Migraine and Cluster Headache

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Introduction to Migraine and Cluster Headache

Migraine

Migraine is a common primary episodic headache disorder. The most common migraine form is migraine without aura, with an estimated prevalence of 10–12 % in most Western societies. It is more frequent in women and usually starts before the age of 20, peaking between 35 and 45. In women, migraine often develops post menarche, worsens during menses, and may vanish during the last two trimesters of pregnancy or after menopause, suggesting an endocrine component to be involved. Two forms of migraine without aura are recognized: episodic (0–14 days per month with headache) and chronic (15 or more days per month with headache; Table 1). Usually, headache is unilateral, in the frontotemporal region, reaches its peak intensity gradually, is moderate to severe, is usually throbbing, and is aggravated by movements. It lasts 4–72 h (untreated or unsuccessfully treated) and can be associated with other symptoms, such as phonophobia, photophobia, nausea, and vomiting. Premonitory symptoms occur in 20–60 % of patients with migraines, hours to days before headache onset. They can include depression, fatigue, irritability, sensory sensitivity, anorexia/hunger, diarrhea/constipation, sensations of heat or cold, and sweating. In migraine with aura, focal neurological symptoms, mainly in the visual field, precede the headache and last about 15–30 min.

Cluster Headache (CH)

CH is a rare primary headache disorder characterized by severe painful attacks of strictly unilateral headache, mainly in the orbital and temporal regions, lasting 15–180 min accompanied by ipsi-

Table 1 Diagnostic criteria of migraine without aura [1]

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

ICHD3 International Classification of Headache Disorders, 3rd edition

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Table 2 Diagnostic criteria of cluster headache [1]

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min (when untreated)
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
(a) Conjunctival injection and/or lacrimation
(b) Nasal congestion and/or rhinorrhea
(c) Eyelid edema
(d) Forehead and facial sweating
(e) Forehead and facial flushing
(f) Sensation of fullness in the ear
(g) Miosis (pupil constriction) and/or ptosis (droopiness of body parts, mostly face)
2. A sense of restlessness or agitation
D. Attacks have a frequency between one every other day and eight per day or more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis

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lateral oculofacial autonomic symptoms, such as lacrimation, rhinorrhea, conjunctival injection (inflammation of the conjunctiva; see chapter "Overview" under part "Eye"), tearing, facial sweating, or ptosis; a sense of restlessness may be present (Table 2). The prevalence of CH is estimated to be at least 0.05–0.3 % [2] in the overall population. CH is predominant in males, but increasing in women; the ratio is now 2.5:1. The most common age of onset is the third or fourth decade of life. There are two forms of CH: episodic and chronic CH. About 80 % of CHs are episodic and are characterized by periods with daily or almost daily attacks, up to 8 per day, followed by spontaneous remission. In chronic CH, remission periods are usually absent or last less than 1 month. CH attacks often occur at fixed times of the day and of the night with a typical circadian periodicity. In episodic CH, most of cluster periods occur during spring or autumn. Alcohol; nitroglycerine, a vasodilator used in chronic heart failure (see chapter "Heart failure"); and exercise are recognized precipitants of acute cluster attacks. It is of interest to note that alcohol triggers attacks only during a cluster period but not during remission.

Although CH attacks are clearly distinguishable from migraine attacks, the two conditions share involvement of the trigeminovascular system at peripheral level and derangement of pain modulating structures within the brain. Today, both migraine and CH are regarded as neurovascular headaches, meaning that they are triggered by a complex series of neural but also vascular events.

Pathophysiology of Head Pain and the Trigeminovascular System

The trigeminovascular system consists of trigeminal neurons innervating cranial pain-sensitive structures such as dural, meningeal, and cerebral arteries and veins, venous sinuses, and bones. Pain information is transmitted via peripheral trigeminal first-order sensitive neurons to the trigeminal nucleus caudalis in the caudal brain stem and higher cervical spinal cord. The latter form the so-called trigeminocervical complex (Fig. 1). Pain information from the craniofacial district is further transmitted via this complex to the ventroposterior thalamus and then to the sensory cortex, the frontal cortex, insulae, cingulate cortex, and other pain-related brain areas (the so-called pain matrix), resulting in the experience of pain (Fig. 1).

Pain-sensitive information from the trigeminal nerve may also activate brain stem parasympathetic autonomic neurons of the superior salivatory nucleus due to a direct connection between the two systems in the brain stem. Fibers from this nucleus then run through the facial nerve to peripheral parasympathetic ganglia (e.g., the sphenopalatine ganglion); from these ganglia, neurons project to cranial vessels including dura mater vascular system and are responsible for vasodilation there (Fig. 1) [4]. Activation of parasympathetic fibers accounts for autonomic phenomena (such as lacrimation, rhinorrhea, facial sweating) accompanying CH attacks (see above, Table 2).

In addition to activation of the central pain pathway, trigeminal sensory nerve endings antidromically ("backward/upward") release vasoactive and pro-inflammatory neuropeptides around cranial vessels provoking dilation of cranial and

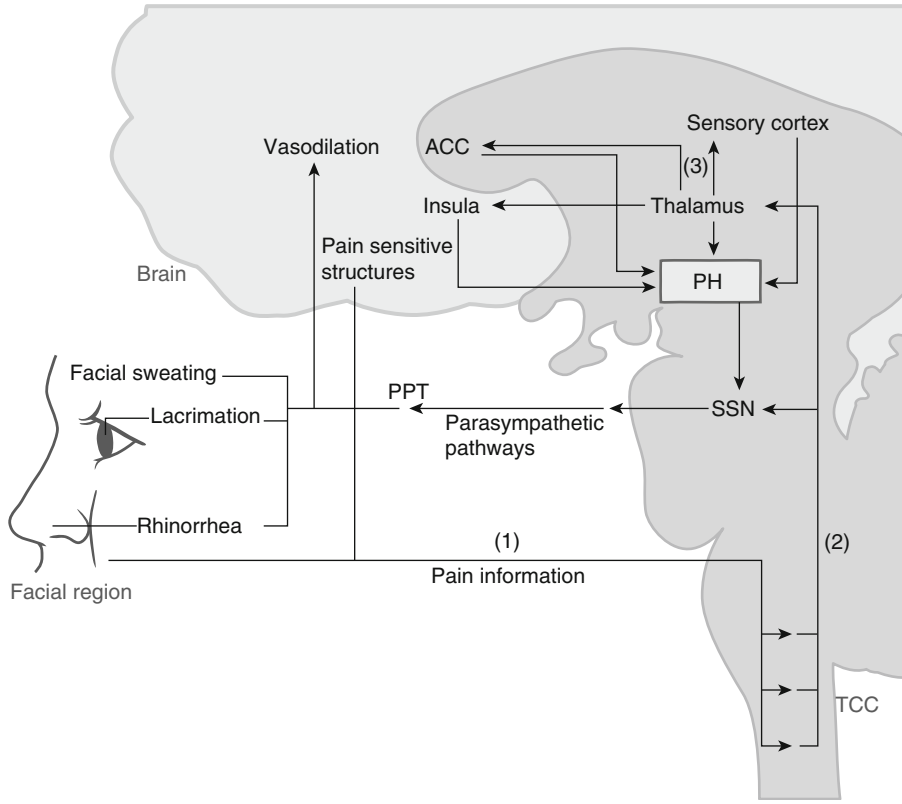

Fig. 1 Structures and centers implicated in migraine and cluster headache. The trigeminovascular system consists of the trigeminocervical complex (*TCC*), which includes the trigeminal nucleus caudalis (TNC) located in the brain stem and the upper cervical spinal cord (C1 and C2) and the afferent trigeminal nerve(s), which receives and transfers pain information from facial and cranial pain-sensitive structures (e.g., blood vessels in the dura mater). The afferent first-order neurons (*1*) are interconnected in the TCC to second-order neurons (*2*) projecting to the thalamus. Subsequently, cortical areas involved in pain transmission (third-order sensory neurons, (*3*) the pain matrix) are activated (including insula, sensory cortex, and anterior cingulate cortex (*ACC*)). The posterior hypothalamus (*PH*) might have a role in terminating and regulating attacks. It receives input from the thalamus, but also from the pain matrix, directly. The PH is implicated in autonomic phenomena occurring during headache attacks. These (mostly) parasympathetic symptoms can be caused by a direct effect of the hypothalamus (not shown) or by the TCC/ipsilateral trigeminal system via activation of the superior salivatory nucleus (*SSN*). This nucleus activates parasympathetic efferents mainly via the sphenopalatine (or pterygopalatine) ganglion (*PPT*). The PPT causes lacrimation, rhinorrhea, and facial sweating and is also connected to the dura mater where it can cause vasodilation. A dysfunction or disturbance in interactions between these pain areas might enable headache attacks to take place (Adapted from Leone and Bussone [3])

meningeal vessels and inducing a so-called sterile neurogenic inflammation. Involved neurotransmitters are calcitonin gene-related peptide (CGRP), substance P, neurokinin A, enkephalins, endothelin 1, somatostatin, and vasoactive intestinal peptide. CGRP and substance P are thought to sensitize pain receptors by inducing the release of inflammatory mediators such as histamine, bradykinin, tumor necrosis factor-α, nitric oxide, and serotonin (5-hydroxytryptamine, 5-HT). 5-HT has long been implicated as a key neurotransmitter in migraine (and CH), and some antimigraine drugs exert their effect by binding to 5-HT receptors (most importantly 5-$HT_{1B/1D}$, see below).

Treatment of Migraine and Cluster Headache

An effective management plan must include acute treatment to relieve the pain and may also include prophylactic treatments with the aim of decreasing

attack frequency, severity, and duration and of promoting an improved responsiveness to acute treatments. Comorbidities will influence drug choice, as will the side effect profile of the drug.

Treatment of Acute Migraine

Acute antimigraine treatment includes ergot alkaloid derivatives (ergotamine and dihydroergotamine), triptans, analgesics, and nonsteroidal anti-inflammatory drugs. Before intake of ergots, nonsteroidal anti-inflammatory drugs, analgesics, and, to a lesser extent, triptans, oral metoclopramide, or domperidone can be recommended to control nausea and vomiting. Migraine prophylaxis should be considered when attacks are frequent (more than 4 headache days per month), disabling, and acute medication is failing. Prophylaxis also helps to prevent medication overuse headache.

Prophylactic Treatment of Migraine

Preventive medication must be given for at least 3–6 months, usually aiming at a 50 % reduction in headache frequency. Secondary end points are reduction of pain intensity and duration, reduction of acute medication intake, and an improved acute treatment efficacy. First-line preventive drugs include β-blockers (such as propranolol and metoprolol), flunarizine (an atypical calcium channel antagonist), pizotifen (see above), and antiepileptic drugs (such as topiramate and valproate). Second-line preventive drugs with lower efficacy include other β-blockers, such as bisoprolol, timolol, and atenolol; tricyclic antidepressants (see chapter "Major depressive disorder"), mainly amitriptyline; selective serotonin reuptake inhibitors; and calcium channel antagonists, such as verapamil (see above). Avoidance of food or environmental triggers; stabilization of bedtimes, mealtimes, and exercise times; limitations on the frequency of use of acute medications or analgesics; and implementation of cognitive behavioral therapies or stress management strategies are also recommended [5].

Treatment of Acute Cluster Headache

In episodic and chronic CH, the drug of choice to treat acute attacks is subcutaneous sumatriptan. Nasal spray formulation of sumatriptan or zolmitriptan can also be used. The triptans are the first-line medication and have revolutionized the acute treatment of both migraine and CH. Triptans exert an agonistic effect on both 5-HT_{1B} and 5-HT_{1D} receptors. The primary sites of action are cranial blood vessels, where they lead to vasoconstriction and block the release of pro-inflammatory neuropeptides. Activation of 5-HT_{1D} receptors on nerve endings decreases the release of pro- inflammatory peptides such as CGRP and substance P.

Second-line acute treatments include intranasal lidocaine (an anesthetic) and subcutaneous injection of octreotide (a somatostatin analog), which likely acts via vasoconstrictive effects. Inhalation of pure oxygen via a non-rebreathing facial mask is also effective but to a lesser extent.

Prophylactic Treatment of CH

Prophylaxis of episodic and chronic CH should be tried first with verapamil. Verapamil is an L-type calcium channel blocker that is also used to treat hypertension (see chapter "Hypertension") and angina pectoris (see chapter "Atherosclerotic heart disease"). It acts by relaxing smooth muscle cells around blood vessels, causing vasodilation. The maximum dosage depends on tolerability, and electrocardiography monitoring is recommended especially when increasing doses, to prevent atrioventricular block.

Lithium, valproic acid (likely interacting with γ-aminobutyric acid transmission), methysergide, and pizotifen can be used if verapamil is ineffective or contraindicated. All these prophylactic drugs can be used in combination when single therapy did not produce improvement. Methysergide is the most effective of these, yet it is ineffective in acute attacks. Today, it is no longer recommended due to its side effects. Pizotifen, while effective, is also limited by its side effects (weight gain and drowsiness) and used when other approaches fail.

When these prophylactic drugs fail, corticosteroids can be used for short periods of time and with caution. Corticosteroids such as prednisolone, prednisone, and dexamethasone are the most effective preventive agents for CH, but prolonged use leads to potentially serious adverse events, such as insulin resistance (see chapter "Diabetes mellitus"), osteoporosis (see chapter "Osteoporosis"), and hypertension (see chapter "Hypertension"). Intramuscular dexamethasone can be administered when CH attacks are aggressive [6]. At the same time, other preventive medication is to be started. Injection of local corticosteroids plus local anesthetic in the area of the greater occipital nerve ipsilateral to the pain may exert some benefit. In drug-resistant chronic CH, greater occipital nerve stimulation and deep brain stimulation of the hypothalamus are recognized procedures to treat the condition.

Perspectives

In the last years, neuroimaging findings and the introduction of neurostimulation for the treatment of primary headache such as migraine and CH have provided considerable contributions to better understand the pathophysiology of these headache syndromes.

Functional imaging studies showed that several brain regions are involved in head pain processing and modulation. Hopefully, future studies will improve our knowledge on neuronal networks operating in migraine and CH, possibly offering rationale for new therapeutic targets.

In previous years, the increased CGRP levels in jugular vein blood, during both migraine and CH attacks, suggested a fundamental role for this substance in the origin of neurovascular headaches. New treatments based on anti-CGRP antibodies for both migraine and CH are currently being developed.

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