Headache in Transient or Permanent Cerebral Ischemia

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We studied headache features in 3,126 patients with acute cerebral or retinal ischemia. Headache occurred in 18% of these patients (in 16% of all patients with transient ischemic attacks, in 18% of patients with reversible ischemic neurologic deficits, and in 19% of patients with minor strokes) and was mostly continuous in all types of attacks. Headache was present in 16% of patients with monocular visual symptoms. The occurrence of headache was not related to the mode of onset, mode of disappearance, or duration of the attack. Patients with headache more often were known to have heart disease. Headache was less frequent in patients with small deep infarcts, who were more often hypertensive, and in patients with infarcts in the anterior circulation; headache was more frequent in patients with cortical infarcts and in patients with infarcts in the posterior circulation. Patients with a relevant small deep infarct on computed tomography scan and accompanying headache relatively often reported symptoms compatible with cortical ischemia, such as language disorders or a visual field defect. We conclude that headache is a frequent accompanying symptom in patients with acute cerebral and retinal ischemia and that the occurrence of headache is partly related to the underlying cause of the ischemic lesion. (Stroke 1991;22:754-759)

Previous reports have shown that headache is a common feature in acute cerebrovascular disease, but its frequency varies widely among different studies.1-8 The main cause of the variation is that only two of the eight surveys used a prospective design to study the occurrence and nature of headache in acute cerebrovascular events.4,5 Moreover, most previous studies have included patients with widely different types of cerebrovascular disease, including transient ischemic attacks, cerebral infarction of all types, intraparenchymal bleeding, and subarachnoid hemorrhage. These studies mainly addressed the question of whether certain headache features help to distinguish infarction from bleeding or to locate the lesion.

Some studies suggest that headache is more common in patients with occlusive disease of major extracranial or intracranial blood vessels than in patients with small vessel disease.1,3,5,6,8,9 The frequency of headache in small deep infarcts differs among various studies, however, ranging from 4% to 17%.3,5,6,8,9 There also is disagreement about the occurrence of headache in patients with transient monocular blindness3,4,10 and about whether headache occurs relatively more often in women.1,4,8 Little is known about the relationship to vascular risk factors, the time course and duration of the attack, or the number of previous attacks.

We have prospectively studied headache features in 3,126 patients with acute cerebral ischemia of variable duration who were entered into a multicenter treatment trial. We attempted to relate the occurrence and nature of headache to the presence of vascular risk factors, the probable site of origin of the neurologic symptoms (cerebral cortex, deep white matter, or retina), the time course of the attack, and computed tomography (CT) scan findings.

Subjects and Methods

All patients had been entered into the Dutch TIA Trial. The background and design of this study have been described elsewhere.11 In this trial, we used a checklist to record the symptoms in plain language.12 The list contains a number of detailed multiple-choice questions about the nature and time course of the symptoms. One question pertains to the presence...
Headache in Acute Cerebral Ischemia

Hypertension (206/351; 1100/1447)
Diabetes (38/510; 209/2360)
Hyperlipidemia (19/538; 94/2475)
Smoking (233/325; 1162/1406)
Claudication (29/528; 127/2442)
Angina pectoris (72/488; 222/2347)
Past myocardial infarct (70/468; 245/2325)
Enlarged heart (56/494; 263/2282)
Coronary bypass (16/541; 49/2520)

FIGURE 1. Vascular risk factors and headache. Numbers between parentheses indicate: number of patients with headache and with/without risk factor; number of patients without headache and with/without risk factor. Horizontal line represents 95% confidence limits.

and nature (throbbing versus constant) of the headache. The investigators also were encouraged to specify where the headache occurred (side of the head), but as this item was not included in the checklist, the data were incomplete in this respect and could not be analyzed. The degree of handicap was graded by means of the modified Rankin scale. To be included in the trial, patients had to be independent in most activities of daily life, corresponding to grade 3 or better on this scale.13

Between March 1, 1986, and March 1, 1989, 3,150 patients were randomized. Twenty-four patients were incorrectly diagnosed at the time of randomization and were excluded from the analysis. Computed tomographic scans available at the time of analysis in 2,988 patients were independently and blindly reviewed by at least two neurologists or by one neurologist and a neuroradiologist. In case of disagreement, a third neurologist or neuroradiologist arbitrated. Only then were the observers given access to clinical details to assess the clinical relevance of the CT scan abnormalities.

Cerebral infarcts were defined as circumscribed hypodense lesions and subdivided into small deep lesions, cortical end zone infarcts (radiolucent lesions in the territory of one or more cortical arteries), and cerebral border zone infarcts (wedge-shaped hypodensities in the boundary area between two major cerebral arteries or between deep and superficial branches of the middle cerebral artery). Small deep infarcts were further subdivided according to their location. Depending on the clinical details, the scans were classified as showing a relevant infarct only, an irrelevant infarct only, or both relevant and irrelevant infarcts.

Data were analyzed by means of the Statistical Package for the Social Sciences (SPSS) and EPISTAT statistical software. Yates' corrected $\chi^2$ test was used where appropriate. Comparisons between the groups were expressed as odds ratios (with headache:without headache), with the corresponding 95% confidence interval (CI).14 A level of $p<0.05$ was considered statistically significant.

Results

In 557 of the 3,126 patients, headache accompanied the cerebral ischemic attack (18%; 95% CI, 17-19%). The occurrence of headache was not related to sex (odds ratio men:women, 0.93; 95% CI, 0.76-1.13; $p=0.48$) or Rankin handicap grade at the time of randomization ($\chi^2=1.325$, df=3; $p=0.71$).

Figure 1 shows the relationship between headache and vascular risk factors. Patients with headache more frequently had evidence of ischemic heart disease: angina pectoris (odds ratio, 1.56; 95% CI, 1.17-2.10; $p=0.002$), past myocardial infarction (odds ratio, 1.42; 95% CI, 1.06-1.90; $p=0.01$), and past coronary bypass surgery (odds ratio, 1.52; 95% CI, 0.82-2.77; $p=0.17$). This difference could not be explained by a higher frequency of a specific type of infarction, particularly cortical infarction, among patients with a history of heart disease. The association may have been related to the use of medications commonly given in ischemic heart disease, such as nitroglycerin, but unfortunately our data did not permit an accurate testing of this hypothesis. Patients with headache less frequently were known to have hypertension (odds ratio, 0.79; 95% CI, 0.65-0.96; $p=0.02$). This finding could be explained by the higher frequency of small deep infarcts, which were associated with a lower frequency of headache among hypertensive patients.

Table 1 shows the relationship between the time course of symptoms and the occurrence of headache.
We found no significant difference between patients with and without headache with regard to onset, duration and disappearance of symptoms, or number of attacks. Conversely, Table 1 also shows that the presence of headache could not be predicted from any of the time course variables, particularly because, in each category, patients without headache were a large majority. Headache occurred in 16% of patients with transient ischemic attacks, 18% of patients with reversible ischemic neurologic deficits, and 19% of patients with minor strokes ($\chi^2=2.02$, df=2, $p=0.36$).

Figure 2 compares the nature of the main symptoms between patients with and without headache. Patients with headache less often had a lacunar syndrome (odds ratio, 0.55; 95% CI, 0.45–0.66; $p=0.000001$) and more often had symptoms favoring a cortical localization (odds ratio, 1.62; 95% CI, 1.28–2.04; $p=0.00004$). Of 180 patients with transient monocular blindness, 28 (16%) reported accompanying headache, which is the same as for all other patients (odds ratio, 0.84; 95% CI, 0.52–1.29; $p=0.65$).

Figure 3 shows the relationship between CT findings and the presence of headache. Small deep infarcts were significantly less frequent (odds ratio, 0.58; 95% CI, 0.44–0.76; $p=0.000006$) and cortical infarcts more frequent in patients with headache (odds ratio, 1.78; 95% CI, 1.31–2.41; $p=0.0001$). Conversely, headache occurred in 74 of the 606 (12%; 95% CI, 11–14) patients with a relevant small deep lesion compared to 84 of the 290 (29%; 95% CI, 26–31%) patients with a relevant cortical infarct. Seventy-four patients with a relevant small deep infarct on CT had accompanying headache. Apart from symptoms that could be attributed to the side and site of the lesion, 20 of these patients (27%) complained of one or more symptoms compatible with aphasia, alexia, or agraphia (12 patients), aphasia and hemianopia (one patient), or hemianopia (seven patients) compared to 67 of the 532 (13%) patients with a deep infarct without headache (odds ratio, 2.23; 95% CI, 1.18–4.16; $p=0.01$). In these cases, cortical structures may have been involved as

| Table 1. Relationship Between Time Course of Cerebral Ischemic Attack and Presence of Accompanying Headache |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Onset                                           | Onset                                           | Onset                                           | Onset                                           |
| n      | % Total | n      | % Total | Total                                                                                                                                 |
| 1 sec  | 1,274   | 56     | 245     | 50     | 16                                                                                                                                 |
| Seconds| 630     | 28     | 159     | 32     | 20                                                                                                                                 |
| 1–5 min| 151     | 7      | 42      | 8      | 0.07  22                                                                                                                                 |
| 6–60 min| 58     | 3      | 9       | 2      | 14                                                                                                                                 |
| Hours  | 97      | 4      | 24      | 5      | 20                                                                                                                                 |
| Days   | 53      | 2      | 15      | 3      | 22                                                                                                                                 |
| Total  | 2,263   | 494    |         |        |                                                                                                                                 |
| Duration|         |        |         |        |                                                                                                                                 |
| Seconds| 29      | 1      | 7       | 1      | 19                                                                                                                                 |
| Minutes| 501     | 20     | 92      | 17     | 16                                                                                                                                 |
| Hours  | 306     | 12     | 65      | 12     | 0.65  18                                                                                                                                 |
| Days   | 338     | 13     | 73      | 13     | 18                                                                                                                                 |
| Weeks  | 158     | 6      | 39      | 7      | 20                                                                                                                                 |
| Persisting | 1,237 | 48     | 281     | 50     | 19                                                                                                                                 |
| Total  | 2,569   | 557    |         |        |                                                                                                                                 |
| Disappearance|     |        |         |        |                                                                                                                                 |
| 1 sec  | 90      | 6      | 15      | 4      | 14                                                                                                                                 |
| Seconds| 210     | 14     | 36      | 11     | 15                                                                                                                                 |
| 1–5 min| 247     | 16     | 58      | 17     | 0.38  19                                                                                                                                 |
| 6–60 min| 215    | 14     | 42      | 13     | 16                                                                                                                                 |
| Hours  | 278     | 18     | 72      | 21     | 20                                                                                                                                 |
| Days   | 496     | 32     | 113     | 34     | 21                                                                                                                                 |
| Total  | 1,536   | 336    |         |        |                                                                                                                                 |
| Number of attacks |     |        |         |        |                                                                                                                                 |
| 1      | 1,760   | 69     | 377     | 68     | 18                                                                                                                                 |
| 2–3    | 595     | 23     | 133     | 24     | 18                                                                                                                                 |
| 4–10   | 157     | 6      | 32      | 6      | 0.80  21                                                                                                                                 |
| >10    | 54      | 2      | 15      | 3      | 21                                                                                                                                 |
| Total  | 2,566   | 557    |         |        |                                                                                                                                 |

*p* $\chi^2$ test.
probable cortical
Motor + dysphasla (42/515; 202/2387)
Sensory + dysphasla (4/553; 9/2560)
Dysphasla + dyslexia (0/548; 25/2544)
Visual field defect (87/490; 145/2424)
Any of these (122/435; 379/2190)

probable lacunar
Motor only (104/453; 716/1969)
Sensory only (11/546; 15/2488)
Sensorimotor (116/441; 833/1936)
Any of these (285/292; 1416/1153)

monocular blindness (28/529; 152/2417)

less common in patients with headache
more common in patients with headache

odds ratio

FIGURE 2. Symptoms and headache. Numbers between parentheses indicate: number of patients with headache and with/without symptom; number of patients without headache and with/without symptom. Horizontal line represents 95% confidence limits. Dotted line indicates upper limit of more than 3.5.

well, without evidence on CT. The presence of headache was not related to the location of the ischemic lesion.

Figure 3 also shows that headache was less frequent in patients with infarcts in the anterior circulation, that is, in the territory of the middle and anterior cerebral artery compared to all other patients, with or without infarct on CT (odds ratio, 0.62; 95% CI, 0.50-0.78; p=0.00003). Headache was more frequent in patients with infarcts in the posterior circulation, that is, the territory of the posterior cerebral artery, the basilar artery, or cerebellar arteries (odds ratio, 2.47; 95% CI, 1.73-3.51; p=0.0000001). Table 2 shows that these differences were independent of a small number of small deep infarcts in the posterior circulation.

The nature of headache was mostly continuous and not throbbing in the majority of patients with headache, regardless of the main symptom or the findings on CT (94%; 95% CI, 92-96).

FIGURE 3. Computed tomography (CT) findings and headache. Numbers between parentheses indicate: number of patients with headache and with/without CT finding; number of patients without headache and with/without CT finding. Horizontal line represents 95% confidence limits. Dotted line indicates upper limit of more than 3.5.
Discussion

Our study confirms that headache frequently accompanies a transient ischemic attack or the onset of a nondisabling stroke, although its overall frequency of 18% in our series is somewhat lower than in previous reports.\textsuperscript{1-9} The headache was mostly continuous in all types of attacks. Furthermore, our study shows two distinctive subgroups that were particularly associated with headache. First, headache occurred more than twice as often in patients with a relevant cortical infarct on CT as in patients with a symptomatic small deep infarct (29% versus 13%). Second, headache was much more common among patients with infarcts in the posterior circulation than in patients in whom the anterior circulation was involved. The latter difference was independent of the relative frequencies of deep and superficial infarcts. Both patterns have been recognized in earlier studies\textsuperscript{1,5,6,8,9} but never have been convincingly proved because of the small numbers of patients studied. No relationship was found between the presence of headache on the one hand and sex, the mode of onset, mode of disappearance, duration of the attack, or number of previous attacks on the other. In particular, headache was equally common among patients with transient ischemic attacks (16%), reversible ischemic neurologic deficits (18%), or minor strokes (19%).

Headache occurred in 16% of patients with transient monocular blindness, which is surprisingly high in view of earlier reports. Fisher\textsuperscript{1} reported headache in none of his 58 patients with monocular blindness, and Goodwin et al\textsuperscript{19} in only one patient from a group of 37. Grindal and Toole\textsuperscript{4} noted headache in five patients with amaurosis fugax but did not mention the total number of patients investigated. We found no relationship between the occurrence of headache and the nature of the visual symptoms.

The low frequency of headache among patients with small deep infarcts compared to those with cortical infarcts confirms earlier reports,\textsuperscript{1,5,6,8,9} although all previous studies except one\textsuperscript{6} report an even lower rate than the 13% we found. Yet the mere presence of headache in patients with small deep lesions is a puzzling finding. We found that a quarter (27%) of these patients with an appropriate lesion and headache also reported symptoms compatible with aphasia, agraphia, alexia, or visual field defects, suggesting cortical ischemia. Other investigators have demonstrated cortical dysfunction in patients with deep infarcts and aphasia by means of positron emission tomography.\textsuperscript{15} It is conceivable that some occlusions in the stem of the middle cerebral artery affect perforating arteries as well as cortical branches, with or without local atherosclerosis.\textsuperscript{16} Thus, it might well be that the ischemic lesion in patients with a small deep infarct and headache is indeed more extensive than the results of CT scanning alone suggest.

The cause of headache in patients with cerebral ischemia is unknown. Stress alone is a very unlikely explanation; a visual field defect, for example, cannot be expected to produce more anxiety than a complete hemiplegia from a small deep infarct. Headache has been commonly related to deformation and stretching of intracranial pain-sensitive structures, such as the intracranial internal carotid artery and the dura. This mechanism explains well the headache in hemorrhagic stroke but does not clarify the headache in transient ischemic attacks and minor cerebral infarction. Edmeads\textsuperscript{8,2} suggested that this headache may be caused by the release of vasoactive substances from activated platelets, such as serotonin and prostaglandins. Several authors have reported platelet activation in cerebral ischemia.\textsuperscript{17-21} This interesting hypothesis could explain the lower frequency of headache in patients with small deep lesions in whom, according to other studies, platelet activation could not be demonstrated.\textsuperscript{20}

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References


**KEY WORDS** • cerebral ischemia • cerebral ischemia, transient • headache.
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