Headache in Cerebrovascular Disease

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SUMMARY Two hundred fifteen consecutive patients with cerebrovascular events were evaluated prospectively for the incidence and characteristics of headache. Of 163 patients able to communicate, headache occurred in 29% with bland infarcts, 57% with parenchymal hemorrhage, 36% with transient ischemic attacks and 17% with lacunar infarcts. Patients with a history of recurrent throbbing headache were significantly more likely to have headache, usually throbbing in quality, during the present illness. Women developed headache significantly more often than men. Headache began prior to the vascular event in 60% of patients and at its onset in 25%. The quality, onset and duration of the headache varied widely among patients.

Headache in cerebrovascular disease is common, though neither its occurrence nor characteristics predict lesion type or location. Though the pathogenesis of the headache is unknown, its association with prior throbbing headache suggests that similar factors may operate in both.

HEADACHE occurs commonly in cerebrovascular disease. Numerous reports have evaluated headache in patients with ischemic stroke, intracerebral hemorrhage, and transient ischemic attacks. Headache incidence has varied widely in these series, in part due to differences in patient sampling. Most studies are limited by the problems inherent in the evaluation of transitory symptoms with a retrospective chart review. No prospective study has determined the incidence and characteristics of headache in a single population with such diverse lesions as lacunar and hemispheric infarcts, transient ischemic attacks and parenchymal hemorrhages.

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This prospective study was undertaken in order to characterize the prevalence and quality of headache in a variety of cerebrovascular lesions. Factors which may predispose to headache, including prior headache history, were also evaluated.

**Methods**

Two hundred fifteen consecutive patients with cerebrovascular events were evaluated after admission to the neurology services at two teaching hospitals of the Albert Einstein College of Medicine. Each patient was questioned about current symptoms and prior history of headache. Diagnosis was determined by clinical evaluation and computerized tomography (CT). When available, the results of other tests, eg., angiography, lumbar puncture or radionuclide scintigraphy, were used to confirm the diagnosis.

Four categories of vascular events were evaluated. Bland infarct (BI) included all infarcts without evidence of parenchymal hemorrhage whose clinical manifestations did not conform to a lacunar syndrome, as defined below. Since the clinical differentiation between thrombotic and embolic infarcts is often difficult, no attempt was made to separate them.

Parenchymal hemorrhage (PH) comprised all lesions in which hemorrhage was demonstrated by CT. This category included both primary intracerebral hemorrhage and hemorrhagic infarct, a distinction often difficult to make on clinical grounds.

Lacunar infarcts (LI) included those patients who presented with either pure motor hemiparesis, pure sensory stroke, ataxia hemiparesis or clumsy hand-dysarthria, and whose CT was either normal or demonstrated a small zone of hypodensity in the internal capsule or brainstem.

Patients with transient ischemic attacks (TIA) had a neurologic deficit which cleared within 24 hours of onset and a normal CT scan.

The data was analyzed using chi square or Fisher exact tests and significant relationships were sought among patient sex; type and location of lesion; headache incidence and quality; and occurrence of prior headache. Due to the limited number of cases, all vascular lesions of the brainstem and cerebellum were combined as posterior circulation events.

**Results**

The median age of the sample was 71 years (range: 16–96 years). Forty-nine percent of the patients were male and 51% female. There were no differences in sex distribution among the various lesions. BI occurred in 119 (55%) of patients, PH in 50 (23%), LI in 18 (8%) and TIA's in 28 (13%). Thirty-nine percent of all events were in the right hemisphere, 42% in the left hemisphere and 19% in the distribution of the posterior circulation. Type and location of the lesion were not significantly associated.

Incidence of headache: fifty-three patients (25%) could not respond to questions due to aphasia or altered mental status. Twenty-seven percent of patients with BI and 40% of those with PH were nonresponders. All patients with TIA and LI were able to respond. Headache occurred in 34% of respondents and was significantly associated with the type of lesion (p < .05). Headache was reported by 57% (17/30) of patients with BI and 40% of those with PH were nonresponders. All patients with TIA and LI were able to respond.

Headache occurred in 34% of respondents and was significantly associated with the type of lesion (p < .05). Headache was reported by 57% (17/30) of patients with PH, 36% (10/28) with TIA, 29% (25/87) with BI and 3/18 (17%) with LI (table 1). There was no difference in the incidence of headache between cerebrovascular events in the anterior or posterior circulations.

One hundred forty-five respondents reliably described the occurrence of prior headache. Eighty-nine percent reported either no headache or occasional non-throbbing headache, while 11% described prior episodic throbbing headache (table 2). A history of throbbing headache was significantly associated with both headache (p < .001) and specifically throbbing headache (p < .05) during the present illness. The incidence for bland infarct limited to anterior circulation events only.

<table>
<thead>
<tr>
<th>Table 1: Incidence (%) of Headache by Type of Cerebrovascular Lesion: Comparison of Current Data with Prior Studies</th>
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<tbody>
<tr>
<td><strong>Bland infarct</strong></td>
</tr>
<tr>
<td>Throm</td>
</tr>
<tr>
<td>Fisher²</td>
</tr>
<tr>
<td>Mohr et al³</td>
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<tr>
<td>Aring &amp; Merritt²</td>
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<tr>
<td>Wells⁴</td>
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<tr>
<td>McDowell¹⁰</td>
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<tr>
<td>Williams &amp; Wilson⁶†</td>
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<tr>
<td>Bradshaw &amp; McQuaid⁷†</td>
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<tr>
<td>Edmeads¹</td>
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<tr>
<td>Silverstein¹²</td>
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<tr>
<td>Grindall &amp; Toole¹⁷</td>
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<tr>
<td>Medina et al¹⁶</td>
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<tr>
<td>Portenoy et al</td>
</tr>
</tbody>
</table>

Throm = thrombotic; Emb = embolic; Comb = combination.
*Incidence for bland infarct limited to anterior circulation events only.
†Posterior circulation events only.
Incidence of Prior Headache in Patients with and without Headache during the Present Illness. Current Headache and Prior Throbbing Headache were Significantly Associated (p < 0.001)

<table>
<thead>
<tr>
<th>Current headache</th>
<th>No prior headache/rare tension headache</th>
<th>Prior throbbing headache</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>32 (25%)</td>
<td>14 (88%)</td>
<td>46</td>
</tr>
<tr>
<td>Absent</td>
<td>97 (75%)</td>
<td>2 (12%)</td>
<td>99</td>
</tr>
<tr>
<td>Total</td>
<td>129 (100%)</td>
<td>16 (100%)</td>
<td>145</td>
</tr>
</tbody>
</table>

dence of prior headache did not vary among different cerebrovascular lesions.

Headache was significantly associated with sex (p < .05) occurring in 43% of women and 23% of men. This difference could not be explained by an increased incidence of prior throbbing headache among women.

Headache characteristics: Most of the 55 patients experiencing headache were able to characterize it. Half of all headaches were lateralized and 28% were bifrontal. Of lateralized headaches, pain was ipsilateral to the side of the lesion in half the patients. Headache location did not vary with the type of vascular event. Approximately 50% of headaches during the event were throbbing in quality, with no distinction among lesion type or location.

Sixty percent of headaches began prior to the event; a quarter began at the onset of the neurological deficit and the remainder after it had occurred. The duration of the headache was divided equally between those lasting less than 8 hours and those continuing beyond 24 hours. Headaches were equally likely to be abrupt or gradual in onset. Neither timing, duration, nor onset of headaches varied significantly with the type or location of cerebrovascular event.

Discussion

Headache was associated with cerebrovascular events of all types in this series. These results are summarized and compared to those of previous studies in table 1.

Headache occurred in 29% of patients with bland thromboembolic infarcts, with no difference between lesions in the anterior and posterior circulations. Fisher2 described headache in none of five patients with thrombosis of the anterior cerebral artery and 35 of 109 patients with internal carotid artery thrombosis. Embolism was associated with headache in 14% (5 of 37) of cases with middle cerebral artery occlusion and 3 of 7 involving the common carotid artery. In the posterior circulation, Fisher2 noted headache in 71% (37 of 51) of thrombotic and 44% (4 of 9) of embolic posterior cerebral artery occlusions, as well as 33–43% of cases with occlusion of the basilar artery or its branches.

Other series have reported headache incidence within this range. Mohr et al3 noted headache in 31% of large artery thrombosis and 25% of embolic stroke. In several large series5, 6, 11 of patients with anterior circulation embolic stroke, headache was reported in 8–43% of cases. Finally, infarction in the basilar territory was associated with headache in 25% and 54% of patients in two other studies.6, 7

Headache was noted by 57% of patients with PH, including those with gangliocytic and lobar hemorrhage, as well as a limited number with hemorrhagic infarction. In the Harvard stroke registry,3 headache occurred at the onset of intracerebral hemorrhage in 33% of patients and at some time in 60%. This is similar to the headache incidence of 46–68% described in lobar hemorrhage,13, 14 but higher than the 23% reported by Fisher.2

In the present series, headache occurred in 10 of 28 (36%) patients with TIA. Medina16 reported an incidence of 44%, while others1, 13 have found headache in 25% of these patients.

Fisher2 reported only 5 patients complaining of headache in a series of 104 cases of lacunar stroke, while Mohr et al3 found headache to be present in 11%. An incidence of 17%, (3 of 18 cases) was found in the present survey.

This prospective study has confirmed that the characteristics of headache during various cerebrovascular events do not predict either lesion type or location. Fisher2 found that headaches associated with strokes in the anterior circulation were generally frontal, usually ipsilateral to the lesion, while posterior circulation events tended to be occipital. Headache usually occurred shortly before or during the event, and the quality of pain varied widely among patients. However, exceptions to this characterization were many and clinically relevant conclusions could not be drawn from the data. Most studies1, 9, 15, 16 depict similar variability, though some6-7 present a remarkably consistent clinical profile of occipital and throbbing headache in patients with infarction in the posterior circulation.

Except for the timing of headache onset, the patients reported here did not conform to the trends described by Fisher.2 Headache location was equally divided between generalized and lateralized headache, with the latter ipsilateral to the lesion only half the time. Occipital headaches were distinctly unusual, even for posterior circulation events. Others11 have also noted generalized or frontal headache with lesions in this circulation, though less commonly than was found here. Similarly, headache quality, rate of onset and duration all varied widely. Though headache is a common accompaniment of cerebrovascular events, it cannot be used to define the underlying process.

Eleven percent of patients in this study had a history of episodic throbbing headache, similar to the incidence of migraine in the general population.17 An increased occurrence of headache with acute vascular events has not been reported in migraineurs previously. Edmeads1 sought this association and found none. These results suggest that migraineurs may be predisposed to headache when cerebrovascular events occur and that the pain in these two situations may have mechanisms in common. Medina et al16 found a history of late-onset vascular headache in 53% (18 of 34) of patients with TIA and noted that nearly three-quarters of patients who had headache associated with a TIA
had similar headaches independently. Similarly, a recent study\(^1\) demonstrated a connection between prior migraine and headache during transient global amnesia. It is possible that ischemia in the region of susceptible blood vessels may trigger components of the migraine cascade in vulnerable individuals. Alternatively, Edmeads\(^1\) postulated an important role for platelet adhesion, aggregation and release in headache of atherothrombotic disease, processes which have been implicated in the production of migraine headache.\(^1\) Though the underlying pathophysiology of pain in both these conditions remains to be elucidated, a common process in some patients is implied by our data.

**References**


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**Moderate Homocysteinemia — A Possible Risk Factor For Arteriosclerotic Cerebrovascular Disease**

**LARS E. BRATTSTROM, M.D., JAN ERIK HARDEBO, M.D., AND BJORN L. HULTBERG, M.D.**

**SUMMARY** Highly elevated concentrations of homocysteine measured as homocysteine or cysteine-homocysteine mixed disulfide (MDS) are found in plasma and urine in subjects with inherited abnormalities of the methionine metabolism. These subjects have a high incidence of arteriosclerotic vascular complications during childhood. Homocysteine causes endothelial cell injury and cell detachment that initiates the development of arteriosclerosis. The present study demonstrates a significantly elevated mean plasma MDS concentration in 19 patients with arteriosclerotic cerebrovascular disease compared to 17 controls. Our findings suggest that moderate homocysteinemia might be a risk factor for arteriosclerotic cerebrovascular disease.

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HOMOCYST(E)INE/MURIA IS usually secondary to deficiency of cystathionine-\(\beta\)-synthase, a pyridoxal phosphate dependent enzyme in the transsulfuration pathway (fig. 1). It is an autosomal recessive inborn error of methionine metabolism. Homocysteinemia can also be due to a reduced capacity for homocysteine remethylation via the folate and cobalamin dependent transmethylation pathway. It is characterized by elevated concentrations of homocysteine and its two disulfides homocystine and cysteine-homocysteine mixed disulfide (MDS) in plasma and urine.\(^1\) The main cause of morbidity and mortality in homocysteinemic patients is progressive premature arteriosclerosis and associated thromboembolic complications.\(^1\) Histopathologically there are widespread arterial focal lesions with fibrous intimal plaques and medial fibrosis with fraying and splitting of the internal elastic membranes. Homocysteine or its derivatives are considered to cause these changes.\(^2\)\(^3\) Experimental studies with homocysteine thiolactone in rabbits have in some but not all studies induced arteriosclerotic lesions.\(^4\)\(^5\) Continuous infusion of ba- boonos with homocysteine thiolactone caused patchy...
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