Vertebrobasilar Stenosis Predicts High Early Recurrent Stroke Risk in Posterior Circulation Stroke and TIA

Giosué Gulli, MD; Sofia Khan, MRCP; Hugh S. Markus, FRCP

Background and Purpose—20% of ischemic stroke is in the posterior circulation, but there is little prospective data on early recurrent stroke risk and whether vertebrobasilar stenosis predicts a high recurrence risk. This natural history data are important as it is technically possible to stent such lesions. Contrast enhanced MRA (CE-MRA) and CT angiography (CTA) now allow noninvasive identification of vertebrobasilar stenosis.

Methods—216 consecutive patients presenting with posterior circulation TIA or stroke were recruited and prospectively followed for 90 days. 8 patients with vertebral dissection were excluded. CE-MRA or CTA at presentation and 90-day follow-up was available in 182. Any posterior circulation TIA/stroke in the month before the presenting episode was recorded.

Results—Taking the first event (including TIA/stroke in the previous month) as the index case recurrent stroke risk in patients with stenosis was 30.5% versus 8.9% in those without; RR 3.4 (95% CI 1.7 to 7.0), \( P < 0.001 \). Taking the presenting episode as the index case the risk was 13.8% versus 4.1%; RR 3.4 (95% CI 1.1 to 10.5) \( P = 0.0274 \). The probability of recurrence was highest soon after the initial event.

Conclusions—The presence of vertebro-basilar stenosis identifies a group of patients with posterior circulation stroke who have a high early recurrent stroke risk. Early intervention might reduce recurrent stroke risk. Vertebral stenosis can now be treated by stenting, but determining whether this reduces the early stroke risk requires randomized controlled trials. (Stroke. 2009;40:2732-2737.)

Key Words: stroke • TIA • posterior circulation • vertebrobasilar • prognosis

Minor stroke and TIA is associated with a high risk of early recurrent stroke.\(^1\)\(^-\)\(^3\) Previously underestimated, this is now appreciated to be as high as 10% to 12% in the first week. The risk is particularly high in patients with carotid artery stenosis.\(^4\) Large trials have shown that early carotid endarterectomy reduces recurrent stroke risk.\(^5\) The benefit is much greater if patients are operated on within the first 2 weeks after their initial event.\(^6\)

Vertebrobasilar (VB) or posterior circulation territory stroke accounts for 20% of all strokes.\(^7\) However, investigation and treatment of VB stroke has lagged behind that of carotid artery disease. There are a number of reasons for this. First, conventionally it was thought that the risk of recurrent stroke was lower for posterior compared with anterior circulation stroke. However, a meta-analysis has suggested that the risk is as high for posterior circulation stroke.\(^8\) Second, until recently it has been more difficult to noninvasively identify posterior circulation stenosis. Carotid stenosis is easily identified using Duplex ultrasound. However, this technique only allows visualization of a portion of the vertebral artery. Noncontrast magnetic resonance angiography (MRA) is poor at identifying stenosis at the vertebral origin, which is the most common site. Recently both contrast enhanced MRA (CE-MRA) and contrast CT angiography (CTA) have been developed, and these offer good visualization of the whole VB tree. Both CE-MRA and CTA appear to have high sensitivity for identification of posterior circulation stenosis.\(^9\)

Third, until recently identifying posterior circulation stenosis has not altered management, as there has been no specific treatment. Surgical endarterectomy or bypass has not been widely practiced because of difficulties in accessing the VB arteries. In contrast, recently stenting has been shown to be feasible, and promising results have been obtained from uncontrolled series.\(^10\)\(^-\)\(^12\)

An important question is: what is the recurrent stroke risk associated with posterior circulation stroke and TIA and does the presence of stenosis predict an increased risk? There is little data from prospective follow-up studies in which modern imaging techniques have been used to identify stenosis and then patients have been prospectively followed up. If acute intervention of stenting is planned for VB stenosis, it is important to demonstrate that it has a similarly early stroke risk to that seen in carotid artery stenosis.

To answer this question we performed CE-MRA or CTA in a consecutive series of patients presenting with posterior circulation stroke and TIA. We prospectively collected data
on early stroke recurrence and determined the association between VB stenosis and recurrence rates.

Methods

Study Population

Consecutive patients presenting with posterior circulation ischemic stroke or TIA to our stroke service (both in patient acute stroke unit and outpatient TIA clinics) were prospectively recruited. All cases are reviewed with original imaging by a single consultant neuroradiologist. In addition we recorded any history of TIA or minor stroke in the 30 days before hospital admission. For this study data were analyzed from November 2004 when our policy for investigating posterior circulation stroke changed to include routine CE-MRA or CTA imaging of the VB circulation. Data collection was approved by the local ethics committee. Cases in whom symptoms lasted less than 24 hours, but in whom there was an acute infarct on diffusion weighted imaging (DWI), were classified as stroke. A diagnosis of posterior circulation event was made by the neuroradiologist on the basis of clinical and structural brain imaging findings. The results of vascular imaging were not used for this categorization.

Hypertension was defined as persistent elevation of systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at least 1 week from stroke onset, or current treatment with antihypertensive drugs. Diabetes mellitus was defined as a previous diagnosis of type I or type II diabetes, or 2 random glucose readings of >11.1 mmol/L or fasting blood glucose >7.0 mmol/L. Hypercholesterolemia was defined as serum total cholesterol >5.2 mmol/L or current treatment with lipid lowering therapy. Smoking history was recorded.

Neuroradiology Evaluation

All patients had head computerized tomography (CT), and in 180 structural brain MRI, including DWI, was also performed. 194 patients had VB circulation imaging with either CE-MRA or CTA. CE-MRA in 163, CTA alone in 31. Our standard imaging modality was CE-MRA. CTA was used when MRA was contraindicated or unavailable. If CE-MRA was performed CTA was only then performed if there was remaining uncertainty about the presence or degree of stenosis. 39 subjects had both CE-MRA and CTA. In addition, where intracranial views were suboptimal, time of flight (TOF)-MRA was also performed (in 33). In 22 patients imaging was not performed because of: contraindications to contrast injection in 5 (straints), 22 patients imaging was not performed because of: contraindications to contrast injection in 5 patients, patient too ill/died in 12, lack of consent in 5.

All CE-MRA and CTA were performed on the same equipment using the same protocols. CE-MRA was performed on a Philips 1.5 T Excite, using an extremity belly coil and a head all body coil. Intravenous contrast medium (20 mL gadodiamide (“Omniscan,” GE) with a 25 mL saline chaser) was infused via a pump injector at 2.5 mL/s. The great vessels were imaged from the aortic arch to the circle of Willis (T1FFE sequence, FoV 320, coronal orientation, slice thickness 0.6 mm, slice number, and sequence parameters patient dependent). Maximum intensity projections (MIPs) are produced on the scanner console. Source data and MIPs are reviewed on the picture archiving and communication system (PACS). CTA was performed on a General Electric (GE) 16-slice multidetector scanner. Intravenous contrast medium (100 mL iohexol (“Omnipaque 300,” GE)) was infused via a pump injector at 4 mL/s. A bolus tracking technique (“Smart Prep”) is used to monitor contrast delivery with a region of interest placed over the aortic arch and imaging triggered manually when contrast enters the aorta. The great vessels were imaged from the aortic arch to the vertebra using 06.25 mm axial slices. Images are reviewed on an Advantage Windows (GE) workstation using reformat and MIPs in multiple planes and 3D surface rendered techniques.

All angiographic images were reviewed by a consultant neuroradiologist to determine the presence of 50% to 99% stenosis using a method similar to the NASCET method of measuring carotid stenosis and to the WASID method of measuring intracranial VB stenosis.13 Comparison was made of the diameter of the vessel at the site of stenosis (D stenosis) with the normal vessel diameter just distal to the stenosis (D distal) using the following formula: % stenosis=(1−D stenosis/D distal)×100%. Localization of the stenosis in the vertebral arteries was defined according to the anatomic division: V1 (extracranial foramen magnum), V2 (extracranial foraminar artery), and V3 (extracranial postforaminar artery). The V4 section forms the intracranial vertebral artery. Occluded or absent vessels were also reported.

Follow-Up

Patients were prospectively followed up for 3 months to identify recurrent TIA or stroke. If a recurrent event was suspected, patients underwent brain CT or MRI. All patients were formally reviewed at 3 months by a consultant neurologist/stroke physician. Patients who did not attend the follow-up appointment were contacted by phone. All patients were treated with a standard regimen of aspirin 75 mg in combination with dipiridamole slow release 200 mg bid. In patients with contraindications clopidogrel 75 mg od was used, and in a few patients with recurrent events a combination of aspirin and clopidogrel was used. One patient with vertebral stenosis received stenting.

End Points and Data Analysis

Our predefined primary end point was any clinical stroke in the VB territory. Secondary end points were TIA or stroke in the VB distribution and stroke in any arterial territory. We determined the relationship between stenosis and recurrent events with reference to both the first TIA or stroke and the presenting stroke/TIA. The first event was defined as any first stroke or first TIA in the VB distribution which occurred at the time of hospitalization or within the prior 4 weeks before hospitalization. A presenting event was defined as the stroke/TIA that resulted in hospitalization. First event and presenting event coincided when the first ever event led to hospitalization.

Because of differing pathophysiology, cases of vertebral dissection were not included in the analysis although prospective outcome data were collected in a similar manner.

Statistical analysis was performed using the software package SPSS (SPSS Inc). Values were expressed in real numbers (%) or mean values ±SD.

Cumulative event-free rates for the time to a recurrent cerebrovascular event were estimated by Kaplan–Meier survival analysis with patients stratified for the presence or absence of VB stenosis. Risk ratios with 95% CI were calculated by χ2 analysis. Cox-regression analysis was then performed to determine whether any associations were independent of risk factors. The following risk factors were entered as covariates: age, gender, diabetes, hypercholesterolemia, hypertension, current smoking. Hazard ratios with 95% CI were determined.

Results

216 patients were recruited between November 2004 and May 2008. Demographic characteristics are summarized in Table 1. The presenting event was stroke in 191 (88.4%) and TIA in 25 (11.6%). Nineteen patients had a cerebrovascular event (14 TIA and 5 strokes) in the 30 days before the presenting event. In these patients symptoms were: visual symptoms (diplopia or visual field defect) in 7/19, focal weakness or focal sensory disturbance in 7/19, unsteadiness/ataxia in 7/19, vertigo in 3/19, and nausea in 2/19 patients. Patients often had more than 1 symptom.

Imaging Results

Imaging of the VB circulation with CE-MRA, or CTA was obtained in 194 patients. In 8 radiographic appearances consistent with vertebral dissection were diagnosed. In the
remaining 186 patients VB stenosis was detected in 36 (19.4%). The distribution of stenoses is shown in Table 2. A typical vertebral stenosis is shown in Figure 1. The most common sites were the V1 (21/36) and V4 (17/36) sections of the vertebral artery. Of the 21 V1 segment stenoses, 12 were at the vertebral origin. Of the 17 V4 stenoses, 7 were at the vertebro-basilar junction. Multiple stenoses were present in 18 patients. Absence of the vertebral artery attributable to presumed occlusion or atresia was present in 12/186 (6.5%) patients. 24 patients also had a >50% stenosis of the internal carotid artery, in 9 of whom there was both a VB and carotid stenosis. 39 patients had both CE-MRA and CTA; in 25 CTA confirmed the MRA result (10 stenoses and 15 non stenoses), and in 10 cases CTA clarified a nondiagnostic CE-MRA (2 stenosis and 8 non stenoses). In 4 cases the presence and degree of stenosis remained uncertain after both CE-MRA and CTA and intraarterial digital subtraction angiography was performed (1 stenosis and 3 nonstenosis).

### Recurrent Events

The 8 cases of dissection were excluded from analysis. Of the 208 patients without dissection, prospective follow-up, until 90 days or death, was available in 203 (97.6%). Death within the first 90 days occurred in 23 (11.3%). Five (2.4%) were lost to follow-up; 2 were overseas patients, and 3 had moved out of area and were uncontactable. Therefore there were 182 patients with imaging at presentation and follow-up. Analysis was performed in those 182 subjects with imaging of the VB circulation and follow-up. Taking the first event as the index case, the presence of VB stenosis was 33.3% compared to 10.9% in those without stenosis; Kaplan–Meier analysis RR 3.4 (95% CI 1.7 to 7.0), P<0.001. The risk of any VB recurrence (including both stroke and TIA) at 90 days for patients with stenosis was 33.3% compared to 10.9% in those without stenosis; Kaplan–Meier analysis RR 3.0 (95% CI 1.3 to 7.2), P=0.001. Taking the presenting episode as the index case the risk of recurrent stroke at 90 days for patients with stenosis was 13.8% (5/36) compared to 4.1% (6/146) in those without stenosis; Kaplan–Meier analysis RR 3.4 (95% CI 1.1 to 10.9, P=0.0274. The risk of any VB recurrence (including TIAs) at 90 days for patients with stenosis was 16.6% compared to 6.1% in those without stenosis; Kaplan–Meier analysis RR 2.7 (95% CI 1.1 to 11.1) P=0.0401.

Kaplan–Meier survival curves for risk of recurrent stroke alone are shown in Figure 2A and 2B. They demonstrate that the probability of recurrence is higher soon after the initial event, and most recurrences occurred within the first 20 to 30 days. Cox proportional hazard regression analysis was performed to determine whether these relationships were independent of major risk factors. Results are reported in Table 3. This analysis was performed for stroke alone. Considering the first event as the index case, the presence of VB stenosis...
was an independent risk factor for recurrent strokes (OR 3.4 [95% CI 1.5 to 8.0], \( P = 0.002 \)).

Considering the presenting event as the index case, VB stenosis tended to confer higher recurrent stroke risk but this did not reach statistical significance (OR 3.3 [95% CI 1.0 to 11.1], \( P = 0.064 \)).

**Recurrent Stroke in Any Vascular Territory**

Taking the first event as the index case, the risk of recurrent stroke in any vascular territory (including strokes in the carotid distribution), at 90 days for patients with VB stenosis was 33.3% compared to 9.5% in those without stenosis; \( \chi^2 \) analysis RR 3.5 (95% CI 1.6 to 6.4, \( P < 0.001 \)).

Taking the presenting event as the index case the risk of stroke in any distribution for patients with VB stenosis was 16.6% compared to 4.8% in patients without stenosis; \( \chi^2 \) analysis RR 3.5 (95% CI 1.3 to 10.7, \( P = 0.013 \)).

**Discussion**

This prospective study demonstrates that, in patients presenting with posterior circulation TIA and stroke, the presence of VB stenosis is associated with a greatly increased risk of recurrent stroke. It identifies a group of patients who have a risk as high as 33% in the first month after their initial event.
Table 3. Results of Cox Regression for Looking for Independent Predictors of Recurrent Vertebrobasilar (VB) Stroke Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Cox Regression Hazard Function Analysis of Risk Factors Recurrence From First Event</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VB stenosis</td>
<td>3.9</td>
<td>1.7 to 9.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.9</td>
<td>0.8 to 4.3</td>
<td>0.152</td>
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<tr>
<td>Hyperchol</td>
<td>1.5</td>
<td>0.6 to 3.6</td>
<td>0.388</td>
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<tr>
<td>Hypertension</td>
<td>0.9</td>
<td>0.3 to 2.8</td>
<td>0.847</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.8</td>
<td>0.3 to 1.9</td>
<td>0.836</td>
</tr>
<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0 to 1.0</td>
<td>0.908</td>
</tr>
<tr>
<td><strong>B. Cox Regression Hazard Function Analysis of Risk Factors Recurrence From Presenting Event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VB stenosis</td>
<td>3.2</td>
<td>0.9 to 11.4</td>
<td>0.064</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9</td>
<td>0.2 to 3.7</td>
<td>0.889</td>
</tr>
<tr>
<td>Hyperchol</td>
<td>0.6</td>
<td>0.2 to 2.1</td>
<td>0.451</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.3</td>
<td>0.2 to 7.0</td>
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<tr>
<td>Smoking</td>
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<td>0.4 to 5.0</td>
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<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0 to 1.1</td>
<td>0.522</td>
</tr>
</tbody>
</table>

Traditionally, posterior circulation stroke and TIA have been thought to have a lower recurrent stroke risk than other types of stroke. In contrast, this series demonstrates that it is associated with a high early stroke risk and is consistent with a meta-analysis suggesting the risk is as high as that seen in anterior circulation stroke.

There is little previous data on predictors of increased stroke risk in posterior circulation stroke, and particularly on whether the presence of stenosis is associated with a high early recurrence. Accurate noninvasive imaging of the posterior circulation has only recently become available, and there is little data from prospective series using these techniques. A subgroup analysis of 68 patients in the WASID study showed that patients with symptomatic intracranial VB stenosis were at high risk of recurrent stroke; 22% during a median follow-up of 13.8 months. However, in this study, only the intracranial portion of the VB arteries were considered, and prospective risk of recurrence was not compared in those patients with stroke in the VB distribution without VB stenosis.

Our data demonstrate that the presence of stenosis is a strong independent predictor of future stroke risk. Kaplan–Meier survival curves demonstrate that is largely accounted for by a markedly increased risk seen within the first 2 weeks. This is consistent with recent data demonstrating a much higher than previously appreciated early risk of recurrent stroke after all minor stroke and TIA.

Our results have a number of important implications. First, because posterior circulation stroke and TIA is associated with a high early recurrent stroke risk, rapid assessment and preventative treatment is important. Secondly, the particularly high risk associated with VB stenosis suggests that treatment of the stenosis may be of potential benefit. Vertebral angioplasty and stenting offers a potential treatment. Case series suggest that this can be performed with a high technical success rate and low complication rate. Only 1 randomized trial of angioplasty and stenting for vertebral artery disease was started. However, only 16 patients were randomized between vertebral angioplasty or stenting and best medical treatment. Therefore, there is no robust data from randomized trials providing information on the safety and efficacy of this therapy. Although a few hundred patients have been reported in case series using this technique, these reports are subject to considerable bias from case selection and publication bias. Our data, demonstrating the high risk of early stroke associated with stenosis, emphasize the need for randomized trials to assess vertebral stenting against best medical therapy. The feasibility phase of 2 such trials is just commencing (Vertebral Ischemia Stenting Trial [VIST], see www.controlled-trials.com/ISRCTN95212240; VIST; and Vertebral Artery Stenting Trial [VAST], see www.controlled-trials.com/ISRCTN29597900).

The fact that much of the recurrent stroke risk occurs within the first few days presents significant challenges for such treatment approaches. First, patients will need to be identified and assessed rapidly after both TIA and stroke. The higher recurrence rate after first event compared with presenting event is consistent with recent data showing delays from TIA and minor stroke to assessment. Second, routine investigation to exclude stenosis will be necessary in all patients presenting with posterior circulation TIA who are fit enough for intervention. Ultrasound cannot visualize the whole vertebral artery and has only modest sensitivity in detecting stenosis. Although studies comparing the sensitivity and specificity of different imaging modalities are few, a recent meta-analysis suggested CTA and CE-MRA have a high sensitivity for detection of VB stenosis and are more sensitive than ultrasound. Third, stenting would need to be carried out as an urgent procedure soon after the initial event.

In our analysis we excluded patients with dissection. This is because the pathophysiology of atherosclerotic stenosis differs from that seen in dissections. Only 1 recurrence occurred in 8 individuals, and adding these few patients did not significantly alter the results.

Our study was in a consecutive group of patients all seen in the same unit with prospective data collection and follow-up and standard imaging protocols. However, it is a hospital-based rather than community-based series. Therefore, the absolute risks of recurrent stroke may differ slightly from that seen in a community population. Nevertheless, the risks we described represent those associated with patients presenting to a typical stroke service in whom treatment decisions need to be made. Furthermore, the risk of recurrent stroke associated with stenosis is likely to be an accurate estimate.

There are limited data directly comparing CE-MRA and CTA with the current gold standard, intraarterial angiography, in estimating vertebral stenosis. However, a meta-analysis of available data suggests both appear to have high sensitivity for identification of posterior circulation stenosis. Our primary imaging modality was CE-MRA, but in cases where this did not reveal definitive results we also performed CTA, and in 4 cases where both gave equivocal results intra-arterial angiography was necessary. We graded stenosis into ≥50 or <50%. We did not subdivide the degree of
stenosis further because the numbers of recurrent events in each category become small if we did this. Larger studies will be required to determine the relationship between degree of stenosis and recurrent events. In clinical practice it can be difficult knowing whether small infarcts in the brain stem are attributable to embolism from VB stenosis or are attributable to small vessel disease. For this reason, and to avoid introducing any bias attributable to preconceptions about the relationship of any particular infarct to stenosis, we included all posterior circulation strokes, regardless of infarct size, in the analysis. Of relevance to this it is interesting that the carotid endarterectomy trials showed a benefit whether patients had a presumed lacunar stroke or cortical stroke.

In conclusion we have shown that VB stenosis identifies a subgroup of patients with posterior circulation stroke and TIA who have a high early recurrent stroke risk. This may be an appropriate group for interventional approaches and trials of stenting in this area are required.

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Disclosures
None.

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