stroke as a clinical feature of VBD has come from case reports involving a small number of patients.1,7–9,11,13,14,17–20 Little is known about factors predisposing to bleeding and its prognostic significance.

In this study, hemorrhagic stroke was investigated in a large cohort of patients with VBD to determine the risk for intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) and to identify predisposing factors for bleeding.

Subjects and Methods

We prospectively collected information of consecutive patients with VBD, hospitalized or seen as outpatients at the units of neurology, neurosurgery, and otorhinolaryngology since 1980. A total of 156 patients were enrolled in the database. All patients were evaluated by CT scan (n=24), MRI (n=43), or both (n=89). Fifty-three patients underwent additional angiographic examination performed by the Seldinger method and 46 underwent MRA. According to Smoker et al,21 the basilar artery (BA) was considered to be elongated if at any point along its course it lay lateral to the margin of the clivus or dorsum sellae or bifurcated above the plane of the suprasellar cistern. Ectasia was diagnosed if the minimum diameter of the artery was >4.5 mm. Although vertebrobasilar nonsaccular intracranial aneurysms may be different manifestation of the same underlying disorder, we restricted our study to dolichoectasia because it has distinct features and a quite different natural history. We only included patients with BA elongated and uniformly enlarged over its entire course (Figure 1) without limitations regarding age or presenting symptoms. Elongation and uniform ectasia of other posterior circulation vessels corroborated the diagnosis of dolichoectasia in almost all patients. Patients with segmental "spindle" shape enlargements of the BA or fusiform enlargement superimposed on dolichoectasia, a condition recently described as a transitional type,22 were thus excluded, as were those with "giant" aneurysms (diameter >25 mm).

For the purpose of this study, the following concomitants were examined: history of hypertension (previous diagnosis of arterial hypertension: systolic blood pressure >160 mm Hg or diastolic >90 mm Hg or both and/or past or present use of antihypertensive agents), diabetes mellitus (previous diagnosis of diabetes and/or past or present use of antidiabetic agents), current smoking, alcohol abuse (>400 mL/wk of pure ethanol), hyperlipidemia (cholesterol >250 mg/100 mL or triglycerides >180 mg/100 mL, or both), and use of antiplatelet or anticoagulant agents.

Hemorrhagic lesions were classified according to the anatomical site and the presumed vascular territory involved. The diameter of

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the BA at midpons level, maximum diameter of the BA, height of bifurcation, and lateral displacement were evaluated as suggested by Smoker et al. The height of the BA bifurcation was scored as 1 (within the suprasellar cistern), 2 (at level of third ventricle floor), and 3 (indenting and elevating the floor of the third ventricle); lateral displacement was scored as 1 (medial to lateral margin of clivus or dorsum sellae), 2 (lateral to lateral margin of clivus or dorsum sellae), and 3 (in cerebellopontine angle cistern). Scores of left and right displacement were averaged to obtain an index of “laterality.” The maximum diameter of the BA was dichotomized based on the median value (6.4 mm).

After the initial diagnosis, patients were followed-up with annual visits. Imaging studies were repeated if new symptoms or signs appeared or every 3 to 4 years in the absence of new events. If patients were hospitalized during follow-up, we retrieved medical records from the hospital where the patient had been treated. Intracranial bleeding was considered as such only when documented by imaging studies. For this analysis, December 2003 was the end date for follow-up surveillance.

Statistical Analysis

The \( \chi^2 \) test for categorical variables and the Mann–Whitney test for continuous variables were used as needed. The influence of age, sex, hypertension, diabetes, alcohol abuse, smoking, dyslipidemia, use of antiplatelet or anticoagulant agents, maximum diameter of BA, height of BA (score), lateral displacement of BA (score), and dolichoectasia of the anterior circulation on the occurrence of hemorrhagic stroke was evaluated by univariate and multivariate logistic regression analysis. Survival analysis was used to illustrate the incidence of intracranial bleeding in the whole cohort and in predefined groups of subjects. The log-rank test was used to test for differences across groups. For survival analysis, only patients who had intracranial bleeding during follow-up were included. Statistical analysis was performed with the SPSS package.

Results

Of the 156 patients, 118 were men and 38 women. Age ranged from 10 to 88 years (mean, 60.5 ± 11.6 years). The most common concomitant was arterial hypertension observed in 100 patients (64%); 18 patients (12%) had diabetes, 57 patients (37%) had hyperlipidemia, 43 patients (28%) were current smokers, 25 patients (16%) were alcohol abusers, and 75 patients (48%) were using antiplatelet (n = 70) or anticoagulant (n = 5) agents. Nine patients were using antiplatelet or anticoagulant agents before diagnosis and continued the treatment unless the presenting event was an intracranial hemorrhage. The remaining 66 patients began to take these agents after diagnosis. All patients using antiplatelet treatment also used aspirin (100 to 500 mg/d) and all patients using anticoagulant treatment also used Coumadin.

The maximum diameter of the BA ranged from 4.6 to 13.4 mm (mean, 6.8 ± 1.80 mm). In 128 patients, the bifurcation of the BA was at the level or indented the floor of the third ventricle. In 44 patients the index of lateral displacement of the BA was >1. As judged by the neuroradiologist, dolichoectasia also involved the vertebral or posterior cerebral arteries in 135 patients (86%). Some degree of dolichoectasia of anterior circulation was observed in 71 patients (43%). Initial presentation included cranial nerve or brain stem dysfunction (n = 56), ischemic stroke (n = 56), and hemorrhagic stroke (n = 10). 34 patients had unrelated symptoms or symptoms with an unclear but possible relationship.

Patients were followed-up for an average period of 9.35 years (up to 23.8 years). Twenty-eight patients (18%) had one or more hemorrhagic stroke. Ten patients experienced intracranial hemorrhage as the diagnostic event (3 SAH and 7 ICH), and 3 of the 7 patients with ICH had a second and even third hemorrhage in a mean 8.1 years of follow-up with a crude annual incidence rate of 5.3%. Eighteen patients had intracranial bleeding in the course of follow-up. Of the 32 hemorrhagic events, 6 (19%) were SAH and 26 (81%) were ICH. Of these, 11 (42%) involved the thalamus, 5 (19%) involved the superficial territory of the posterior cerebral artery (occipital and temporal lobes), 5 (19%) involved the brain stem or cerebellum, and 4 (15%) involved other sites (2 striatocapsular area, 1 frontal lobe, and 1 parietal lobe). Of the 4 recurrent hemorrhages, 3 occurred in the same site as the initial bleeding, ie, thalamus (n = 2) and pons (Table 1). All SAH were confined to one or more cisterns around the brain stem (interpeduncular, superior, preptontine, and ambient cisterns) suggesting a pattern of perimesencephalic SAH on initial CT scan. Conventional angiographic examination did not show saccular aneurysms of the posterior circulation in any of the 6 patients with SAH; 1 patient had a saccular aneurysm of the ACA and 1 had a bilateral saccular aneurysm of the ICA. None of the patients with SAH lost consciousness at onset and outcome was good in all but 1 who had extensive rebleed within 24 hours of onset and then died. In this patient, autopsy showed that intracranial bleeding was caused by the rupture of VBD.

Univariate analysis showed that patients with hemorrhagic stroke were more often women (P = 0.006), hypertensive (P = 0.002), and treated with antiplatelet or anticoagulant agents (P = 0.023), had a greater maximum diameter of the BA (P < 0.001), a higher lateral displacement score (P = 0.002), and higher height of BA score (0.044) than patients without intracranial bleeding. Diabetes (P = 0.045) and alcohol abuse (P = 0.049) were more frequently observed in patients without hemorrhagic stroke. Other factors, such as age, smoking, dyslipidemia, and presence of anterior circulation dolichoectasia, did not show any significant differences between the 2 groups of patients (Table 2).

Multivariate analysis found an association between intracranial hemorrhage and diameter of BA (OR, 4.29; 95% CI, 1.43 to 12.87), degree of lateral displacement of BA (OR,
4.53; 95% CI, 1.62 to 12.64), hypertension (OR, 4.74; 95% CI, 1.23 to 18.30), use of antiplatelet or anticoagulant agents (OR, 3.07; 95% CI, 1.10 to 8.57), and female sex (OR, 6.33; 95% CI, 2.11 to 19.06; Table 3). The same factors emerged when multivariate analysis was repeated, only taking ICH into account. A separate analysis for SAH was not performed because of the small number of patients. However, all these patients were hypertensive, all had severe dolichoectasia, and 4 were treated with antiplatelet or anticoagulant agents.

Considering only intracranial bleeding occurring during follow-up, survival analysis found a cumulative proportion of survivors free of hemorrhagic stroke of 88.6 (85.8 to 91.4) at 5 years and 84.4 (80.8 to 87.9) at 10 years (Figure 2). As shown in Figure 2, survival curves were significantly different between patients with diameter of BA ≥ 6.4 mm and those with diameter of BA < 6.4 mm (log-rank test statistic 8.75; P = 0.0031), with a cumulative proportion of survivors free of hemorrhagic stroke at 10 years of 73.7 and 95.2, respectively. Patients initially presenting with ischemia had a cumulative proportion of survivors free of hemorrhagic stroke of 83.2 at 10 years, which was not dissimilar from the cumulative proportion (85.3) of patients initially presenting with other symptoms (log-rank test statistic 0.01; P = 0.91).

One patient with SAH and 4 patients with ICH died of the first hemorrhagic event. Two patients died of a recurrent hemorrhage.

**Discussion**

This study showed that patients with VBD experienced intracranial hemorrhage with an unexpectedly high frequency. Considering only hemorrhagic strokes occurring during follow-up, we observed a crude incidence rate of 2.2 per 1000 person-years for SAH and 11.0 per 1000 person-years for ICH. These figures are somewhat higher than those reported in recent population-based studies, which ranged from 0.06 to 0.09 per 1000 person-years for SAH and from 0.24 to 0.48 per 1000 person-years for ICH, suggesting that patients with VBD are particularly susceptible to intra-

**TABLE 1. Intracranial Hemorrhages in 156 Patients with Vertebrobasilar Dolichoectasia**

<table>
<thead>
<tr>
<th>Location of Hemorrhage</th>
<th>No.</th>
<th>Rebleeding</th>
<th>Patients Initially Presenting With Ischemia (n=56)</th>
<th>Patients Initially Presenting With Others Symptoms (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAH</td>
<td>3</td>
<td>0</td>
<td>2 (4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>7</td>
<td>3</td>
<td>5 (9)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>4</td>
<td>2*</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lobar (PCA)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Brainstem and cerebellum</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other sites</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Values are No. (%). PCA indicates posterior cerebral artery.
*One patient had 2 recurrent hemorrhages.

**TABLE 2. Demographic and Clinical Characteristics in 156 Patients With VBD in Relation to the Occurrence of Hemorrhagic Stroke**

<table>
<thead>
<tr>
<th></th>
<th>No Hemorrhagic Stroke (n=128)</th>
<th>Hemorrhagic Stroke (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.9±11.9</td>
<td>59.0±10.1</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>25 (20)</td>
<td>13 (46)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (59)</td>
<td>25 (89)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>35 (27)</td>
<td>8 (29)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (14)</td>
<td>0</td>
<td>0.045</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>24 (19)</td>
<td>1 (4)</td>
<td>0.049</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>46 (36)</td>
<td>11 (39)</td>
<td>0.83</td>
</tr>
<tr>
<td>Use of antiplatelet/anticoagulant drugs</td>
<td>56 (44)</td>
<td>19 (68)</td>
<td>0.023</td>
</tr>
<tr>
<td>Maximum diameter of BA, mm</td>
<td>6.60±1.71</td>
<td>7.99±1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum diameter of BA ≥6.4 mm*</td>
<td>59 (46)</td>
<td>22 (79)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Height of BA (score ≥1)</td>
<td>110 (86)</td>
<td>28 (100)</td>
<td>0.044</td>
</tr>
<tr>
<td>Lateral displacement of BA (score ≥1)</td>
<td>29 (23)</td>
<td>15 (54)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ectasia of anterior circulation</td>
<td>56 (44)</td>
<td>15 (54)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Values are N (%) or mean±SD.
*Median.
The occurrence of hemorrhagic events was associated with the degree of ectasia and elongation of the BA. These parameters are an index of the severity of the defect of the vessel wall, which was not confined to the BA, but very often involved other large arteries of the posterior circulation and presumably also the small perforating vessels as suggested by the fact that most of the ICHs were located in arterial territories perfused by vessels branching from dolichoectatic parent vessels.

Other factors, such as arterial hypertension, use of antiplatelet or anticoagulant drugs, and female sex seem to be associated with intracranial bleeding. Chronic hypertension produces vasculopathy in perforating arteries of the brain and also in the superior and anterior inferior cerebellar arteries. The lenticulostriate arteries seems to be the most frequently affected because bleeding in this vascular territory occurred in more than half of all hypertensive hemorrhages.26 The fact that in our series only 2 ICHs out of 26 had this site may mean that the effect of hypertension manifest more strongly in previously damaged vascular beds, ie, the posterior circulation. Anticoagulation therapy at conventional doses increases the risk of intracranial bleeding27 and there is no lack of examples of patients with VBD who had intracranial bleeding during anticoagulation therapy for acute ischemic stroke28–29 or during chronic treatment.7,30 In our series, patients treated with anticoagulants were too few for separate statistical analysis of this risk factor. Less clear is the role of antiplatelet agents in promoting intracranial bleeding. However, the meta-analysis of He et al31 and some recent studies32 suggest that use of aspirin is associated with increased risk of hemorrhagic stroke. Unfortunately, patients with VBD are prone to ischemic stroke and coronary artery disease as well.12,33 At some stage or other of their illness, more than half of our patients experienced ischemic stroke and one-third had coronary artery disease. In patients with VBD, the risk of brain ischemia clearly is higher than that of intracranial bleeding. However, many mechanisms other than superimposed atherosclerosis contributed to the occurrence of brain ischemia,12 and this may explain why in patients initially presenting with ischemia, treatment with antiplatelet or anticoagulant agents is not as effective in preventing recurrent brain ischemia as one may expect. Forty-seven percent of our treated patients had 1 or more recurrent ischemic events. The risks and benefits of aspirin in subgroups at risk for both ischemic and hemorrhagic events, such as patients with VBD, would be worth studying. The present observational study demonstrated that treatment with antiplatelet or anticoagulant agents increased the likelihood of future intracranial bleeding in patients initially presenting with ischemia and in those initially presenting with other symptoms, and that the occurrence of intracranial bleeding was strongly associated with the severity of dolichoectasia, whereas the occurrence of brain ischemia was not associated with parameters indicating severity of dolichoectasia.12 These data suggest that caution is warranted in prescribing antiplatelet or anticoagulant agents for patients initially presenting with symptoms other than ischemia and, among patients presenting with ischemia, in those with severer forms of dolichoectasia without superimposed atherosclerosis.

TABLE 3. Factors Associated With the Occurrence of Intracranial Hemorrhage in 156 Patients With Vertebrobasilar Dolichoectasia

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>6.33 (2.11 to 19.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diameter of BA ≥6.4 mm</td>
<td>4.29 (1.43 to 12.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Lateral displacement of BA (score &gt;1)</td>
<td>4.53 (1.62 to 12.64)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.74 (1.23 to 18.30)</td>
<td>0.024</td>
</tr>
<tr>
<td>Use of antiplatelet/anticoagulant drugs</td>
<td>3.07 (1.10 to 8.57)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Logistic regression analysis.
The relation between intracranial hemorrhage and female sex was an unexpected finding. The higher incidence of ICH in men and SAH in women is well known. Although some recent studies did not find any difference between genders or found a higher incidence of ICH in women than men, our female/male crude incidence ratio (3.22) for ICH is too high. Our data do not allow us to explain why ICH was 3-times more frequent in female patients with VBD than in male patients. VBD is a condition that tends to worsen with time, but the progression of ectasia and elongation of the vessels is quite variable. In our experience, some patients showed progression in a few years, whereas in others the condition remained stable for many years. This divergence may be influenced by genetic factors, arterial hypertension, and perhaps hormonal status.

In conclusion, patients with VBD are at substantial risk for hemorrhagic stroke (both SAH and ICH). Its occurrence is associated with the degree of ectasia and elongation of the basilar artery and may be favored by hypertension and use of antiplatelet or anticoagulant agents.

Acknowledgments
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