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Thunderclap headache attributed to reversible cerebral vasoconstriction: view and review

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Abstract Thunderclap headache attributed to reversible cerebral vasoconstriction (THARCV) is a syndrome observed in a number of reported cases. In this article we reviewed this new headache entity (idiopathic form) using the clinical-radiological findings of 25 reported patients. In this series of patients 72% were women, the mean age at the onset of first headache episode was 39.4 ± 2.3 years. In addition to the *sine qua non* condition of being abrupt and severe (thunderclap) at the onset, the headache was usually described as being explosive, excruciating, or crushing. The feature of pulsatility, accompanied or not by nausea was described by 80% of the patients. Forty percent of the cases manifested vomiting and 24% photophobia. Usually the headache was generalized, and in three cases it was unilateral at least at the onset. In 21 of 25 patients (84%) there was at least one recurrence or a sudden increase in the intensity of the headache. A past history of migraine was present in 52% of the patients. Precipitating factors were identified in 56% of the patients. Sexual intercourse was described by six patients. Of the 25 patients with THARCV syndrome studied, 12 (48%) developed focal neurological signs, transitory ischemic attack ($n = 1$), or ischemic stroke ($n = 11$, 44%), and two (8%) of them manifested seizures. The THARCV syndrome is a neurological disturbance perhaps more frequent than expected, preferentially affecting middle aged female migraineurs, and having an unpredictable prognosis, either showing a benign course or leading to stroke.

Keywords Headache · Vasospasm · Stroke · Thunderclap headache · Pathophysiology · Criteria

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Introduction

Thunderclap headache attributed to reversible cerebral vasoconstriction (THARCV) is a clinical-radiological entity observed in a number of cases reported since 1978 [1]. The THARCV syndrome may include several of the patients experiencing thunderclap headache [2–8], headache associated with sexual activity [2, 8–12], isolated benign cerebral vasculitis [13, 14], or migranous vasospasm or stroke [15–17].

It is widely accepted that the aura of a migraine crisis is associated with a vasoconstriction or vasospasm in the arterial territory of the aura-related cerebral cortex, which seems to be correlated with spreading depression, oligemia, or both [18–21]. In rare situations this arterial constriction is severe enough to cause brain ischemia [15–17]. Other conditions may induce much longer and

intense cerebral artery narrowing [22–44], such as: subarachnoid hemorrhage (SAH; largely the leading cause of cerebral vasospasm) [22], drug abuse or sympathomimetic drug administration (methamphetamine, heroin, ephedrine, and cocaine) [23–25], intracranial surgical manipulation [26], head injury [27], herpes zoster [28], pheochromocytoma [29], eclampsia [30], ergot derivatives [31], angiographic contrast material [32], Lyme disease [33], systemic lupus erythematosus (SLE), periarteritis nodosa, primary granulomatous angiitis of the central nervous system (GACNS), and other types of cerebral arteritis [34–36]. Some of these disorders may course with headache as well.

Intracranial aneurysm rupture is a relative frequent event ($\approx 10/100,000$/year) and it is very important to identify those high-intensity headaches of abrupt onset mimicking that of ruptured cerebral aneurysm. Primary thunderclap headache (4.6) and reversible cerebral vasoconstriction syndrome (6.7.3) are two clinical entities that may simulate a headache associated with subarachnoid hemorrhage [45]. The combination of both—thunderclap headache and reversible cerebral vasoconstriction—is being increasingly identified in a number of patients assisted in the emergency unit [44].

According to the IHS 2004 classification [45], the diagnostic criteria of *primary thunderclap headache* are the following: (A) severe headache fulfilling criteria B and C; (B) Both of the following characteristics: (1) sudden onset, reaching maximum intensity in <1 min; (2) lasting from 1 h to 10 days; (C) irregular occurrence over subsequent weeks or months and (D) not attributed to another disorder. The headache may recur within the first week after onset and a normal cerebrospinal fluid (CSF) and normal brain imaging are required.

On the other hand, the IHS 2004 criteria for headache attributed to benign (or reversible) angiopathy of the central nervous system are: (A) diffuse, severe headache of abrupt or progressive onset, with or without focal neurological 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 neurological 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 [45].

In the present article, we review the concept of this new headache syndrome (i.e., THARCV) using the clinical-radiological findings of 25 patients. Considering the management of patients with the THARCV syndrome, we shall discuss the diagnostic criteria and the differential diagnosis.

Review of reported patients

A Medline[TM] search was performed using the English keywords: thunderclap headache, explosive headache, sudden headache, headache and vasospasm. Patients with a clear history of thunderclap headache and angiograph confirmation of cerebral vasoconstriction were selected to be studied as a group.

In order to achieve a more uniform diagnosis of the THARCV syndrome we propose the diagnostic criteria listed in Tables 1 and 2. Since we consider the THARCV as a secondary form of headache attributed to the reversible cerebral segmental vasoconstriction it is further divided into (I) idiopathic, or (II) symptomatic headaches.

The medical literature until 2003 was reviewed, and 25 reported cases of patients (Table 3), including the one described by our own group, were selected according to the proposed diagnostic criteria for idiopathic THARCV syndrome (Table 2). Although several other cases were published in the recent years, we believe those 25 individuals represent a sample of the increasing number of THARCV cases described in the literature.

Analysis of the data shown in the Table 3 shows a profile of this particular headache subtype. In this series of patients, 72% were women, the mean age at the onset of first headache was 39.4 ± 2.3 years, ranging from 19 to 62 years (women, 26–62 years of age, mean 41.4 ± 2.7, median 38.5; men, 19–49 years of age, mean 34.1 ± 4.2, median 31.0). No significant difference in age was observed between women and men (Student t-test; $P = 0.1665$). Eight percent of the patients were 16–25 years of age, 28% 26–35 years of age, 32% 36–45 years of age, 24% 46–55 years of age, and 8% 56–65 years of age.

The characteristics of the headache described, in addition to the *sine qua non* condition of being abrupt and severe at the onset, differed according to patient description. The duration of the headache attack ranged from a short period of time, i.e., 10–15 min, to as much as 3–4 weeks (Table 4). In approximately half of the cases the headache persisted up to 3 days. In one-third of the patients the pain continued for a few hours (less than 24 h). The

Table 1 Proposed classification of reversible cerebral vasoconstriction syndrome as idiopathic or symptomatic

I	Idiopathic
II	Symptomatic
IIa	Associated with intracranial abnormalities other than cerebral vasoconstriction (i.e., aneurysm, vascular malformation, brain tumor, hemorrhage, venous thrombosis, etc.)
IIb	Associated with systemic diseases
IIc	Associated with use of vasoactive drugs
IId	Associated with pregnancy

Table 2 Proposed diagnostic criteria for thunderclap headache attributed to idiopathic reversible cerebral vasoconstriction (THARCV) syndrome

A. At least one headache attack with the following characteristics

    1. Abrupt and explosive headache

    2. Severe

B. Presence of reversible intracranial arterial narrowing

C. No association with conditions such as

    1. Vascular malformation, aneurysm, subarachnoid hemorrhage, CNS vasculitis or trauma

    2. Pheochromocytoma, systemic vasculitis

    3. Use of illicit drugs or other known vasoactive (constrictor) substances

    4. Pregnancy, post-partum or eclampsia

Obs.: the following characteristics when present strongly suggest THARCV syndrome: (a) female sex, (b) pulsating quality, (c) recurrence of headache, (d) precipitation or aggravation of the headache attack by physical or sexual activities, and (e) past history of migraine

quality of being explosive, excruciating, pounding, or crushing was registered. Other headache features were reported, such as throbbing, pulsatility, or pounding (68%), being accompanied by nausea (44%), vomiting (40%), and photophobia (24%). Furthermore, some of the patients manifested blurred vision (8%). The headache was described usually as generalized (32%) and bilateral; in three cases it was unilateral at least at the onset.

In 21 of the 25 patients (84%) there was at least one recurrence or a sudden increase in headache intensity. Three or more recurrences were observed in five individuals (Table 4). The time interval between the first headache and recurrent attacks varied from a few hours up to 3 years. In 15 of 21 patients, recurrence was observed within the first week, and in one patient five such recurrences took place within this short period of time. In seven patients, recurrence was observed on the first day after the onset of headache. In three it occurred from 8 to 30 days. Two patients presented several headache recurrences within a 2–4 year-period.

A past history of headache was present in 15 of the 25 reported cases (Table 4), including migraine in 13 patients (52%), at least four of them with aura, one associated with hormonal contraceptives and another after headaches that had begun 8 years before during the first trimester of pregnancy.

Precipitating factors were identified by 14 patients (56%; Table 5), with sexual intercourse being the major precipitating factor, reported by six patients (24%). Of the 25 patients with THARCV syndrome studied, 12 (48%) developed focal neurological signs, transitory ischemic attack ($n = 1$), or ischemic stroke ($n = 11$, 44%), and two (8%) of them manifested seizures. Two other patients presented seizures that were not related to stroke. Stiffness of the neck was observed in one patient.

Probably cerebral artery narrowing was present for several days after the onset of headache. In the different reports vasoconstriction was diagnosed by arteriography between two days and three weeks after the onset of

headache in 18 of the reported cases. Even though the cerebral vasoconstriction was confirmed by angiography in all 25 patients, in the other seven cases the interval between the headache and the observed vasoconstriction was not informed. In seven patients a control angiography, performed 3–24 weeks later, was normal. In seven other patients a second angiography performed 2–32 weeks later demonstrated that most of the previously identified focal narrowing had resolved. In one case (patient # 8 in Table 3) an arteriography done 16 days later still demonstrated diffuse arterial narrowing. In another patient (# 9 in Table 3) an arteriography was repeated 15 days later showing normalization of the previously stenotic left internal carotid, but disclosing another arterial narrowing in the right internal carotid. Any of the intracranial major arteries can be affected; in one subject (patient # 2 in Table 3) the external carotid artery was examined, disclosing involvement of the superficial temporal artery in addition to the presence of intracranial artery narrowing.

No drastic abnormalities were observed in the CSF of patient with THARCV syndrome, with the exception of an eventual increase in protein levels.

Discussion

In this article we described the clinical and radiological features of 25 reported cases of patients with a neurological syndrome characterized by THARCV.

The management of patients with the THARCV syndrome can be subdivided into pathophysiology determination and diagnostic and therapeutic strategies.

Diagnosis and initial management

The headache of the THARCV syndrome typically is of acute onset and increases abruptly in severity, reaching

Table 3 Clinical and radiological characteristic of 25 reported cases of patients with thunderclap headache attributed to idiopathic reversible cerebral vasoconstriction syndrome

Patient #	Ref. #	Age/gender	History of migraine	Headache and other characteristics	Duration	Precipitating factor	Recurrence	Arteriography (time after headache)	Arterial narrowing	Side	Ischemic stroke	Seizure	Others
1	1	27 F	NR	Bifrontal, generalized, throbbing, nauseas, vomiting	Several hours	Sneeze	1	2 days	Diffuse, AC, PC	bil.	Yes	No	Penicillin hypersensitivity
2	13	39 F	Yes	Pulsatile, nausea	7 days	NR	No	11 days	MCA, ACA, STA	bil.	Yes	Yes	
3	37	30 F	Yes	Occipital, nausea, vomiting, abdominal cramps, passage of several diarrheal stools, photophobia	13 days	NR	3	3 weeks	Diffuse, AC, PC	bil.	NR		Worsed with propranolol
4	38	51 F	NR	Throbbing occipital	48 h	NR	1	9 days	Difuse?	Left	Yes	No	Diabetic hypertensive, steroid therapy
5	38	25 M	Yes	Throbbing, forehead bilaterally extending down behind the eyes, photophobia, vomiting	1 h to few days	Sit ups, push-ups, skipping rope	Several	12 days	Parieto-occipital arteries	Left	Yes	No	
6	39	48 F	No	Sense of spinning, nausea, vomiting, blurred vision		NR	1	4 days	Diffuse, AC, PC	bil.	Yes	Yes	3 strokes, cortical cerebral artery biopsy normal
7	39	37 F	Yes	Left-side, losing consciousness	6 days	No	No	12 days	Diffuse, AC, PC	bil.	Yes	No	
8	39	19 M	NR	Awoke with a frontal and bitemporal headache, nausea, vomiting, photophobia	More than 16 days	Worsened following angiogram	1	5 days	Diffuse, AC, PC	bil.	TIA	No	
9	16	27 F	Yes	Throbbing bitemporal, associated with acute onset of right hemiparesis and expressive dysphasia		NR	7	Few days	ICA at C1 vertebral level	Left	Yes	No	Stroke 4 days after discharged with amitriptyline
10	12	30 M	NR	Throbbing occipital; generalized	6 h	Sexual intercourse, exertion	1	76 h	Diffuse, AC, PC	bil.	No	No	
11	10	55 F	NR	Bifrontal, throbbing that later became a dull ache, vomiting	Few hours to 10 days	Orgasm	Several	10 days	Diffuse, AC, PC	bil.	No	No	Improved with clonidine
12	40	36 F	Yes	Throbbing, occipito-nuchal, quichly extended over the entire head and face	3 days	NR	1	8 days	VA + ACA + PCA	bil.	No	No	Prophylactic therapy with propranolol
13	41	30 F	Yes	Abrupt exarcebation with nausea and vomiting, throbbing pain in the right temple	>24 h	Get up to drank some lemonade	No	NR	Calcarine artery	Right	Yes	No	
14	14	31 M	Yes?	Associated with vomiting	9 days	NR	1	NR	SCA, MCA	bil.	No	No	

Table 3 continued

Patient #	Ref. #	Age/gender	History of migraine	Headache and other characteristics	Duration	Precipitating factor	Recurrence	Arteriography (time after headache)	Arterial narrowing	Side	Ischemic stroke	Seizure	Others
15	14	37 F	NR	Abrupt, severe headache	Few hours	NR	1	NR	ACA, MCA	bil.	No	Yes	Asthma Hypothyroidism + levothyroxine
16	42	26 F	Yes	Pounding, nausea, vomiting, that worsened by standing up associated with visual blurring and photophobia	Several days	NR	NR	Few days?	ACA + MCA	bil.	No	No	
17	9	44 F	Yes	Explosive, throbing, global	3 h	Sexual intercourse	1	NR	Diffuse	bil.	Yes	No	Familiar history of sex headache. Hormone replacement. Papilloedema with arteriolar narrowing
18	7	55 F	Yes	Nausea, vomiting, shooting pain in the right occipital, entire cranium	Few hours to 2 days	Straining, bending	4	NR	Diffuse, AC, PC	bil.	Yes?	No	
19	7	62 F	Yes	Throbbing, explosive, nausea, supraorbital	1–10 days	Exposure to cold, bending	2	>5 days	ACA + MCA	bil.	No	No	Atrial fibrillation
20	7	60 F	Yes	Excruciating, pulsatile, nausea, photophobia		NR	1	NR	Diffuse, AC, PC	bil.	?	Yes	Lung carcinoma
21	7	38 M	NR	Acute exacerbation of a bifrontal throbbing headache, explosive		Arngiogram	1	3 days	MCA, AComA, PCA	bil.	Yes	No	Prophylactic therapy with propranolol. C6 quadriplegia (diving injury)
22	2	49 M	Yes	Generalized, throbbing, nausea, photophobia, crushing	At least 3 h	Swimming, snorkeling	1	6 days	Diffuse, AC, PC	bil.	No	No	
23	2	47 M	No	Holocephalic	Few hours	Sexual intercourse	1	7 days	Diffuse, AC, PC	bil.	No	No	
24	11	38 F	No	Pulsatile, vertex	3 days	Sexual intercourse	1	>6 days later	Diffuse, AC, PC	bil.	No	No	Past history of neurocysticercosis
25	8	44 F	Yes	Generalized, throbbing	10–15 min	Sexual intercourse, masturbation	1	6 days	MCA	Right	No	No	Posterior fossa arachnoid cyst

AC anterior circulation, *PC* posterior circulation, *MCA* middle cerebral artery, *ACA* anterior cerebral artery, *STA* superficial temporal artery, *ICA* internal carotid artery, *VA* vertebral artery, *PCA* posterior cerebral artery, *SCA* superior cerebelar artery, *PComA* posterior communicating artery, *bil.* bilateral

Table 4 Duration, location, characteristic, number of occurrence of the headache, and past-history of headache in the 25 patients reported with THARCV syndrome

	n	%
Duration[a]		
<24 h	10	40
24 h–3 days	5	20
4 days–7 days	3	12
>7 days	7	28
Location		
Generalized	8	32
Unilateral	3	12
Frontal	5	20
Occipital	4	16
Fronto-temporal	1	4
Temporal	1	4
Vertex	1	4
Characteristic		
Abrupt onset	25	100
Severe intensity	25	100
Throbbing, pulsatile, or pounding	17	68
Nausea	11	44
Vomiting	10	40
Photophobia	6	24
Explosive	3	12
Blurred vision	2	8
Dull ache	1	4
Excruciating	1	4
Crushing	1	4
Sense of spinning	1	4
Losing consciousness	1	4
Number of recurrences		
None	4	16
1	15	60
2	1	4
3	1	4
4	1	4
7	1	4
>7	2	8
Past history of headache	15/25	60
Migraine	13	52
With aura	4	16
Without aura	3	12
Unclassified	6	24
Tension-type headache	1	4
Associated with CCD	1	4
Associated with pregnancy	1	4

CCD contraceptive drug

[a] Some of the patients presented recurrent headaches of different duration

Table 5 Precipitating factors identified in 14 of the 25 reported cases of patients with THARCV syndrome

Precipitating factor	n	%
Sexual intercourse	6	24
Exertion[a]	5	20
Angiography	2	8
Sneezing	1	4
Exposure to cold	1	4
Total number of patients	14/25	56

[a] Activities defined as exertion were calisthenics (i.e., sit ups, push-ups, and skipping rope), getting up from bed, straining, bending, swimming, snorkeling, and chasing off and screaming at an attacking dog

peak severity in less than 60 s (thunderclap headache) [46]. The pain can be precipitated or aggravated by physical or sexual activities. The duration of the headache can be 5 min or longer. Thus, we propose some minor changes in the thunderclap diagnostic criteria modified by Dodick et al. [2]: (a) time to reach peak severity up to 60 s; (b) headache duration of 5 min or longer, since the explosive type of headache occurring during sexual activity is considered to be a thunderclap headache [46] and may be of short duration. Even though the International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria stipulate that the pain of primary thunderclap headache last from 1 h to 10 days (Code 4.6) [45].

We could subdivide the THARCV syndrome into idiopathic and symptomatic. The symptomatic THARCV syndrome should fulfill the A and B items of the proposed diagnostic criteria, and is categorized into four subgroups: (IIa) associated with intracranial abnormality (vascular malformation, aneurysm, subarachnoid hemorrhage, CNS vasculitis or trauma); (IIb) associated with systemic disease (e.g., pheochromocytoma or systemic vasculitis); (IIc) associated with drug abuse and use of vasoactive drugs (e.g., ergotamine, cocaine, heroin, methamphetamine, ephedrine, tryptans, intravenous use of contrast substances); or (IId) associated with pregnancy, post-partum or eclampsia. As exclusion criteria we consider the presence of systemic vasculitis or a central nervous system (CNS)-meningeal biopsy showing inflammatory features related to CNS vasculitis.

More specifically, during the management of a patient with a thunderclap headache, as a general rule a CT brain scan without contrast is required. If a diagnosis is not made by this CT, lumbar puncture and CSF examination is mandatory during the acute phase to rule out any intracranial symptomatic lesion, particularly SAH and its causes. Both the CT scan and CSF are expected to be normal, with the exception of patients with stroke, cerebral

edema, or intracranial hypertension, in which CSF abnormality is the result of these complications. Conventional cerebral angiography should be avoided, since the contrast medium could enhance the vasospasm and this, in turn, would increase the chance of a stroke or even cause the deterioration of a previously critical neurological condition, particularly in migraineurs [16, 47]. The next step would be the request of a good-quality magnetic resonance (MR) angiography or angio-computed tomography (CT) of intracranial vessels as soon as possible, in such a way that any moderate to severe (reversible) vasoconstriction would be visualized. The conventional arteriography should be performed later, 3–4 weeks after the last severe headache attack. During the arteriography a study of the external carotid artery and its branches should be included in an attempt to find a segmental narrowing in a superficial artery. This could allow an easier (extracranial) approach to an eventual vessel biopsy.

Patients with thunderclap headache in the absence of cerebral vasospasm have been reported [48, 49]. This probably is factual, but the possibility of a short-lived cerebral arterial spasm occurring only at the onset of or during headache still needs to be excluded. Rothrock et al. [16] discussed why delayed arteriography would miss a transient spasm/stenosis to confirm migrainous stroke, to justify the lack of abnormality found in angiograms of patients who developed stroke during a migraine attack.

Differential diagnosis

The idiopathic THARCV syndrome is a disease with cerebral vasoconstriction. Hence, all the other possibilities that could provoke an intracranial arterial narrowing should be taken into account. The lack of systemic features enhances the possibility of a given arterial luminal narrowing to be part of the more benign THARCV syndrome when compared with CNS vasculitis, in which no resolution of the vascular disease is expected without adequate treatment. Although reversibility of intracranial arterial narrowing is anticipated in the THARCV syndrome it may take weeks to happen. Even though the reversibility of the vasoconstriction is not important during the initial diagnostic criteria, the reversibility of the condition needs to be proved, as the syndrome is called reversible. Since this has not always been made in previous studies as well as in IHS 2004 classification [45], the confirmation of the reversibility of the vasoconstriction should be included in the final diagnostic criteria, thanks to the reliability of less expensive or invasive techniques (e.g., angio-RM or angio-CT).

In the discussion of some of the particularities that should differentiate the THARCV syndrome from other identified causes of arterial narrowing we may mention some features, particularly those concerning CNS vasculitis [37], a rare inflammatory disease of vessel walls associated with many causes (i.e., infection, malignancy, ionizing radiation, drug abuse, and autoimmune disease). Since angiographic features in cerebral arteritis are not completely specific, the associated radiologic and clinical findings often are fundamental elements for a diagnosis [34]. Narrowing of a vessel may be the result of spasm, edema, cellular infiltration, or proliferation of the vessel wall as well as compression by adjacent thickened meninges, exudates, or fibrosis [34].

Cerebral arterial narrowing might be subdivided into four groups: (1) vasospasm (contraction of arterial smooth muscle); (2) thickening of the vessel wall; (3) extrinsic compression; and (4) developmental or congenital [40]. Very probably the THARCV is a form of headache attributed to reversible cerebral vasoconstriction syndrome (benign or reversible angiopathy of the CNS, ICHD-II Code 6.7.3) [39, 45].

According to the IHS 2004 criteria for *headache attributed to benign (or reversible) angiopathy of the central nervous system,* a severe headache of progressive onset occurring during the clinical presentation of the syndrome is permitted [45]. In the present article we intend to study the thunderclap headache attributed to reversible cerebral vasoconstriction syndrome. Furthermore, we do not agree with the IHS D criterion [45]: "Headache (and neurological deficits, if present) resolves spontaneously within 2 months". It is well known that an ischemic stroke may course with permanent neurological deficit.

Mechanical, biochemical, or neurogenic causes may explain the arterial spasm. Vasoactive substances may cause vasospasm, such as chemical substances (ergotamine, amphetamine, cocaine), metabolite substances (in eclampsia or pheochromocytoma), and toxins (angiographic contrast material) [40].

In the group of autoimmune mediated diseases we may mention primary GACNS, SLE, polyarteritis nodosa, giant cell arteritis, and Sjögren syndrome. The physician should also search for other conditions that are known to cause vasculitis, such as drug hypersensitivity, cancer, infection, rheumatoid arthritis, and inflammatory bowel disease [36]. Noninfectious vasculitides can be classified on basis of the predominant type of vessel affected: large-vessel vasculitis (giant-cell arteritis and Takayasu′s arteritis), medium-sized-vessel vasculitis (polyarteritis nodosa, Kawasaki′s disease, and primary GACNS vasculitis), and small-vessel vasculitis (ANCA-associated small-vessel vasculitis, immune-complex small-vessel vasculitis, paraneoplastic small-vessel vasculitis, and inflammatory bowel disease vasculitis) [36]. Infectious arteritis includes bacterial, tuberculous, fungal, yeast, luetic (meningovascular

syphilis), cysticercosis, rickettsia, and viral disorders [34]. Sarcoidosis and chemical and radiation arteritis should also be kept in mind.

Primary granulomatous angiitis of the CNS is a process usually restricted to vessels of ≤0.5 mm diameter, an arteriopathy that frequently is not visualized by angiography. But this inflammatory disorder may also involve large cerebral vessels [37]. The diagnosis of isolated angiitis of the CNS should be taken into consideration if the patient is young, presenting focal neurological signs, seizures, or constant severe headache. Without treatment (i.e., glucocorticoid) the clinical course of the GACNS, as may be expected, is often progressive. To establish a definitive diagnosis a leptomeningeal biopsy is necessary [14, 50]. To decide which patients are candidates for biopsy it does depend on the gravity of the neurological picture, the functional importance of the cerebral artery to be biopsied, and lack of response to corticoid therapy.

Similar segmental narrowing was also reported in atypical cluster headache involving proximal portions of the middle and anterior cerebral arteries [51]. Additionally, hyperventilation induced by pain might cause vasoconstriction as well [52].

Several cases of women with preeclampsia-eclampsia and a history of sudden, severe headache accompanied by cerebral artery narrowing have been reported previously [30, 39, 53]. Preeclampsia is a frequent disorder characterized by hypertension, abnormal peripheral edema, and proteinuria. Most of the patients experience neurological signs and symptoms, such as headache, visual changes, confusion, disturbances of consciousness, or seizures. Such manifestations of the disease are identical to those of hypertensive encephalopathy. Clinical and radiographic signs of hypertensive encephalopathy probably are related to the consequences of an acute increase in systemic blood pressure, which, in turn, would affect the autoregulation of the cerebral vasculature.

Call et al. [39] reported four patients with reversible cerebral segmental vasoconstriction and concluded that their cases may represent a severe "clustering" form of migraine. These authors identified 12 other cases reported in the literature with clinical and angiographic similarities to their four cases, six occurring in the postpartum period, five being idiopathic, and one associated with an unruptured aneurysm. The cited authors also commented that the clinical feature of presentation resembles the rupture of an intracranial aneurysm, with a sudden, high-intensity headache associated with nausea, vomiting, and photophobia. In six cases biopsy or autopsy of one vasoconstricted artery disclosed no anatomic abnormalities.

On the other hand, the occurrence of vascular abnormality (narrowing) in young women and during the postpartum period, strongly suggests a hormonal influence exerted by sex steroids [39].

Cerebral postpartum angiopathy was described by Rascol et al. [54] in four women with distal arterial occlusion. None of them had arterial hypertension or renal disease. Hansen et al. [55] evaluated the effect of preeclampsia on cerebral artery blood flow velocity and concluded that cerebral vasospasm of the smaller diameter vessels is a major component of preeclampsia. Trommer et al. [30] reported that eclampsia might cause spasm of large- and medium-caliber cerebral vessels. They described the case of a 27-year-old woman, who 15 min postpartum complained of headache, nauseas, and epigastric pain and whose cerebral angiogram showed diffuse spasm.

Henry et al. [31] reported the case of a 34-year-old woman that during delivery, 10 min after receiving an intravenous administration of methylergometrine, experienced violent headache, associated with vomiting and arterial blood hypertension. Hours later the patients suffered seizures and mental confusion, with evolution to coma. An arteriography revealed marked segmental narrowing of the first middle cerebral artery branch. The authors postulated that the ergot-derived drug caused vasoconstriction through noradrenergic and serotoninergic actions. This class of drugs is particularly used during labor. Additionally, bromocriptine for lactation suppression in combination with a sympathomimetic agent caused hypertension, severe headache, seizures and cerebral vasospasm in a patient during the puerperium [56]. These facts may indicate that, during delivery or the postpartum period, patients are more susceptible to administration of vasoactive drugs and this, in turn, can precipitate arterial spasm.

Sudden surges in blood pressure may trigger a cerebral vasospasm, as also observed after adrenergic stimulation by the use of cocaine [25], by pheochromocytoma [29], or eclampsia [30]. Kaye and Fainatat [25] described the case of a cocaine addict, a 22-year-man, who developed right-sided headache associated with transient blurring of his vision. Four days later he presented weakness of the left side, and an arteriogram performed 5 days after the onset of the hemiparesis demonstrated the presence of narrowing of the supraclinoid portion of the right internal carotid and the occlusion of the proximal segment of the middle cerebral artery.

Patients with pheochromocytoma usually experience bilateral paroxystic episodes of bifrontal headache, radiating to temporal regions or secondarily generalizing, described as pulsating, moderate to severe in intensity. Lying down, moving, coughing, or straining makes the headache worse [57]. The above-mentioned features are similar to the headache described by patients with THARCV syndrome, which may suggest that sudden

increases in arterial blood pressure in the presence of a cerebral arterial narrowing may trigger a headache attack [8].

Serdaru et al. [13] stated that during a migraine attack narrowing of the internal carotid artery usually involves either its extradural [18] or intracavernous [58] portion.

Pathophysiology

Two important questions should be answered: "What are the precipitants of vasoconstriction?" and "Is vasoconstriction the cause of pain?" Considering the vasospasm due to SAH and the biology of blood vessels, we could speculate about the pathophysiology of the supposed vasospasm found in THARCV syndrome.

The smooth muscle cell contraction occurring during SAH is still poorly understood. Vascular caliber may reflect adrenergic tone and sympathetic receptor sensitivity. Several factors participate in the regulation of vascular tone. The regulation of cerebral blood flow (CBF) is a fast and selective phenomenon and dramatic changes in blood flow or volume can be induced within a short period of time (seconds or minutes) regarding specific or regional brain areas either in normal [59] or abnormal (e.g., epilepsy) [60] physiologic conditions. The oscillations present in intracranial pressure are secondary to spontaneous changes in CBF velocity as a result of rhythmic changes in cerebral vessel diameter triggered by monoaminergic and serotonergic centers present in the brainstem [61].

In addition, arterial constriction followed by dilatation is postulated to be part of the pathophysiology mechanism of migraine [18]. The vascular endothelium synthesizes vasorelaxant substances, e.g., endothelium-derived relaxing factor (EDRF), acetylcholine (ACh), bradykinin, purines (i.e., ATP), histamine, vasopressin, substance P, neurokinin A and B, and prostaglandin F2α. On the contrary, endothelium-derived constricting factors may also be involved in the control of vascular tone, including serotonin, norepinephrine (NE), prostaglandin E2, thromboxane A2, leukotriene C4, endothelin (ET)-1, and ET-3. In addition, ACh releases EDRF. NE also induces release of EDRF and substance P, which seem to attenuate the vasoconstrictor response to NE. EDRF was identified as being nitric oxide (NO), which is produced by neurons, glia, and endothelium. Sympathetic nerve varicosities release NE and other putative transmitters such as ATP, neuropeptide Y (constrictor), vasoactive intestinal peptide (dilators), and calcitonin gene-related peptide (dilator) [62].

Blood-borne NE and stimulation of sympathetic nerves do not affect significantly brain circulation [63]. After chronic trigeminal ganglionectomy there was an increase in the constrictor response of pial arteries to NE [64]. Also,

inhibition of EDRF synthesis of or endothelial denudation enhances the vasoconstriction induced by NE. Likewise, acute hypertension allows the occurrence of important vasoconstrictor effects induced by sympathetic stimulation [65], indicating that, under certain circumstances, cerebral vessels may respond to noradrenergic stimuli. Interestingly, acute hypertension generates superoxide anion, which, in turn, inactivates EDRF [66]. This may reverse the ACh-induced cerebral arterial dilatation and augment cerebral vasoconstriction induced by NE, or sympathetic stimulation.

High levels of vasoactive and spasmogenic substances are present in the CSF and plasma of patients with SAH and vasospasm [22]. In the presence of SAH, endothelium-dependent relaxation is impaired by the production of potent endothelium-derived contracting factors (cyclooxygenase products of arachnoid acid and ET). Endothelin, a 21 amino acids peptide, has very potent and long-lasting constrictive effects. Many lines of evidence suggest that ET may be intimately involved in the genesis of the cerebral vasospasm. The plasma concentration of ET-1 is higher in patients with vasospasm than in patients without symptomatic vasospasm, with the peak concentration coinciding with the occurrence of the vasospasm. In isolated human cerebral artery segments, ET produced intense and sustained vascular constriction, which was inhibited by sodium nitroprusside or verapamil. The enhanced vascular tone induced by ET is resistant to NE antagonists, serotonin, isoproterenol, histamine, ACh, and angiotensin II. In canine basilar artery, calcium-channel blockers such as nicardipine and papaverine reversed the contraction induced by ET-1. The arterial contraction induced by both NE and serotonin is amplified by the addition of low concentrations of ET-1 [22]. During experimental SAH the cerebral vessels are hyperreactive to ET, indicating that in a given situation of higher reactivity of a particular segment of the cerebral arterial system (by a reason not yet known) sudden release of NE, serotonin, or any other vasoconstrictor into the circulation could precipitate a severe and long-lasting segmental arterial constriction. Or yet again, the lack of action of endogenous substances with vasodilator properties would facilitate vasoconstriction.

Nitric oxide also inhibits ET-1 synthesis. A close interaction between ET (a vasoconstrictor) and NO (a vasodilator) appears to take place and to play a major physiologic role in the control of CBF and vessel caliber. So, any disturbance that may occur in the equilibrium between constrictor and dilator factors could generate arterial spasm.

Endothelin-1 levels increase during [67–69] and between migraine attacks [67], suggesting that the peptide is implicated in the physiopathogenesis of migraine. It was reported that a variant of the ETa receptor gene modulates

the risk for migraine [70]. This may imply that migraineurs with qualitatively or quantitatively altered ETa receptor may present dysregulation of arterial tone, resulting in inadequate dilatation or constriction of cerebral vessels in response to different stimuli.

Supporting the hypothesis that NO might also participate in the genesis of pain, nitroglycerin, by provoking vasodilatation via NO formation, is able to induce in healthy subjects an immediate, short-lasting, bilateral fronto-temporal and pulsating headache, that can be aggravated by routine physical activity [71]. Intriguingly, nitroglycerin causes a more severe pain in migraine patients [72, 73]. Alteration of intracranial vessel tone and regional instability of the CBF were documented in migrainous patients during the headache-free interval [74–77]. This suggests that cerebral arteries of migraineurs might react differently to diverse stimuli. If so, this fact may justify the frequent occurrence of the syndrome in migranous subjects.

Buckele et al. [78] described the case of a 16-year-old girl experiencing an attack associated with headache, when she suddenly felt tired and faint (not well characterized if it was abrupt or severe) that was repeated several times within a period of four months. Such attacks were thought to be the expression of migraine events, in view of the slow progress of some episodes, accompanied by fatigue, drowsiness, and cold hands. An arteriogram revealed widespread intense intracranial vasospasm. The clinical course progressed to death due to intracranial hypertension and cerebral edema. No evidence of primary vascular disease was found at autopsy. This case led to the assumption that the THARCV syndrome may eventually course with atypical headache episodes or even without any pain at all, including a number of young adult patients with stroke. Most but not all the headaches associated with reversible cerebral vasoconstriction have the characteristics of thunderclap headache according to most recent findings [79]. Such reported cases were not included in our analyzed series to study better the profile of typical patients with THARCV syndrome.

Dr. Robert H. Ackerman [37] commented about the multiple areas of narrowing, beading, and sausage-shaped dilation of cerebral vessels observed during angiography of patient # 3 in Table 3 as follows: "These segmental changes are nonspecific signs that can be found in a number of primary and secondary disorders affecting the pial vessels, which lie in the subarachnoid space and receive an investiture of pia as they enter the brain." These data suggest the possibility of a local relationship between CSF, arterial vessels, and brain parenchyma to explain segmental vasospasm.

Interestingly, the pattern of the cerebral arterial spasm generated by a number of different etiologic causes has the particular feature of being segmental in nature. In addition, it is a short lasting (hours or days), reversible phenomenon.

This may suggest that the constriction of a major cerebral artery is segmental and does not involve the entire extension of the vessel, particularly during high-intensity stimulation. Are those localized vascular constrictions observed in intracranial arteries during the conditions discussed above anatomic-functional sphincters controlling local blood flow? Or is the vasospasm occurring in the THARCV syndrome primarily a sphincter disturbance?

Precipitating factors, such as sexual activity, may induce vascular changes with profound hemodynamic fluctuations, which may trigger the pain if an arterial narrowing is present. In this regard, during continuous monitoring of intra-arterial blood pressure Mann et al. [80] documented that during coitus, peaks values of up to 300/175 mmHg were registered, with a mean of 237/138 mmHg for men and of 216/127 mmHg for women, in hypertensive subjects.

Tricyclic antidepressants (i.e., amitriptyline), potent inhibitors of the neuronal uptake of NE, systemically administered to humans caused a reduction of the whole body NE spillover to plasma, due to the reduction in nerve firing rates. Propranolol had a similar effect on NE overflow [81]. Propranolol, by blocking vascular β-receptors, could impair the anticipated vasodilatation induced by activating β-adrenergic receptors. So, propranolol could facilitate a predominance of the vasoconstrictor effect. Nonselective beta-blockers can also have the adverse effect of increasing platelet aggregability. In this regard, the association of propranolol with stroke in migraineurs has been mentioned previously [82, 83]. Lance and Goadsby [84] advise to avoid the use of beta-blockers in migraineurs with prolonged aura or severe focal neurological symptoms. In this respect, three of the patients presented in Table 3 (# 4, 12, and 21) were under prophylactic use of propranolol, and patient # 3 had aggravation of the neurological manifestation after introduction of propranolol in her prescription. Similar vascular changes in reactivity to endogenous substances can happen with the therapeutic use of amitriptyline. By the way, two patients of the 11 cases described as isolated angiitis of the CNS [14] were using either propranolol (case 6) or tricyclics (case 9). Do these pharmacological substances facilitate the development of cerebral vasospasm? This question remains to be answered.

The diagnosis of a growing number of patients with the THARCV syndrome is anticipated nowadays, mainly with the broad use of the harmless CT or MR angiography and a greater knowledge of the syndrome. This study was previously presented at the Brazilian Headache Congress in 2002 [85] as a new headache syndrome named "Abrupt severe headache associated with segmental artery narrowing (ASHCAN)" [8, 86] and since then several other cases of the syndrome have been reported [44, 79, 87–89].

In conclusion, the present article was written in an attempt to better characterize the profile of the patients

with THARCV syndrome. This syndrome is a neurological disturbance; perhaps more frequent than expected, preferentially affecting migrainous middle-aged women, with an unpredictable prognosis, either having a benign course or leading to stroke.

Conflict of interest   None.

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