Chapter 91

Synthesis of Cluster Headache Pathophysiology

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Cluster headache (CH) is a distinct syndrome, unusually causing diagnostic problems with its strictly unilateral, often excruciating head pain that occurs with cranial autonomic features and a striking circannual and circadian periodicity. Challenging issues are the relapsing–remitting course, the clocklike occurrence of attacks, the strictly unilateral pain, and the male preponderance (10). There is no unifying pathogenetic model that explains all the various symptoms and findings of CH, although recent human imaging suggests an important role for the posterior hypothalamus.

CIRCADIAN RHYTHMS AND NEUROENDOCRINOLOGY

Due to its central role in rhythm regulation and integration of the autonomic nervous function, the hypothalamus has been hypothesized to be involved in CH pathogenesis (36). The temporal pattern of CH together with altered neuroendocrine, vascular, and pain control indicates that circadian and circannual rhythm regulation is affected. The cluster periods tend to occur at regular intervals, in a seasonal pattern, and they are sometimes interrupted by changing work schedules and sleep patterns. The "clockwise regularity" of CH attacks also appears to be governed by the dark–light cycle, sleep, and activity. Accordingly, there is an afternoon peak of CH attacks in Italy (28), which is not observed in Scandinavia (44), where there is no siesta during the work day. Neuroendocrine data show altered 24-hour secretory patterns with phase shifts/advances for a number of hormones during active periods but also during remission, as well as altered responses to various neuroendocrine tests (51). Twenty-four–hour data for certain hormones, blood pressure, body temperature, or pain sensitivity show that more patients than controls lack a significant circadian rhythm when the data are analyzed by cosinor rhythmometry (16). Some of the neuroendocrine changes may in part be related to pain, stress, or interrupted sleep; others, such as blunted nocturnal prolactin secretion during remission and permanently reduced melatonin urinary concentrations around the year, are interpreted to reflect central pathology and hypothalamic involvement in CH.

Functional neuroimaging with positron emission tomography (PET) and anatomic imaging with voxel-based magnetic resonance imaging (MRI) morphometry have made it possible to show directly that the posterior hypothalamic gray matter indeed is a key area in CH. A PET study using $H_2{}^{15}O$ as a marker showed increased activity in the ipsilateral hypothalamus during nitroglycerin-induced attacks of CH (32), but not during the cluster period between attacks or in a control group in remission after a negative nitroglycerin provocation. Recently, it was reported that hypothalamic activation also occurred in a patient during a spontaneous attack of CH (48). A similar activation pattern has been seen with functional MRI in a series of patients with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) (33) but not in migraine (53) or other spontaneous or experimentally induced cranial pain (35). Activation of this particular area in the hypothalamus appears to be unique to the trigeminal autonomic cephalalgias.

With voxel-based morphometric analysis of T1-weighted MRI scans it was possible to demonstrate an increase in gray matter volume in a small region coinciding with the inferior hypothalamus in right-handed men with CH compared with healthy controls (31). The gray matter change was bilateral, but when mirror images were used to normalize for pain side, the structural change seemed slightly lateralized to the pain side. Although conventional imaging was normal in all patients, the voxel-based morphometry was capable of showing subtle changes in the gray matter by averaging across subjects. The nature of the

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structural changes is unknown. The activation of the inferior posterior hypothalamus and corresponding structural changes ask fundamental questions about what is a "primary" headache disorder and has inspired a completely new approach to treatment of intractable CH (15).

Deep brain stimulation of posterior hypothalamus ipsilateral to the side of attacks has been shown to improve otherwise drug-resistant chronic CH (26,52). Five patients with intractable chronic CH were treated with long-term, high-frequency electrical stimulation of the posterior hypothalamus ipsilateral to pain. In one patient with bilateral pain an additional contralateral implant was required to achieve pain relief. Electrodes were implanted 3 mm behind and 5 mm below the midcommissural point and 2 mm lateral to the midline. After 2 to 22 months of follow-up, two of five patients had remained pain free without any medication, whereas three patients required low doses of methysergide or verapamil (26). Pain disappearance was never immediate but occurred from a few hours up to 4 weeks after starting stimulation, and the insertion of the electrode as such appeared not to affect pain attacks. In this series of patients there were no major adverse events recorded. Another study reported preliminary good results in four pilot patients but, unfortunately, a fifth patient died from an intracerebral hemorrhage (52). Since there was no immediate cessation of attacks by deep brain stimulation, a more complex mechanism involving several brain structures rather than simple inhibition or stimulation of hypothalamic nuclei was suggested. This would be consistent with the results of recent PET studies showing that hypothalamic stimulation activate certain brain areas and deactivate others (34).

GENETICS

A very recent publication reports a polymorphism of the hypocretin receptor 2 (HERTR2) gene to be associated with CH (43). Interestingly, this gene is primarily expressed in the hypothalamus. The study suggests that the HCRTR2 gene or a linked locus significantly modulates the risk for CH.

UNILATERALITY OF PAIN

One of the main diagnostic criteria for CH attacks is the strict unilaterality, suggesting a locus, either constitutional or acquired, where pain is generated or to which it is referred. Rarely does a CH shift sides for a complete cluster period. The risk of having a cluster period on the previously asymptomatic side is about 200 times higher (46) than the overall incidence. This indicates an increased vulnerability in subjects already suffering from CH (18,21,39). Infections, trauma, or toxic effects have been put forward as possible initiators of CH. Studies of the disorder during the very first episode of CH may help to clarify the initiating etiologic event.

PAIN CHARACTER

The maximum intensity of pain is generally localized behind the eye, radiating toward the temple or to the upper cheek. It is described as excruciating, as almost intolerable, and as if the eye is pushed out of the orbit or a knife is being turned around. During pain most patients appear restless or agitated.

The ophthalmic, anterior cerebral, and middle cerebral arteries dilate during attacks of CH (12,20,50). Vascular dilation together with lowering of the pain threshold by sensitization of pain receptors may contribute to pain. Vascular pain, however, would be expected to be throbbing, which is rather uncommon in CH (11). Alternatively, pain may be caused by dilated and edematous vessels pressing against surrounding tissues in narrow passages such as the bony carotid canal and the pterygopalatine fossa, or by obstructed venous outflow from the cavernous sinus (21). CH has been proposed to be caused by a remitting venous phlebitis in the cavernous sinus based on pathologic orbital phlebograms (18,19), and inflammatory signs in blood (18) and cerebrospinal fluid (22) in some patients during the cluster period. However, there was no consistent correspondence between phlebopathic signs and the symptomatic side, and similar phlebographic findings have been reported in healthy controls (1).

AUTONOMIC DISTURBANCES IN CLUSTER HEADACHE

Opinions diverge over the source of autonomic disturbances in CH, but most likely there is a combination of central and peripheral mechanisms. Autonomic dysregulation may originate centrally in association with a hypothalamic disturbance that compromises inhibitory pain control mechanisms. Vasodilation and venous stasis during attacks may compromise sympathetic fibers. Autonomic disturbance may occur secondary to the trigeminal discharge.

DISTURBANCES IN BLOOD PRESSURE AND HEART RATE

Blood pressure typically increases, whereas heart rate decreases during attacks of CH. Sympathetic traffic in the peroneal nerve was recorded (41) during attacks of CH and showed corresponding increases in blood pressure and pulse-synchronous bursts of sympathetic vasoconstrictor

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activity. This was interpreted as a normal response to pain (40). Heart rate and blood pressure in response to head-up tilt also seemed to be normal in CH patients during the headache-free interval (25). The mechanism of bradycardia in CH is uncertain. Spectral analysis of heart rate fluctuations suggests that sympathetic activation causes mild tachycardia at the start of the attack and that a parasympathetic influence develops later on to produce relative bradycardia (4). Activation of trigeminal depressor or oculocardiac reflexes may contribute. Respiratory sinus arrhythmia, an index of vagal modulation of heart rate, was lower in patients than in controls but within normal limits in most cases (24), and did not change consistently during attacks of CH.

OCULAR DISTURBANCES

In the vast majority of CH patients, persistent signs of ocular sympathetic deficit on the symptomatic side seem to be due to postganglionic sympathetic deficit. However, pupillary dilation in response to painful stimulation has been reported to be attenuated bilaterally (37,38) during the active phase of CH, although more on the symptomatic side. Findings of ocular sympathetic deficit on the nonsymptomatic side (5) or bilaterally in patients with CH (23) have been argued to support a hypothesis of a central lesion. Others find this less likely since a central sympathetic lesion would be expected to block sweating and sympathetic vasoconstrictor tone in the symptomatic upper limb (27), but these sudomotor responses were symmetrical in patients with CH (7).

FACIAL FLUSHING AND SWEATING

Thermoregulatory flushing and sweating are impaired on the symptomatic side of the forehead in CH patients with persistent signs of ocular sympathetic deficit (9). During CH attacks, paradoxical sweating and increased blood flow often occur in this region (8,47). Drummond and Lance suggested that this paradoxical response may be explained by collateral sprouting of parasympathetic lacrimal fibers into sympathetically denervated blood vessels and sweat glands (9).

LACRIMATION, NASAL SECRETION, AND SALIVATION

Lacrimation, nasal stuffiness, and nasal secretion develop on the symptomatic side during attacks. Minor increases in sweating, lacrimation, and nasal secretion on the nonsymptomatic side during attacks of CH may be mediated by a central disturbance (46). Alternatively, a minor normal crossover of the trigeminal–parasympathetic lacrimal reflex in the brainstem offers another possible explanation to the bilateral findings (6). Unlike the sympathetic innervation of the face, trigeminal–parasympathetic reflexes appear to function normally without evidence of denervation supersensitivity in CH patients (45).

VASCULAR REGULATION

A breakthrough in the understanding of CH pathophysiology was the finding that calcitonin gene–related peptide (CGRP) and vasointestinal peptide (VIP) concentrations are increased in external jugular vein blood on the symptomatic side both during spontaneous (17) and nitroglycerin-induced (14) headache attacks. Furthermore, the CGRP plasma levels normalize concomitant with pain relief after treatment with oxygen inhalation or subcutaneous injection of sumatriptan but not after injection of pethidine (17). Nitroglycerin-induced attacks generally do not start until the first painless phase of vasodilation is about to end. One hypothesis is that nitroglycerin may trigger a cluster attack by stimulating trigeminal nociceptive fibers to release CGRP (13), but this view seems unlikely because the CGRP levels do not increase until the attack is well established (14).

CGRP in external jugular venous blood remains higher than normal between attacks of CH (14), possibly because of repeated discharge of the trigeminovascular system during attacks or because of abnormal cyclical activation of the trigeminovascular system (14,30). Raised plasma levels of CGRP and VIP in the cranial venous blood reflect activation of a brainstem reflex with the trigeminal nerve as the afferent arm and the parasympathetic fibers of the facial nerve as the efferent arm (17). This, however, does not clarify the starting point for the CH process.

The role of the vasodilator nitric oxide (NO) is not clear in CH. Basal levels of nitrite, a metabolite and marker of NO, have been reported to be higher in CH patients (either in remission or in the active period) than in controls as a possible sign of a hyperactive l-arginine NO pathway (3), or to be normal (in the active period between attacks) (2, 29). The increase of nitrite after nitroglycerin provocation did not differ between healthy controls and patients who suffered an induced CH attack (2). Other factors, at present not clarified, may render the CH patient hypersensitive to NO and other vasodilators (2). A most challenging issue is to clarify the mechanism of nitroglycerin provocation leading to the painful second phase of vasodilation, the parallel increase of CGRP and VIP, and to identify why this occurs only during the active cluster period (14).

Peptide markers of sympathetic activity are not altered during CH attacks (17). This is not surprising, because some of the autonomic signs in CH indicate lowered rather than increased sympathetic activity, at least regionally. Accordingly, in the morning and at night when CH attacks

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frequently occur, lowered plasma norepinephrine levels as well as lowered spinal fluid levels of norepinephrine and catecholamine metabolites also have been observed compared with healthy controls (49). In contrast, muscular sympathetic activity show normal responses to vasodilation after nitroglycerin administration and CH pain as regards blood pressure (41).

SYNTHESIS

Recent findings favor a central cause of CH. Functional neuroimaging techniques have provided a better understanding of the anatomic and physiologic basis of CH. A locus within the hypothalamus may disturb rhythm regulation of importance for pain regulation and for autonomic and vascular control, thereby offering an explanation for the periodicity of attacks and cluster periods. CH is not considered to be a primary vascular disorder anymore. A trigeminal–parasympathetic reflex explains vasodilation and parasympathetically derived local autonomic symptoms. As regards sympathetic deficit, several findings indicate a peripheral third neuron dysfunction while bilateral symptoms in the face and systemic effects on the circadian regulation of blood pressure, temperature, and endocrine circadian rhythmicity suggest a central disturbance. The presence of a peripheral sympathetic third neuron lesion in CH is not an argument against the central hypothesis and may be considered a complication of CH. A previous hypothesis proposed a pathologic focus within the cavernous sinus, such as a venous phlebitis or local anatomic factors (42). Pain would be produced by obstructed venous outflow, which could be triggered in the prone position or by intermittent dilation of arteries and veins whose sympathetic innervation has been compromised by the phlebitis (21). This hypothesis does not provide a clear explanation of the cyclical features and neuroendocrine changes in CH.

In conclusion, there is evidence for both central and peripheral mechanisms in CH pathogenesis. Hypothalamus has been proven to be involved, and a final common pathway for the CH attacks appears to be a recurrent activation of the trigeminovascular system with secondary parasympathetic recruitment. The nature of the lesion in posterior hypothalamus and its cause, the strict unilaterality of pain, and the male preponderance of CH, however, are still unknown.

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