Comparison of Spontaneous Intracranial Vertebral Artery Dissection With Large Artery Disease

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Objective: To compare clinical and angiographic characteristics and stroke patterns between spontaneous intracranial vertebral artery dissection (VAD) and vertebral large artery disease (LAD) (atherosclerosis).

Design: Retrospective study.

Setting: Tertiary referral center for cerebrovascular diseases.

Patients: Twenty-two patients with spontaneous VAD and 25 with LAD in the intracranial portion of the vertebral artery.

Main Outcome Measures: We compared (1) clinical characteristics, including epidemiologic data, vascular risk factors including inflammatory markers, the presence of headache, and stroke syndromes and severity; (2) stroke pattern on diffusion-weighted imaging, which was classified as vertebral perforator infarct, basilar perforator infarct, small scattered infarct, large scattered infarct, and territorial infarct; and (3) angiographic findings, ie, the distribution of involved arteries, degree of stenosis, and the involvement on the anterior circulation and calcification of vertebral artery.

Results: Although patients with VAD were younger, and more often had headaches and fewer vascular risk factors than those with LAD (P<.01 in all cases), these clinical features were also observed in some LAD patients. Diffusion-weighted imaging data showed that vertebral perforator infarct and small scattered infarct were most common in the VAD group, while territorial infarct and large scattered infarct were most common in the LAD group (P=.02). On angiography, LAD more frequently had anterior circulation arterial involvement (P=.002), higher degree of stenosis (P=.002), and calcifications (P=.008).

Conclusion: Our findings indicate that results of diffusion-weighted imaging and noninvasive vascular studies might provide clues to the clinical characteristics in differential diagnosis between VAD and LAD.

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VESTERBRAE ARTERY DISSEC-
TION (VAD) is an impor-
tant cause of vertebrobasi-
lar territory infarct in
young and middle-aged
adults. Vertebral artery dissection is pos-
tulated to cause cerebral infarct by involv-
ing the subintimal region between the in-
ternal elastica and the media, which
narrow the arterial lumen.3 Thromboem-
bolism may cause infarcts in the distal
brain parenchyma.2,3

There are fewer reported cases of in-
tracranial VAD compared with extracra-
nial dissection.3-7 Extracranial dissection
may be caused by an adjacent bony struc-
ture and the mobility of the neck.2,3 By con-
trast, intracranial dissection may develop
spontaneously, rather than being related
to trauma.9 With recent development of
angiographic techniques, the reported
cases of ischemic stroke attributable to in-
tracranial VAD have increased,3-7 but their
characteristics are poorly understood and
radiological differentiation with large ar-
ttery disease (LAD) (atherosclerosis) is still
difficult. On the other hand, though digi-
tal subtraction angiography has been the
standard for identifying cervicocephalic ar-
terial dissections,3,9 it is an invasive pro-
cedure with possible complications. There-
fore, alternative noninvasive tools must be
sought and might play an important role.

Diffusion-weighted imaging (DWI) and
transcranial Doppler studies in patients
with carotid artery dissection have shown
that most infarcts have a thromboem-
bolic origin.10-12 This can also be true for
intracranial VAD, considering that mul-
tiple cerebellar infarcts may result from ex-
tracranial VAD. However, before now there was no study that analyzed how multiple cerebellar and lateral medullary infarcts accounted for cerebral infarcts from VAD.

We aimed to differentiate spontaneous intracranial VAD from LAD and to investigate the possible mechanisms of ischemic stroke in VAD. Thus, we compared clinical characteristics; vascular risk factors, including inflammatory markers; radiological findings; and DWI patterns between patients with spontaneous intracranial VAD and patients with atherosclerosis of the intracranial vertebral artery.

METHODS

PATIENT GROUP

We retrospectively studied the patients with posterior circulation infarcts in the Departments of Neurology and Neurosurgery at Ajou University Hospital (Suwon, South Korea).

From October 2001 to May 2005, 50 consecutive patients were diagnosed as having VAD. Among the 50 patients with VAD, 22 patients were included in this study. Inclusion criteria for VAD consisted of (1) definite angiographic findings of dissection in the intracranial segment of the vertebral artery, (2) acute infarcts within the vertebralbasilar circulation territory on DWI, and (3) no evidence of atherosclerotic vascular changes at the extracranial portion of the vertebral artery on angiography. Exclusion criteria were (1) extracranial VAD, (2) isolated basilar artery dissection, (3) evident history of head or neck trauma, or sudden neck movement, (4) negative findings on DWI, and (5) hemorrhagic presentation associated with a ruptured VAD. All 3 types of angiography were obtained in 10 patients; both computed tomographic angiography and digital subtraction angiography in 6 patients; computed tomographic angiography and magnetic resonance angiography in 2 patients; digital subtraction angiography in 2 patients; magnetic resonance angiography in 2 patients. In patients in whom digital subtraction angiography was not performed (n=4), 3-dimensional maximum intensity projection images from computed tomographic angiography by multidetector computed tomography, or the source and 3-dimensional time-of-flight magnetic resonance angiography images were evaluated, which showed definitive findings of dissection, including intimal flap and double lumen with good quality. The initial angiography was performed within 72 hours of the onset of neurologic symptoms.

For comparison, 25 patients with LAD were included. Inclusion criteria for LAD consisted of (1) arterial stenosis of more than 50%, consistent with atherosclerosis on angiography; (2) acute infarcts in the relevant territory of posterior circulation on DWI; (3) no evidence of dissection, vasculitis, or other vascular disease on angiography; (4) absence of high- and medium-risk cardioembolic sources on electrocardiogram and echocardiogram, which were defined by Trial of Org 10172 in Acute Stroke Treatment criteria; and (5) proximal stenotic point located in the intracranial vertebral artery. The degree of stenosis was calculated by the ratio of the residual luminal diameter measured at the site of maximal narrowing to the diameter of the adjacent normal vessel. Large artery disease was documented through the angiographic tools, including computed tomographic angiography, digital subtraction angiography, and magnetic resonance angiography. Computed tomographic angiography was obtained in 18 patients; both computed tomographic angiography and digital subtraction angiography in 2 patients; digital subtraction angiography and magnetic resonance angiography in 2 patients; and computed tomographic angiography and magnetic resonance angiography in 3 patients.

PATIENT DATA

We reviewed medical histories, neurologic examination results, and laboratory test results. Vascular risk factors were identified as follows: (1) hypertension: use of antihypertensive agents, systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 95 mm Hg or higher on admission; (2) diabetes mellitus: use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin greater than 6.4%; (3) cardiac problems: any history of coronary heart disease, valvular heart disease, or dysrhythmia; (4) hypercholesterolemia: use of antihyperlipidemic agents or serum cholesterol level higher than 220 mg/dL (3.69 mmol/L); (5) smoking: any cigarette usage within the 28 days preceding the index stroke; and (6) stroke history: history of more than 1 stroke.

Stroke syndromes were divided into 4 groups: lacunar syndrome, cerebellar syndrome, lateral medullary syndrome, and other neurologic signs. Presence of headache was defined as the patient having experienced headache or nuchal pain within 1 week of onset of neurologic symptoms. Neurologic status was evaluated by the National Institute of Health Stroke Scale. Early course was defined by changes in the National Institute of Health Stroke Scale during the first 7 days as follows: (1) improved course: decrease of 2 or more points; (2) stable course: decrease of less than 2 points; and (3) worsened course: increase of 1 or more points. To evaluate the levels of highly sensitive C-reactive protein and fibrinogen, peripheral blood samples were drawn from each patient at the time of admission.

DEFINITION OF DWI PATTERNS

Cerebral infarct patterns were identified based on the DWI findings (Figure 1). The subtypes were classified as follows: (1) vertebral perforator infarct: a small perforating arterial infarct in the medulla, including lateral medullary infarct and medial medullary infarct; (2) basilar perforator infarct: a small perforating arterial infarct in the pons, including paramedian pontine infarct; (3) small scattered infarct: multiple small (largest diameter <1 cm), scattered dot-shaped infarcts; (4) large scattered infarct: multiple large infarcts (largest diameter ≥1 cm); and (5) territorial infarct: huge infarcts involving full territory of the vertebral artery, basilar artery, posterior inferior cerebellar artery, anterior inferior cerebellar artery, superior cerebellar artery, or posterior cerebral artery.

ANGIOGRAPHIC DATA

Distribution of vertebrobasilar arterial involvement was classified as follows: (1) ipsilateral vertebral artery: isolated involvement of relevant vertebral artery; (2) ipsilateral vertebral artery + basilar artery: extended involvement of basilar artery from the relevant vertebral artery; (3) bilateral vertebral artery: concomitant abnormal finding of contralateral vertebral artery in addition to relevant vertebral artery; and (4) bilateral vertebral artery + basilar artery: extended involvement of the basilar artery from the bilateral vertebral artery. When the arterial lesion was longer than 2 cm, it was designated as the long segment involvement. To investigate systemic involvement, we also checked the presence of anterior circulation arterial involvement, which included internal carotid, middle cerebral, and anterior cerebral arteries.

The presence of calcification was evaluated only by computed tomographic angiography because of its superiority to other images in detecting calcification.
Figure 1. Schematic drawings of brain parenchymal lesions on diffusion-weighted imaging. A, Vertebral artery dissection (VAD) group. B, Large artery disease (LAD) group. BPI indicates basilar perforator infarct; F, female; LSI, large scattered infarct; M, male; Pt, patient; SSI, small scattered infarct; TI, territorial infarct; VPI, vertebral perforator infarct. Numbers indicate age of patient in years.
Clinical characteristics of patients with VAD and LAD are summarized in Table 1. Male sex was significantly more frequent in the VAD group compared with the LAD group ($P = .03$). The patients with VAD were significantly younger than those with LAD ($P < .001$); there were 19 patients (86.4%) in the VAD group and 6 patients (20.4%) in the LAD group younger than 55 years. As for vascular risk factors, hypertension and diabetes mellitus were less frequent in patients with VAD than in patients with LAD (31.8% vs 64.0%; $P = .04$; and 13.6% vs 44.0%; $P = .03$, respectively). However, the percentage of patients with 1 or more risk factors was not significantly different between the groups ($P > .05$).

There were 17 patients (77.3%) with occipital headache or posterior neck pain in the VAD group, whereas only 2 patients (8.0%) had such symptoms in the LAD group ($P < .001$). According to neurologic signs on admission, lateral medullary syndrome was more frequently present in the VAD group than in the LAD group (36.4% vs 4.0%; $P = .007$). Initial National Institute of Health Stroke Scale score, early course, and preceding transient ischemic attack history were not significantly different. The serum levels of C-reactive protein and fibrinogen tended to be lower in the VAD group, but they were statistically insignificant ($P = .82$ and $P = .19$, respectively; $t$ test).

Cerebral infarct patterns were identified based on the DWI findings. As shown in Figure 2, vertebrobasilar infarct (45%) and small scattered infarct (36%) were more common in the VAD group, whereas territorial infarct (28%) and large scattered infarct (20%) were more common in the LAD group ($P = .02$ on $x^2$ analysis). Patients with the DWI pattern of vertebrobasilar infarct had lateral medullary syndrome and showed infarcts on the lateral medulla. In VAD patients with the vertebrobasilar infarct pattern, digital subtraction angiography showed that posterior inferior cerebellar artery was intact in 4 of 6 patients. In terms of the infarct size, infarcts greater than 1 cm were more frequently observed in the LAD group (12 of 25 patients) than in the VAD group (2 of 22 patients) ($P = .004$).

Figure 2. Distribution of stroke pattern. Vertebral perforator infarct (VPI) and small scattered infarct (SSI) were common in the vertebrobasilar lesion (VAD) group compared with territorial infarct (TI) and large scattered infarct (LSI) in the large artery disease (LAD) group ($P = .02$ on $x^2$ analysis). BPI indicates basilar perforator infarct.

Table 1. Characteristics of Patients in the VAD* and LAD† Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VAD, No. (%)</th>
<th>LAD, No. (%)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>19 (86.4)</td>
<td>14 (56.0)</td>
<td>.029†</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>46.91 ± 8.55</td>
<td>64.76 ± 11.36</td>
<td>&lt;.001§</td>
</tr>
<tr>
<td>Vascular risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (31.8)</td>
<td>16 (64.0)</td>
<td>.041‡</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (13.6)</td>
<td>11 (44.0)</td>
<td>.029‡</td>
</tr>
<tr>
<td>Cardiac problem</td>
<td>3 (13.6)</td>
<td>10 (40.0)</td>
<td>.06‡</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>5 (22.7)</td>
<td>11 (44.0)</td>
<td>.22‡</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (63.6)</td>
<td>9 (36.0)</td>
<td>.06‡</td>
</tr>
<tr>
<td>Stroke history</td>
<td>0 (0)</td>
<td>4 (16.0)</td>
<td>.11†</td>
</tr>
<tr>
<td>Presence of</td>
<td>17 (77.3)</td>
<td>24 (96.0)</td>
<td>.09‡</td>
</tr>
<tr>
<td>≥1 risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17 (77.3)</td>
<td>2 (8.0)</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>Stroke syndrome</td>
<td></td>
<td></td>
<td>.007‡</td>
</tr>
<tr>
<td>Lateral medullary syndrome</td>
<td>8 (36.4)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>8 (36.4)</td>
<td>11 (44.0)</td>
<td></td>
</tr>
<tr>
<td>Other neurologic signs</td>
<td>3 (13.6)</td>
<td>12 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Lacunar syndrome</td>
<td>3 (13.6)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Initial NIHSS score</td>
<td>2.05 ± 3.00</td>
<td>3.64 ± 6.35</td>
<td>.29§</td>
</tr>
<tr>
<td>Early course</td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>Improved</td>
<td>5 (22.7)</td>
<td>3 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>14 (63.6)</td>
<td>18 (72.0)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>3 (13.6)</td>
<td>4 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Inflammation markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.43 ± 0.60</td>
<td>0.48 ± 0.84</td>
<td>.82§</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL (mean ± SD)</td>
<td>355.24 ± 107.72</td>
<td>396.32 ± 101.45</td>
<td>.19§</td>
</tr>
</tbody>
</table>

Abbreviations: LAD, large artery disease; NIHSS, National Institute of Health Stroke Scale; VAD, vertebrobasilar artery dissection.*n = 22. †n = 25. ‡Fisher exact test. §§Test.
ings. Calcifications in the computed tomographic angiography were observed less frequently in the VAD group than in the LAD group (5.6% vs 41.7%; \( P = .008 \)).

**Figure 3** shows an LAD case with calcification (Figure 3A, patient 3 in LAD group) and a VAD case with intimal flap (Figure 3B, patient 15 in VAD group) on computed tomographic angiography.

### Table 2. Angiographic Findings in the VAD* and LAD† Groups

<table>
<thead>
<tr>
<th>Finding</th>
<th>VAD, No. (%)</th>
<th>LAD, No. (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution of involved arteries</td>
<td></td>
<td></td>
<td>.58‡</td>
</tr>
<tr>
<td>Ipsilateral VA</td>
<td>11 (50.0)</td>
<td>9 (36.0)</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral VA + BA</td>
<td>4 (18.1)</td>
<td>7 (28.0)</td>
<td></td>
</tr>
<tr>
<td>Bilateral VA</td>
<td>4 (18.1)</td>
<td>3 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Bilateral VA + BA</td>
<td>3 (13.8)</td>
<td>6 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Long segment of arterial lesion ( (&gt;2 \text{ cm}) )</td>
<td>12 (54.5)</td>
<td>16 (64.0)</td>
<td>.56§</td>
</tr>
<tr>
<td>Involvement on anterior circulation</td>
<td>0</td>
<td>9 (36)</td>
<td>.002§</td>
</tr>
<tr>
<td>Calcification</td>
<td>1 (5.6)</td>
<td>10 (41.7)††</td>
<td>.008§</td>
</tr>
</tbody>
</table>

Abbreviations: BA, basilar artery; LAD, large artery disease; VA, vertebral artery; VAD, vertebral artery dissection.

*\( n = 22 \).  †\( n = 25 \).
‡\( \chi^2 \) Analysis.
§Fisher exact test.
†\( n = 18 \).
††\( n = 24 \).

Although spontaneous intracranial VAD is difficult to differentiate from LAD, no comparative study has assessed the vascular risk factors, DWI pattern, and vascular status of patients with VAD and LAD. Because VAD may occur in older patients with vascular risk factors, and performing an invasive study in patients with advance atherosclerosis runs the risk of adverse effects including stroke, documentation of the differences between VAD and LAD is of clinical importance. We compared the clinical and DWI characteristics of VAD with those of LAD. This study is distinguishable from other studies in that only patients who had both spontaneous intracranial VAD and acute stroke documented on DWI were included.

### CLINICAL FEATURES

Our patients with VAD were younger and had fewer stroke risk factors and more occipital headaches or nuchal pain than patients with LAD. However, although there were fewer patients with 1 or more conventional risk factors in the VAD group than in the LAD group, about 80% of the patients in the VAD group had at least 1 risk factor. Therefore, it may be difficult to exclude VAD clinically in patients with stroke risk factors. In addition, occipital headache or nuchal pain is typical in patients with VAD and is important in the diagnosis of VAD; some authors include this point as an essential element for definite VAD.\(^*\) However, some patients in the LAD group, as well as most patients in the VAD group, had these symptoms. It was reported that 41% of patients with atherothrombotic infarcts had headaches.\(^†\)

### DWI LESION PATTERNS

The pattern of lesions on DWI is associated with the pathogenic mechanism of stroke. Most infarcts attributable to carotid artery dissection have a thromboembolic origin.\(^*\) Transcranial Doppler sonography also demonstrated a high incidence of intracranial microemboli in the middle cerebral artery distal to internal carotid artery dissection.\(^*\) In our study, vertebral perforator infarct and small scattered infarct distal to internal carotid artery dissection.\(^*\) Diffusion-weighted imaging patterns may help in differential diagnosis of VAD from diagnosis of LAD in the clinical setting of unusual cases. Among 5 VAD patients without history of headache, 2 of them showed DWI lesion patterns of small scattered infarct or vertebral perforator infarct, whereas none of the LAD patients with headache showed such DWI lesion patterns.

Small scattered infarct is presumed to have an embolic origin,\(^*\) and anticoagulation is needed to prevent stroke recurrence in such patients.\(^*\) Our DWI data showed that small scattered infarct on DWI was the second most common infarct in patients with VAD, whereas larger infarcts (ie, large scattered infarct and territorial infarct) were more common in the LAD group. This might occur because the size of a thromboembolism may differ depending on the underlying vascular conditions (eg, dissection of a nonatherosclerotic vessel vs rupture or erosion of atherosclerotic vessels). On the other hand, vertebral perforator infarct was common in VAD patients. Lateral medullary infarct is thought to result from an impaired lateral medullary perforator located in the vertebral artery distal to the posterior inferior cerebellar artery.\(^*\) Our data support this possibility because in patients with the vertebral perforator infarct pattern in the VAD group posterior inferior cerebellar artery was intact in most patients who underwent digital subtraction angiography.
In the same manner, unlike the carotid artery dissection, a process other than recurrence of thromboembolism may play an important role in the disease progression of VAD. Basilar artery involvement by the extension of dissection from VAD was frequent in our patients. Patient 12 in the VAD group, who deteriorated during early hospital courses, showed such findings: DWI showed the extension of infarcts on the pontine paramedian area, suggesting the obstruction of the small perforating artery of the basilar artery. Similar fatal cases were introduced in the early reports for VAD.

RESULTS OF VASCULAR STUDIES

Absence of concomitant involvement of anterior circulation arteries was an important difference to note between VAD and LAD. Although the distribution of involved vertebrobasilar arteries was not different between the VAD and LAD groups, concomitant lesion of the anterior circulation was frequently found in the LAD group, whereas no such case was found in the VAD group. This may be explained by the fact that atherosclerosis is a systemic disease, while VAD is a localized process. Reported cases of simultaneous vertebral and carotid artery dissection are extremely rare, and most of them were related with collagen vascular disease such as Ehlers-Danlos syndrome and sudden neck movement like chiropractic manipulation.

Our computed tomographic angiography data showed that calcification on the segment of arterial stenosis was more frequent in the LAD than in the VAD group. Although a few pathological studies reported that calcification in the internal elastic lamina was found in patients with VAD, it is well known that arterial calcification is a process of atherosclerosis; cerebral arterial calcification was reported to raise the possibility of a diffuse atherosclerotic process.

LIMITATIONS AND CONCLUSIONS

There are some limitations in this study. First, owing to the retrospective nature of this study, different modalities of vascular study (digital subtraction angiography, magnetic resonance angiography, and computed tomographic angiography) were used. However, it is necessary to mention that the pathognomic findings of VAD were documented in all the patients with VAD by using maximum intensity projection images of computed tomographic angiography or the source images of magnetic resonance angiography. Second, we intended this study to differentiate the spontaneous arterial dissection from atherosclerosis of the intracranial segment of vertebral artery. Because traumatic VAD can be readily differentiated from atherosclerosis in clinical practice, we excluded the cases with history of trauma preceding stroke onset. Thus, the number of patients was relatively small, and further studies with a large cohort are needed. Finally, transcranial Doppler study will be needed to document thromboembolism, as in cases with carotid artery dissection, though it was not used in this study.

In summary, our findings indicate that besides the clinical characteristics of VAD (young male, the presence of a headache, and fewer conventional risk factors), additional information from DWI (DWI lesion pattern of vertebral perforator infarct and small scattered infarct) and unique vascular results (tandem lesions on anterior vascular territory and calcification) may be helpful in differentiating spontaneous intracranial VAD from LAD. We believe that these data from noninvasive tools may play an important role in decision making to avoid possible complications of conventional angiography.

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Author Contributions: Study concept and design: Lee and Bang. Acquisition of data: Lee, Yong, Bang, Shin, Moon Kim, and Yong Kim. Analysis and interpretation of data: Lee and Bang. Drafting of the manuscript: Lee and Yong. Critical revision of the manuscript for important intellectual content: Lee, Bang, Shin, Moon Kim, and Yong Kim. Statistical analysis: Lee and Bang. Obtained funding: Bang. Administrative, technical, and material support: Lee. Study supervision: Moon Kim and Yong Kim.

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Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.