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Chapter 90

Neuroimaging in Trigeminal Autonomic Cephalgias

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Primary short-lasting headaches broadly divide themselves into those associated with prominent cranial autonomic symptoms, so-called trigeminal autonomic cephalgias (TACs), and those where autonomic symptoms are minimal or absent. The group of TACs comprises cluster headache (CH), paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome) (35). The concept of trigeminal autonomic cephalgias underlines a possibly shared pathophysiologic basis for these syndromes that is not shared with other primary headaches, such as migraine or tension-type headache (24). As thus far findings in functional imaging of primary headache syndromes are specific to the disease (60,54), these techniques may be helpful in unravelling the degrees of relationship between clinically analogous headache syndromes.

TACs are relatively rare when compared to migraine or tension-type headache, which is likely to be why they are poorly recognized in primary care. The most remarkable of the clinical features of CH is the striking rhythmicity or cycling of the attacks and bouts. CH is probably the most severe pain syndrome known to humans, with female patients describing each attack as being worse than childbirth. The syndrome is well defined from a clinical point of view (35) and despite the fact that it has been recognized in the literature for more than two centuries (41), its pathophysiology has been hitherto poorly understood. Neuroimaging has made substantial contributions in recent times to understanding this relatively rare but important syndrome best illustrated by the advances in understanding CH.

THE ISSUE OF VASCULAR VERSUS NEUROGENIC MECHANISMS

In contrast to migraine, where at least two experimental models have been developed and tested in clinically relevant settings by pharmacologic means, CH has not been well studied in experimental animals and developments have come directly from human studies. A comprehensive model for CH has to explain the unilateral headache as well as the sympathetic impairment and parasympathetic activation. Recent functional imaging data may allow such a model to be developed.

Despite the large number of investigations in recent years, the issue of peripheral (e.g., vessel or perivascular inflammation) versus central nervous system (e.g., hypothalamic or parasympathetic) mechanisms is still unresolved. The pathophysiologic concept of *vascular headaches* is based on the idea that changes in vessel diameter or gross changes in cerebral blood flow would trigger pain and thus explain the mechanism of action of vasoconstrictor drugs, such as ergotamine (85).

CH specifically has been attributed to an inflammatory process in the cavernous sinus and tributary veins (33,64). Inflammation has been thought to obliterate venous outflow from the cavernous sinus on one side, thus injuring the traversing sympathetic fibers of the intracranial internal carotid artery and its branches. According to this theory, the active period ends when the inflammation is suppressed and the sympathetic fibers partially or fully recover. This theory is based substantially on abnormal findings using orbital phlebography in CH patients (31,28,77) and on the fact that nitroglycerin (NTG) and other vasodilators can induce an acute CH attack (13).

However, in a study on CH patients using magnetic resonance imaging (MRI), no definite pathologic changes were found in the area of the cavernous (78). Using single photon emission computerized tomography (SPECT), parasellar hyperactivity was present in 50 (episodic) to 80% (chronic) of CH patients and in 70% of migraineurs (76). Similar findings on orbital phlebography can be seen in the cavernous region in patients with Tolosa-Hunt syndrome (29), hemicrania continua (3), SUNCT

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TABLE 90-1 Doppler Studies of Different Headache Types

Author	*Year*	*Diagnosis*	*Study Population*	*n*	*BFV Changes*
Afra et al. (1)	1995	CH	Attack/interval	19	↓
Dahl et al. (10)	1990	CH	Attack	25	↓
Kudrow (46)	1979	CH	Attack/interval	26	↓
Schroth et al. (72)	1983	CH	Attack	6	↑
Shen (75)	1993	CPH	Attack	3	↓
Shen et al. (73)	1993	CH	Attack/interval	14	↓
Shen et al. (74)	1994	SUNCT	Interval	4	Ø

BFV = blood flow velocity, CH = cluster headache; CPH = chronic paroxysmal hemicrania; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
↑ = increase; ↓ = decrease; Ø = no change.

syndrome (32,44), and chronic paroxysmal hemicrania (3,29), suggesting the changes are not specific for CH. Moreover, given the circadian rhythmicity of attacks and cycling of bouts (34,48,47), a purely vasogenic cause cannot easily explain the entire picture of CH (23). In view of the striking relapsing–remitting course (48), its seasonal variation (48), and the clockwise regularity (14), the concept of a central origin of CH needs consideration (14,45).

HEMODYNAMICS

Transcranial Doppler

Since CH was regarded as a *vascular headache* and since CH attacks may be provoked by the vasodilators histamine, NTG, and alcohol, several Doppler studies have been carried out to examine possible diameter changes in large intracerebral arteries (Table 90-1). Most studies demonstrated a bilateral decrease in blood flow velocity (BFV) in the middle cerebral artery and the anterior cerebral artery during the attack compared to the headache-free interval (1,10,46,72,74). Three studies used the elegant combination of Doppler and blood flow measurement using SPECT. Dahl et al. (10) and Afra et al. (1) demonstrated a decrease in BFV during the acute CH attack in frontal arteries but failed to show any blood flow changes. Gawel et al. (20) measured CO_2 reactivity of the major intracranial vessels and demonstrated that the CO_2 reactivity was significantly lower during the cluster period, but only in the ipsilateral anterior cerebral artery to the headache side. Using gallium SPECT, they described in three out of six patients during the active cluster period a lesion in the region of the cavernous sinus that faded as the patient moved out of the active period. They suggested that this finding may represent the cavernous sinus plexus lesion postulated as the central defect in CH. In summary, transcranial Doppler studies have shown decreased velocity in the middle cerebral artery after NTG administration and in the acute CH attack. It was also shown that this vasodilation did not alter brain blood flow.

Cerebral Blood Flow

Studies of cerebral blood flow in CH are relatively few. Most have been done with SPECT, and the results of this semiquantitative method have been quite heterogeneous, probably due to methodologic differences (Table 90-2), some reporting an increase (42,65,67,70,84), some a decrease (65,84), and some no differences in cortical blood flow (1,10,37,38,43,63,71). Di Piero and co-workers (12) studied CH patients out of the active period and normal volunteers using the cold water pressor test. They demonstrated changes in pain transmission systems, which bear more detailed examination. The fact that the alterations are also present out of the active period of the disease suggested a possible involvement of central tonic pain mechanisms in the pathogenesis of CH.

FUNCTIONAL NEUROIMAGING

Positron emission tomography (PET) may represent the best currently available technique for visualising *in vivo* changes in regional cerebral blood flow (rCBF) in humans when activations in the brain with a relatively long time constant, such as those in most headache syndromes, are to be investigated. Modern high-resolution PET scanning allows the detection of subtle changes in rCBF during defined behavioral tasks and provides an index of synaptic activity relating networks of regions to tested brain functions (17,18). CH attacks can be elicited with NTG during the active cluster period without significant side effects (13). Clinical and experimental data show NTG-provoked and spontaneous cluster attacks to be comparable (16,22), and NTG does not alter rCBF significantly (40,43). The headache can be rapidly and effectively aborted with sumatriptan. This approach therefore allows detection

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TABLE 90-2 Single Photon Emission Computerized Tomography Studies in Cluster Headache

Author	*Year*	*Diagnosis*	*Method*	*n*	*CBV Changes*
Afra et al. (1)	1995	CH	99mTC-HMPAO	19	Ø
Dahl et al. (10)	1990	CH	133Xenon	25	Ø
Henry et al. (37)	1978	CH	135Xenon	3	Ø
Hering et al. (38)	1991	CH	99mTC-HMPAO	14	Ø
Kobari et al. (42)	1990	CH	133Xenon	5	↑
Krabbe et al. (43)	1984	CH	133Xenon	18	Ø
McHenry et al. (62)	1978	CH	133Xenon	3	Ø
Nelson et al. (65)	1980	CH	133Xenon	26	↑↓
Norris et al. (67)	1976	CH	133Xenon	1	Ø
Sakai et al. (70)	1978	CH	133Xenon	9	↑
Schlake et al. (71)	1990	CH	99mTC-HMPAO	5	Ø
Wesseling et al. (84)	1989	CH	99mTC-HMPAO	8	↑↓

CBV = cerebral blood flow; CH = cluster headache. ↑ = increase; ↓ = decrease; Ø = no change.

of brain regions with increased blood flow during NTG-induced cluster attacks, focusing interest on the hypothalamic region (Table 90-3).

In 1996 the first PET study in CH was reported (40). The authors investigated only four patients and their findings supported their earlier work (39), suggesting a preference of the nondominant hemisphere, especially for the anterior cingulate cortex (ACC), in affective processing of chronic ongoing pain syndromes. These interesting results contribute to understanding central pain transmission systems, but given the small numbers, require confirmation.

Using PET in a larger patient series, significant activations ascribable to the acute CH were observed in the ipsilateral hypothalamic gray matter when compared to the headache-free state (58). This highly significant activation was not seen in CH patients out of the bout when compared to the patients experiencing an acute CH attack

TABLE 90-3 Positron Emission Tomography and Functional Magnetic Resonance Imaging Studies in Headache

Author	*Year*	*Headache Type*	*n*	*Cingulate Cortex*	*Insulae*	*Thalamus*	*Brainstem*	*Hypothalamus*
Derbyshire et al. (11)	1994	AFP	6	√	√	√	X	X
Hsieh et al. (40)	1996	CH	4	√	√	X	X	X
Weiller et al. (83)	1995	MO	9	√	√	X	√	X
Bahra et al. (7)	2001	MO	1	√	√	√	√	X
May et al. (60)	1998	Capsaicin	7	√	√	√	X	X
May et al. (57)	1998	CH	9	√	√	√	X	√
Sprenger et al. (80)	2004	CH	1	√	X	√	√	√
May et al. (56)	1999	SUNCT syndrome	1	X	√	√	X	√
Sprenger et al. (82)	2005	SUNCT syndrome	1	√	√	√	√	√
Cohen et al. (9)	2004	SUNCT syndrome	2	√	X	X	X	√
Matharu et al. (52)	2005	HC	7				√	√
Matharu et al. (50)	2004	Chronic migraine	8	√	√	√	√	X
Gutschalk et al. (27)	2002	FHM	1	Local glucose—hypometabolism				
Andersson et al. (2)	1997	MA, MO	11	No global blood flow changes				
Chabriat et al. (8)	1995	MA, MO	9	No change in 5HT2 receptor distributions				
Sachs et al. (69)	1986	MA, MO	4	Reserpine changes glucose metabolism in migraine				
Bednarczyk et al. (7)	2002	Healthy subjects	12	Local blood flow changes following nitroglycerine infusion				

AFP = atypical facial pain; CH = cluster headache; FHM = familiar hemiplegic migraine; HC = hemicrania continua; MA = migraine with aura; MO = migraine without aura; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. Capsaicin = experimental head pain using capsaicin injection; √ = demonstrated; X = not demonstrated.

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(59). In contrast to migraine (83), no brainstem activation was found during the acute attack compared to the resting state. This is remarkable, because migraine and CH are often discussed as related disorders and identical specific compounds, such as ergotamine and sumatriptan, are currently used in the acute treatment of both types of headache agents (25). These data suggest that while primary headaches such as migraine and CH may share a common pain pathway, the trigeminovascular innervation of intracranial pain-producing structures, the underlying pathogenesis differs significantly as might be inferred from the different patterns of presentation and responses to preventive agents (25).

Just as it is striking that no brainstem activation occurs in CH in contrast to acute migraine (6,83), no hypothalamic activation was seen in experimental pain induced by capsaicin injection into the forehead (61). This is important because injection into the forehead would activate first-division (ophthalmic) afferents, which are the trigeminal division predominantly responsible for pain activation in CH. Thus, two other types of first division of trigeminal nerve pain, while sharing neuroanatomic pathways with CH, do not give rise to posterior hypothalamic activation. This finding clearly implies that the activation specific to CH is involved in the pain process in a permissive or triggering manner rather than simply representing a response to first-division nociception *per se*. From the clinical point of view it is tempting to consider a trait change in the hypothalamus that is converted to a state change when the patient is in the acute bout. Furthermore, given that this area is involved in circadian rhythm and sleep–wake cycling (63,66), these data establish an involvement of this hypothalamic area as a *primum movens* in the acute cluster attack.

MORPHOMETRIC STUDIES: POINTING TOWARD A LESION

Fundamental to the concept of idiopathic or primary headache, including migraine, tension-type headache, and CH, is the currently accepted view that these conditions are due to abnormal brain function with completely normal brain structure (35,36). Given the consistency of the PET findings with the clinical presentation in CH, the subsequent question is whether the brain of such patients is structurally normal. Voxel-based morphometry, an objective and automated method of analyzing changes in brain structure (4,5,26), was used to study the structure of the brains of patients with CH (55).

Using the voxel-based morphometric analysis of the structural T1-weighted MRI scans, a significant structural difference in gray matter density was found in patients with CH when compared to healthy volunteers. This difference consists of an increase in volume and was present for the entire cohort. The difference was also present when patients in and outside a bout were compared with the control group. This structural difference is bilaterally situated in the diencephalon, adjacent to the third ventricle and rostral to the aqueduct, coinciding with the inferior posterior hypothalamus. In terms of the stereotaxic coordinates (15), it is virtually the identical area in which activation during an acute CH attack is demonstrated in the PET study. No other areas of change were noted (55). Interestingly, in migraine, no global or regional structural changes were found (53). It may be that, in contrast to CH, migraine is a purely functional disease or that, more likely, migraine is a too heterogeneous disease to allow us to delineate subtle structural changes using the method of voxel-based morphometry.

Colocalization of morphometric *and* functional changes in CH means that two different imaging techniques separately identify a highly specific brain area previously considered on clinical and biologic grounds to be involved in the genesis of the CH syndrome (49). The structural data relate to a morphometric change of the neuronal density in this region while the functional imaging data are related to the neuronal activity in this area. Together they demonstrate for the first time the precise anatomic location for the central nervous system lesion of CH.

TRIGEMINAL AUTONOMIC HEADACHES: SHARED PATHOPHYSIOLOGIC BACKGROUND?

If it is correct that trigeminal autonomic cephalgias share a common pathophysiologic background, it should be possible to delineate similar structures using functional imaging. SUNCT is among the rarest idiopathic headache syndromes (79). Several clinical features differentiate it from other primary headaches, such as CH and chronic paroxysmal hemicrania (CPH), with the most prominent one being that the paroxysms of the unilateral pain are very short lasting, between 5 and 250 seconds. The attacks are frequent, with a published mean of 30 attacks per day and a range of 6 to 77 attacks per day (68). The pain is accompanied by autonomic features such as conjunctival injection and tearing.

Little is known about its pathophysiology, although the trigeminal pathways seem to be involved in the entire range of the idiopathic headaches, and the trigeminal autonomic reflex has been suggested to account for many of its features (24). Even though there are marked differences in the clinical pictures, such as the frequency and duration of attacks and the different approach to treatment, many of the basic features of SUNCT, such as episodicity, autonomic symptoms, and unilaterality, are shared by other headache types, such as CH and

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CPH. This suggests a pathophysiologic similarity to these syndromes and prompted the suggestion to unify them on clinical grounds as trigeminal autonomic cephalgias (TACs) (24).

Using functional MRI in six consecutive spontaneous pain attacks in a patient with SUNCT, activation was seen in the ipsilateral inferior posterior hypothalamic gray matter when comparing the pain attacks with the resting state (57). These findings have recently been confirmed (82). The activation in the hypothalamus was seen solely in the pain state and was in the same area that was demonstrated to be activated in CH patients (58), suggesting considerable commonalities between SUNCT and CH. Indeed, the data may explain the episodic nature of the pain. Furthermore, a recent case report investigated, using functional MRI, a 68-year-old patient suffering from excruciating trigeminal autonomic headache attacks, in whom frequency, duration, and therapeutic response allowed no clear-cut classification to one of the subtypes of TAC (81). However, the cerebral activation pattern was similar, although not identical, to those previously observed in CH (56) and SUNCT (57), with a prominent activation in the hypothalamic gray matter (81). This case study underlines the conceptual value of the term "TAC" for the group of headaches focusing around the trigeminal autonomic reflex and moreover emphasizes the importance of the hypothalamus as a key region in the pathophysiologic process of this entity.

Another recent case report of two SUNCT patients investigated using functional MRI and blood oxygen level dependent (BOLD) reported a bilateral hypothalamic activation, which even positively correlated to increasing pain levels (9). This report certainly strengthens the role of the hypothalamus in the pathophysiology of TACs, but considering that only two patients were reported, it probably does not justify questioning the basis for the laterality of the attacks.

Hemicrania continua is a strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity that are accompanied by trigeminal autonomic features and migrainous symptoms (51). The syndrome is exquisitely responsive to indomethacin. In seven patients with hemicrania continua, a significant activation of the contralateral posterior hypothalamus and ipsilateral dorsal–rostral pons in association with the headache was described. In addition, there was activation of the ipsilateral ventrolateral midbrain, which extended over the red nucleus and the substantia nigra, and of the bilateral pontomedullary junction. This study demonstrated nicely that the neuroimaging markers of trigeminal autonomic headaches and migrainous syndromes are demonstrated in hemicrania continua, mirroring the clinical phenotype, which in fact exhibits a certain overlap with trigeminal autonomic headaches and migraine (52). Taken together, just as in the case of an atypical trigeminal autonomic headache (81), the functional imaging data in hemicrania continua (52) impressively emphasizes that primary headache syndromes can be distinguished on a functional neuroanatomic basis by areas of activation specific to the clinical presentation.

VESSELS

Using PET, an activation pattern clearly outside the brain parenchyma was observed bilaterally in midline structures over several planes (from –32 mm to –20 mm with respect to the anterior commissure–posterior commissure line (ACPC line), anterior to the brainstem and posterior to the region of the optic chiasm region. Superimposed on an MRI template, the location of the activation corresponded to the intracranial arteries bilaterally and the region of the cavernous sinus (58,61). This holds true in two group studies, as well as in 15 out of 17 single subject analyses. Bilateral activation in this region might be an indication of increased venous inflow from the superior ophthalmic vein draining the ophthalmic artery. Another possibility is that the observed increase in activation might be due to bilateral dilation of the internal carotid artery. Spontaneous and glyceryl trinitrate (nitroglycerin)–provoked attacks are reported to be accompanied by a bilateral decrease in middle cerebral artery blood flow velocities, implying vasodilation (10). It is difficult to assess the contribution of these two sources to the activation, particularly since it is beyond the spatial resolution of scanning to distinguish venous from arterial vessels in the cavernous sinus. However, using magnetic resonance angiography (MRA) and the same experimental design as in the PET study, it was demonstrated that there was dilation of the basilar artery and both internal carotid arteries compared to the headache-free rest state (56). Using PET, significant activity in the region of the cavernous sinus was previously described in CH patients (40). However, given that we have observed vasodilation in large vessels after capsaicin injection to the forehead, again in a PET study (61) in a condition without the influence of a systemic vasodilator and without the pathophysiologic background of CH, it seems likely that the vascular changes are an epiphenomenon of activation of the trigeminovascular system (21). In healthy controls, a pain-provoking application of capsaicin to the nasal mucosa induced vasodilation in the internal carotid, whereas middle cerebral arteries and the basilar artery were narrowed (19). On this background our data raise the possibility that vasodilation, increase in flow, or both in the cavernous region is not specific for CH, or does not form a significant part of the pathophysiology of the acute attack of CH. Our data suggest that activation of the trigeminal system as such is sufficient to trigger vasodilation of these vessels.

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CONCLUSION

Neuroimaging of primary headache syndromes, such as CH and migraine, has begun to provide a better understanding of the neuroanatomic and physiologic basis of the conditions. Although these headache types have been widely described as vascular, due to advanced methods such as PET, functional MRI, and voxel-based morphometry, vascular changes are no longer seen as the primary cause for head pain. The shared anatomic and physiologic substrate for migraine and CH is the neural innervation of the cranial circulation. Functional imaging with PET has shed light on the genesis of both syndromes, documenting activation in the midbrain and pons in migraine and in the hypothalamic gray matter in CH. Furthermore, using the voxel-based morphometric analysis of the structural T1-weighted MRI scans, a significant structural difference in gray matter density of the hypothalamus was found in patients with CH when compared to healthy volunteers. These areas are involved not simply as a response to first-division nociceptive pain impulses, but are also inherent to each syndrome, probably in some permissive or dysfunctional role.

In addition to activation within the brain, there was a highly significant activation observed in the region of major vessels. This phenomenon was seen in CH as well as experimental trigeminal transmitted pain using capsaicin injections into the forehead. MRA demonstrated dilation in both the basilar and intracranial carotid arteries, clarifying the nature of the changes observed in headache that are most likely inherent to the trigeminovascular system.

Taking these new data in acute CH together with what has been observed in experimental head pain and migraine, the data establish that migraine and CH, far from being primarily vascular disorders, are conditions whose genesis is to be found in the central nervous system in pacemaker or circadian regions specific to the syndrome. If further studies confirm these findings, a better understanding will be gained of where and how acute and preventive therapy can be targeted.

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P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
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