Dear Sir,

Headache is commonly reported in acute ischemic stroke (IS) onset, occurring in about one-fourth of patients. However, a sudden and severe headache, with characteristics of thunderclap headache (TCH) as the main manifestation of an IS, is extremely rare and only a few cases have been described [1–5]. We report 2 cases of IS presenting with TCH as the primary clinical feature. In addition, we reviewed the other reports of TCH and IS to assess whether the headache may be the result of a specific stroke mechanism.

Methods

Review of the Literature

We performed an electronic search of MEDLINE using the following combination of medical subject heading (MeSH) terms: headache [MeSH Major Topic] AND (stroke [MeSH Major Topic] OR cerebral infarction [MeSH Major Topic]). We also systematically explored the related articles function of MEDLINE for each relevant reference found. The reference lists of relevant articles and published reviews were further scanned for additional relevant papers.

We looked for studies that primarily addressed IS patients who presented an acute and severe headache that was maximum in intensity at onset, as the solely or the main or manifestation of the ischemic event. We excluded (i) patients with cerebrovascular or intracranial artery dissections, reversible cerebral vasoconstriction syndrome, intracranial infection or cerebral venous sinus thrombosis as the cause of the stroke; (ii) patients with ischemia not demonstrated by computed tomography (CT) or magnetic resonance angiography (MRA); (iii) patients in whom the investigation of the stroke etiology was not performed, and (iv) reports in which clinical and radiological characteristics of the patients were not available.

The following variables were collected from each selected study: (i) age, (ii) gender, (iii) stroke etiology, (iv) localization of the lesion, (v) previous history of migraine or of other headache, and (vi) relationship between the headache and stroke localization.

Results

Case Reports

Patient 1: A 68-year-old right-handed man was admitted to our hospital with an acute, severe headache in the right frontotemporal region. It was spontaneously described as the worst pain ever in his life with a score of 9 in a visual analogue scale (VAS, 0–10 cm) for pain. It had begun while working, urging prompt medical assistance. The pain reached maximum intensity in less than 1 min, lasted about 2 h and was not accompanied by other symptoms. There was no history of chronic headache or risk factors for stroke. The neurological examination was unremarkable, except for motor persistence in the upper limbs and aprosodia. Vital signs and general physical examination were normal. He had no signs of arrhythmia and laboratory examinations showed no abnormalities. However, a few hours later, he presented a high-frequency atrial fibrillation, but with no symptoms. This episode lasted a few minutes, but the rhythm did not become regular again during the first day of hospitalization. Brain MRI revealed an extensive area of recent ischemia in the territory of the posterior division of the right middle cerebral artery (fig. 1a,b). Arterial and venous magnetic resonance angiography of the brain and neck vessels was performed, with no evidence of stenosis or occlusions (fig. 1c).

Patient 2: A 26-year-old right-handed woman was admitted to our hospital with a history of sudden onset occipital headache associated with diplopia, divergent...
strabismus and right arm paresis 3 days before. Although her visual and motor symptoms improved gradually, the headache did not resolve until admission. The pain scored 9 in the VAS, reached maximum intensity in less than 1 min, and lasted about 4 days. The patient reported that 1 month before she presented an episode of sudden frontal headache, the worst pain ever in her life (score of 10 in the VAS), associated with diplopia and lasting less than 24 h. She had a history of migraine with visual aura, but she was not using contraceptive pills nor presented any other vascular risk factors. On the day of admission her neurological examination was unremarkable, except for short-term memory deficit. Cranial CT and cerebral spinal fluid analysis were normal. Angiography of the cervical and intracranial vessels was performed and did not show intracranial aneurysm, artery dissections, venous sinus thrombosis and reversible cerebral vasoconstriction syndrome [6]. Different from the secondary form, primary TCH has a benign prognosis and is a diagnosis of exclusion. IS is not considered to be a typical cause of secondary TCH, and there are only a few reports of IS patients presenting with this type of headache, especially when the pain is the main clinical feature [1–4].

The mechanism by which IS provokes TCH remains uncertain. However, three important hypothesis are considered: direct mechanical or chemical activation of sensitive fibers in the endothelial cells of intracranial vessels; neurogenic inflammation leading to the ‘central sensitization’ phenomena, and platelet aggregation, adhesion and release. These factors may explain the ipsilateral localization of headache in patients with hemispheric stroke. Although IS stroke predominantly affects the anterior circulation, half (3 out of 6) of the patients with IS with TCH as prominent

**Review of the Literature**

We were able to find 9 other cases of IS and TCH in the literature [1–5]. Five of them were reported in a large series of TCH [5], but we did not include them in the comparative table since the characteristics of the patients were not described in detail nor was it specified whether TCH was the main feature of the stroke. The characteristics of the other 4 patients and our 2 patients are shown in table 1.

**Discussion**

TCH is a term that defines a sudden and severe headache that has its climax at onset and is most commonly secondary to other conditions. It has been characteristically associated with subarachnoid hemorrhage, unruptured intracranial aneurysm, cervical artery dissection, cerebral venous sinus thrombosis and reversible cerebral vasoconstriction syndrome [6]. Different from the secondary form, primary TCH has a benign prognosis and is a diagnosis of exclusion. IS is not considered to be a typical cause of secondary TCH, and there are only a few reports of IS patients presenting with this type of headache, especially when the pain is the main clinical feature [1–4].

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**Fig. 1.** a–c Patient 1: MRI showing an acute ischemic lesion in the lower division of the right middle cerebral artery: a diffusion-weighted imaging, b fluid-attenuated inversion-recovery, and c MRI angiography of the brain and neck vessels was performed, with no evidence of stenosis or occlusions. d Patient 2: MRI, T2-weighted imaging, showing a left paramedian thalamic lesion.
A prominent feature presented a lesion in the posterior circulation. The predominance of headache in posterior circulation strokes may be explained by the fact that posterior circulation is more densely innervated by the trigeminal system. Despite of that, in one large study, headache at stroke onset was positively associated with cerebellar strokes but not with other brainstem locations [7].

Similar to most of the previous case reports, our patients exhibited a correspondence between pain localization and stroke distribution and the etiology was also cardioembolic. One patient had atrial fibrillation and no other cause for the stroke and a young woman had a patent foramen ovale and a paramedian thalamic infarct, a territory which is mainly affected by cardiac emboli [8]. Although most studies do not show an association between headache at stroke onset and presumed stroke etiology, there are no specific studies on TCH. The high frequency of a cardioembolism in these patients (5 out of 6, 1 patient had a cryptogenic stroke) may suggest that the cardiac emboli, which are often larger than artery-to-artery emboli [9], can provoke an acute stretch of the intracranial arteries, particularly when they lodge in the proximal, pain-sensitive part of an artery at the base of the brain.

In our patients, the severe headache was the main clinical feature and the reason for seeking the emergency room. The patients did not have other complaints at admission. Both patients presented very subtle focal neurological abnormalities (aprosodia, motor impersistence and short-term memory deficit), that were only noticed after a careful neurological examination. Minor focal signs were also described in other reports of IS patients presenting with TCH [4].

TCH is a serious condition, as it can represent a catastrophic and disabling disease. IS has emerged as a potential and important differential diagnosis for TCH, even when no lateralizing neurological abnormalities are found. In such patients, a cardiac source of emboli should be investigated.

### Table 1. Characteristics of patients with IS presenting with TCH

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Stroke localization</th>
<th>Gender</th>
<th>Age years</th>
<th>Previous history of headache</th>
<th>Relation between headache and stroke localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwedt and Dodick [1]</td>
<td>cardioembolic</td>
<td>cerebellum</td>
<td>female</td>
<td>66</td>
<td>no</td>
</tr>
<tr>
<td>Edvardsson and Persson [2]</td>
<td>cardioembolic</td>
<td>right CSO</td>
<td>male</td>
<td>73</td>
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<tr>
<td>Gossrau et al. [3]</td>
<td>cryptoogenic</td>
<td>cerebellum</td>
<td>male</td>
<td>44</td>
<td>no</td>
</tr>
<tr>
<td>Annic and Lucas [4]</td>
<td>cardioembolic</td>
<td>left CSO</td>
<td>female</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>Present case 1</td>
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<td>MCA territory</td>
<td>male</td>
<td>68</td>
<td>no</td>
</tr>
<tr>
<td>Present case 2</td>
<td>cardioembolic</td>
<td>left paramedian thalamus</td>
<td>female</td>
<td>26</td>
<td>yes</td>
</tr>
</tbody>
</table>

CSO = Centrum semiovale; MCA = middle cerebral artery; NR = not reported.

### References


Thunderclap Headache in Ischemic Stroke

Eur Neurol 2011;66:133–135