Recurrent primary thunderclap headache and benign CNS angiopathy
Spectra of the same disorder?
S.-P. Chen, MD; J.-L. Fuh, MD; J.-F. Lirng, MD; F.-C. Chang, MD; and S.-J. Wang, MD

Abstract—Objectives: To investigate the clinical pictures of patients with recurrent thunderclap headaches of unknown etiology and to field-test two relevant International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria, i.e., primary thunderclap headache (Code 4.6) and benign (or reversible) angiopathy of the CNS (Code 6.7.3). Methods: We prospectively recruited patients presenting with idiopathic recurrent thunderclap headaches from a hospital-based headache clinic. Detailed histories, neurologic examinations, and MRIs and magnetic resonance angiographies (MRAs) were performed in all patients to exclude secondary causes. Patients with cerebral vasoconstriction received serial MRA follow-up. Results: Fifty-six consecutive patients (51 female/5 male, mean age 49.6 ± 9.8 years [range 22 to 76] years) were enrolled. Segmental vasoconstriction (or benign CNS angiopathy) was found in 22 patients (39%). Thunderclap headache recurred in all patients with a median frequency of 0.7 times per day for a median period of 14 days (range 6 to 86 days). The median duration for each single attack was 3 hours. Most patients (84%) reported at least one trigger. Nimodipine effectively aborted further attacks in 83% of the treated patients. Headache attacks subsided within 3 months. Four patients (7%) developed ischemic complications. Patients with and without vasoconstriction based on MRA images were similar regarding demographics and headache profile. Except for the duration criterion, our patients generally mapped well into the proposed ICHD-II criteria. Conclusions: This study suggests that the two diagnostic entities proposed by the ICHD-II may present different spectra of the same disorder. The distinct headache profile may help physicians quickly recognize this disabling headache disorder with risk of stroke and provide timely treatment.

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Thunderclap headache was first coined by Day and Raskin1 to describe the symptoms of a patient with an unruptured aneurysm. However, subsequent reports2,3 found that certain patients with thunderclap headache did not have aneurysms but rather segmental cerebral vasoconstriction, sine qua non of “Call-Fleming syndrome.”4 The initial proposed diagnostic criteria2,3 classified this headache syndrome into three subtypes: 1) thunderclap headache without neurologic signs or symptoms; 2) thunderclap headache with neurologic signs or symptoms; and 3) thunderclap headache associated with intracranial disorders, including subarachnoid hemorrhage (SAH), cerebral venous sinus thrombosis, pituitary apoplexy, etc. In those patients without associated intracranial disorders, i.e., “idiopathic” thunderclap headache, some may exhibit angiographic evidence of reversible segmental vasoconstriction. Recently, the International Classification of Headache Disorders, 2nd edition (ICHD-II)5 adopted primary thunderclap headache as a primary headache disorder (Code 4.6) and proposed criteria for its diagnosis (table 1). These criteria define the headache onset, duration, and recurrence and highlight the need for normal CSF and angiographic findings in the notes; unlike previous criteria, the neurologic symptoms/signs are not mentioned. On the other hand, thunderclap headache with evidence of intracranial vasoconstrictions is treated as a secondary headache disorder and coded as “headache attributed to benign (or reversible) angiopathy of the CNS (Code 6.7.3)” (table 1). However, these two diagnostic criteria have never been field-tested.

Even more perplexing, thunderclap headaches elicited by known triggers, e.g., coughing, exertion, or sexual activity, can also be coded separately by the ICHD-II (Codes 4.2–4.4). Additionally, bathing

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4.6. Primary thunderclap headache
A. Severe head pain fulfilling Criteria B and C
B. Both of the following characteristics:
1. Sudden onset, reaching maximum intensity in <1 minute
2. Lasting from 1 hour to 10 days
C. Does not recur regularly over subsequent weeks or months
D. Not attributed to another disorder

6.7.3. Headache attributed to (benign or reversible) angiopathy of the CNS
A. Diffuse, severe headache of abrupt or progressive onset, with or without focal neurologic deficits and/or seizures and fulfilling Criteria C and D
B. “Strings and beads” appearance on angiography and subarachnoid hemorrhage ruled out by appropriate investigations
C. One or both of the following:
1. Headache develops simultaneously with neurologic deficits and/or seizures
2. Headache leads to angiography and discovery of “strings and beads” appearance
D. Headache (and neurologic deficits, if present) resolves spontaneously within 2 months

**Table 1** Current diagnostic criteria of primary thunderclap headache and benign (or reversible) angiopathy of the CNS in the ICHD-II

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Primary thunderclap headache</td>
<td>A. Severe head pain fulfilling Criteria B and C</td>
</tr>
<tr>
<td>B. Both of the following characteristics:</td>
<td></td>
</tr>
<tr>
<td>1. Sudden onset, reaching maximum intensity in &lt;1 minute</td>
<td></td>
</tr>
<tr>
<td>2. Lasting from 1 hour to 10 days</td>
<td></td>
</tr>
<tr>
<td>C. Does not recur regularly over subsequent weeks or months</td>
<td></td>
</tr>
<tr>
<td>D. Not attributed to another disorder</td>
<td></td>
</tr>
<tr>
<td>Headache attributed to benign (or reversible) angiopathy of the CNS</td>
<td>A. Diffuse, severe headache of abrupt or progressive onset, with or without focal neurologic deficits and/or seizures and fulfilling Criteria C and D</td>
</tr>
<tr>
<td>B. “Strings and beads” appearance on angiography and subarachnoid hemorrhage ruled out by appropriate investigations</td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>1. Headache develops simultaneously with neurologic deficits and/or seizures</td>
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<tr>
<td>2. Headache leads to angiography and discovery of “strings and beads” appearance</td>
<td></td>
</tr>
<tr>
<td>D. Headache (and neurologic deficits, if present) resolves spontaneously within 2 months</td>
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ICHD-II = International Classification of Headache Disorders, 2nd edition

has recently been recognized as a novel trigger of thunderclap headaches. Some patients with such thunderclap headache variants exhibited angiographic findings of reversible segmental vasoconstriction. Owing to the great resemblance in clinical manifestation and angiographic findings with idiopathic thunderclap headaches, whether these headaches should be coded separately based on their triggers or angiographic findings or whether they should be gathered under a primary headache syndrome deserves careful consideration. Additionally, a recent review demonstrated that patients with segmental arterial vasoconstriction faced a risk of developing posterior leukoencephalopathies or ischemic stroke, suggesting that its nature is indeed not always benign.

In this study, we prospectively recruited a large sample of 56 consecutive patients with thunderclap headache with unknown causes from 2000 to 2006. The clinical features of these patients are presented, and the feasibility of the current ICHD-II criteria for diagnosing these headache disorders is tested.

**Methods. Patients and clinical setting.** We prospectively enrolled consecutive patients presenting with sudden-onset severe head pain, reaching maximal intensity within 1 minute, i.e., thunderclap headache, at the headache clinic of Taipei Veterans General Hospital (Taipei-VGH) from July 2000 to March 2006. At Taipei-VGH, patients with known causes of thunderclap headaches were mostly screened out in the emergency room. Only subjects with uncertain diagnosis or recurrent headaches would be referred to the headache clinic for further evaluation. For the subjects presenting at the headache clinic, comprehensive investigations were conducted. Only subjects without a known cause were eligible. Subjects who agreed to join the study and signed the informed consent were enrolled. To consolidate the diagnosis, only subjects with recurrent (at least two) attacks were analyzed. This study did not treat cerebral vasoconstriction as a secondary cause to delineate its clinical significance.

Taipei-VGH is a 2,902-bed national medical center that serves both veterans and nonveteran citizens. This hospital is located in Taipei, which is both the capital and a major urban center in Taiwan, with a population of approximately 2,620,000 in 2005. The headache clinic of Taipei-VGH has been operating since 1997. All patients presenting at the clinic must fill out a detailed headache intake form, have their medical and headache history taken, and complete clinical investigations and neurologic examinations. The patients would also be asked to keep a headache diary to provide a guide for diagnosis and treatment. The pain intensity is evaluated using an 11-point verbal numeric scale (0 = no pain, 10 = the worst pain). Every patient receives additional investigations tailored to his or her clinical diagnosis.

**Neuroimaging studies.** Besides the screening brain CT for some of the subjects, all patients with suspected recurrent thunderclap headache underwent both MRI and magnetic resonance angiography (MRA) studies on 1.5 Tesla. Intracranial aneurysms that have been reported in the literature were carefully evaluated with adequate magnetic resonance (MR) sequences, e.g., SAH with gradient-echo T2 image and fluid-attenuated inversion recovery image, and intracranial aneurysms with three-dimensional time-of-flight MRA. This study used similar methods detailed by a Belgium group to interpret vasoconstriction of MRA images, with a sensitivity of 92%, specificity of 98%, and accuracy of 96%. Segmental vasoconstriction, designated as MRA vasoconstriction, was considered if lumen narrowing > 25% of diameter was detectable at least a short segment of vessels. For subjects with suspected segmental vasoconstriction on first MRI/MRA, at least one MRA follow-up was performed to assess the reversal, progression, or persistence of the vascular abnormalities. The follow-up intervals depended on patient clinical condition and MR scan availability. The results were interpreted by two experienced neuroradiologists (J.-F.L. and F.-C.C.). It is known that MRA has not replaced the gold standard of conventional angiography in evaluating cranial vasculature. Vasoconstrictions at the distal branches of cerebral arteries may not be detected in MRA images; therefore, “not seeing vasoconstrictions on MRA” is not completely equal to “no vasoconstriction.” However, this study chose MRA to investigate cerebral vasoconstrictions because of its acceptable sensitivity, safety, and noninvasiveness for frequent follow-ups.

**Follow-up.** Except for spontaneous headache resolution before presenting to our clinic, all patients received nimodipine treatment. The dosing protocol has been described previously. The efficacy of the nimodipine treatment was recorded as “response” if no further thunderclap headache occurred in 48 hours after the last dose escalation. Presence of mild baseline headaches was allowed.

**Data collection.** The following information was collected: demographics; age at headache onset; previous headache history; previous medical history; non-steroidal anti-inflammatory use; hormone therapy; headache localization, location, intensity, quality, triggers, relieving factors, frequency, duration, and accompanying symptoms; focal neurologic signs; neuroimaging findings; treatment effect; and follow-up results. The presence or absence of accompanying blood pressure (BP) surge was recorded and was defined as systolic BP > 160 mm Hg during headache attacks and > 20 mm Hg higher than that in a previously normotensive person may cause hypertensive encephalopathy. To test the significance of segmental...
Figure 1. Diagnostic scheme of thunderclap headaches with or without magnetic resonance angiography segmental vasoconstriction.
Table 2 Comparison of relevant triggers of thunderclap headache between patients with and without MRA vasoconstriction

| Triggers      | Total (n = 56) | PV (n = 22) | PN (n = 34) | p Value
<table>
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<tr>
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<tbody>
<tr>
<td>Exertion</td>
<td>30 (54)</td>
<td>17 (77)</td>
<td>13 (38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Defecation</td>
<td>18 (32)</td>
<td>11 (50)</td>
<td>7 (21)</td>
<td>0.04</td>
</tr>
<tr>
<td>Bathing</td>
<td>17 (30)</td>
<td>8 (36)</td>
<td>9 (26)</td>
<td>0.55</td>
</tr>
<tr>
<td>Anger</td>
<td>15 (27)</td>
<td>7 (32)</td>
<td>8 (24)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (20)</td>
<td>5 (23)</td>
<td>6 (18)</td>
<td>0.74</td>
</tr>
<tr>
<td>Sexual activities</td>
<td>5 (9)</td>
<td>2 (9)</td>
<td>3 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Singing</td>
<td>5 (9)</td>
<td>1 (5)</td>
<td>4 (12)</td>
<td>0.64</td>
</tr>
<tr>
<td>Loud speaking</td>
<td>2 (4)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Squatting</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Dancing</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diving</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sniffing</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Yoga</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Values represent n (%).

*p Value: PV vs PN by χ² test or Fisher exact test.

MRA = magnetic resonance angiography; PV = patients with MRA vasoconstriction; PN = patients without MRA vasoconstriction.

Treatment. A total of 52 patients were treated with nimodipine. A response was achieved in 43 treated patients (83%) within 48 hours. Nine patients (17%) did not respond to nimodipine. Although severe attacks resolved, 24 patients continued to have lingering headaches, which subsided gradually. No significant adverse effect was observed, except in 2 patients who experienced dizziness during treatment and required dose reduction.

Figure 2. Multifocal segmental cerebral vasoconstriction (black arrows) demonstrated by three-dimensional time-of-flight magnetic resonance angiography.

The average time required for headache resolution in the PV group (n = 22) was 15.9 ± 7.8 (range 7 to 32) days. However, the definite timing of the resolution of vasoconstriction was uncertain because of the availability and timing of the MRA studies. In the 20 patients who received follow-up MRA around 30 days after headache onset, 5 patients achieved complete resolution (25%), 9 achieved partial resolution (45%), and 6 had no improvement (30%). Overall, the mean duration (calculated based on the timing of follow-up MRA) of partial resolution was 33 ± 24 (range 11 to 108) days (n = 16), whereas that of complete resolution was 63 ± 52 (range 13 to 157) days (n = 9). Notably, none of these follow-up MRI and MRA images showed SAH or aneurysms.

Follow-up. The mean follow-up duration was 30.5 ± 19.3 (range 3 to 69) months. Only one patient experienced two relapses of thunderclap headaches in the 25th and 69th months after the first attack. No patients developed SAH. Posterior leukoencephalopathy or ischemic stroke was noted in three patients (14%) on days 6, 20, and 36 in the PV group. All the infarctions were located in the watershed zones corresponding to the areas of posterior leukoencephalopathy. The PN group contained only one patient (3%) complicated with discrete asymmetrical small ischemic infarctions, at the bilateral thalami, occipital lobe, and cerebellum, which were not located in watershed zones and were most likely due to embolism. Among subjects with ischemic complications, all recovered well without sequelae, except that one patient left with permanent left homonymous quadrantanopsia.*

Comparisons between PV and PN groups and field-testing of the ICHD-II criteria. The age and sex distribution, frequency of medical illnesses, previous headache disorders, menopausal status (table E-1 on the Neurology Web site at www.neurology.org), headache laterality, headache location (table E-2), mean duration of single thunderclap headache attack, total number of attacks (figure E-1), presence of BP surge, and frequencies of associated symptoms were similar in both groups. The PV group generally had higher frequencies of triggers, but the difference was noted only in exertion and defecation (table 2). Additionally, the PV group was more likely to develop ischemic complications than the PN group, but the difference was not noted (14% vs 3%, p = 0.29).

Regarding the ICHD-II diagnostic criteria for primary thunderclap headache (Code 4.6, table 1), all patients in the PN group (n = 34) completely fulfilled Criteria A and B1 (100%). Meanwhile, for Criterion B2, “lasting from 1 hour to 10 days,” only 26 (76%) patients fulfilled this criterion when referring to the duration of “a single headache,” whereas 18 (53%) fulfilled it when referring to “the total period of all attacks.” The description in Criterion C, “headaches do not recur ‘regularly’ during subsequent weeks or months,” was not clearly described. With regard to the diagnostic criteria of benign (or reversible) angiopathy of the CNS (Code 6.7.3, table 1), all but three of the patients in the PV group fulfilled the criteria well, and the three who did not fulfill the criteria developed neurologic deficits after repeated attacks of thunderclap headaches rather than simultaneously, as depicted in Criterion C1.
Discussion. After excluding secondary causes, we found that patients with recurrent thunderclap headache without known causes displayed a consistent clinical presentation either with or without cerebral vasoconstriction seen on MRA. Most patients were women (91%) and middle aged (80%), and there was at least one trigger in most cases (84%). These findings differed from those reported in previous studies on thunderclap headache (female ratio: 54% to 57%; trigger: 22% to 34%; recurrent attacks in a short period: 9% to 24%). The discrepancy might be attributed to the fact that this study recruited only patients with recurrent attacks and might thus have extracted a more homogenous group. In fact, several small case series reported clinical pictures similar to the present study cohort.

The disease was generally self-limited: all headache attacks subsided within 3 months, and the accompanying MRA segmental vasoconstrictions, if present, resolved after headache resolution. However, ischemic complications could occur in selected cases. Besides the ischemic complications, patients with delayed diagnosis might experience repeated severe intractable headaches, frequent emergency department visits, and possible ischemic complications. Consequently, recognition of this headache disorder is important. MRI and MRA should be considered the study of choice not only to screen out miscellaneous intracranial causes but also to assess cerebral vasoconstriction. Early treatment with nimodipine can at least abort further attacks in most patients, as in the present study.

Except for the frequencies of exertion and defecation as related triggers, no difference was noted between patients with or without MRA segmental vasoconstriction. Additionally, because segmental vasoconstrictions seen on MRA could persist days to months after headache resolution, the headache could not be considered directly attributed to vasoconstriction (or angiopathy) as the statement of the criteria for benign angiopathy of CNS (ICHD-II) suggests. Because we do not know for sure whether the vasoconstriction is angiopathy or vasospasm, segmental vasoconstriction defined by angiographic findings is best reserved as a neutral term until proven otherwise.

The current ICHD-II criteria of primary thunderclap headache did not provide a precise definition of “duration” in Criterion B2. Specifically, it remains unclear whether this term refers to the duration of a single headache or to the total disease course. To increase the sensitivity, this study’s results suggest adopting a wider range of duration as 30 minutes to 1 week if untreated for a single attack and from days to 3 months for the whole disease course. Additionally, because repeated attacks are the rule during the first weeks but not after 3 months, Criterion C can be revised as “headaches do not recur after 3 months” or alternatively can simply be removed. In contrast, the majority of patients with MRA segmental vasoconstrictions in this study closely fit the criteria of benign angiopathy of CNS. A minor suggestion was to revise Criterion C1 to “neurologic deficits developed following repeated headache attacks.”

The exact underlying mechanisms of thunderclap headache and its relationship with vasoconstriction are unknown. The finding of this study that nimodipine is effective in both patients with and without MRA vasoconstriction suggests that vasoconstriction might not be the sole mechanism underlying the headaches. In contrast, the BP surge and the triggers with elevated sympathetic tone in the present cohort indicated that heightened sympathetic activities were involved in the pathogenesis, which was coherent with the previously proposed neurogenic mechanism stressing the role of aberrant central sympathetic response. Moreover, Fisher reported 10 patients with “catastrophic migraine” and first noticed a strong association between female sex hormone and this thunderclap-like syndrome. An association between hormonal fluctuations and thunderclap headaches with vasoconstriction was also noted in patients with postpartum angiopathy. In the same context, the female predominance in the present sample implies that gender and sex hormones should not be overlooked. We believe that the actual underlying mechanisms may be multifactorial and require further exploration.

References


NeuroImages

Pulsating enophthalmos in an adult patient with type 1 neurofibromatosis

A. Rufa, MD; E. Zicari, MD; A. Cerase, MD; I. M. Vallone, MD; M. T. Dotti, MD; and A. Federico, MD, Siena, Italy

A 36-year-old woman with type 1 neurofibromatosis (NF1) presented with a 10-year history of painless pulsating enophthalmos (PE) of the right eye. Valsalva maneuver induced exophthalmos. Pulsation was synchronous with heartbeat (video at www.neurology.org). Brain imaging showed right smaller sphenoid wing dysplasia (SWD) (figure). Unilateral SWD, possibly associated with orbital plexiform neurofibroma, is a cause of unilateral ocular pulsation in infancy. Enophthalmos usually results from enlargement of superior orbital fissure secondary to absence of part of the sphenoid bone. Development of intraorbital masses or spheno-orbital encephalocele may lead to exophthalmos. Adult onset is uncommon. It is rare that PE is the only symptom, as in this patient.2

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