Cluster headache: review of current understandings

Cefaleia em salvas: revisão dos conhecimentos atuais

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ABSTRACT

Cluster headache (CH) is the trigeminal autonomic cephalalgia whose pain is considered to be one of the most severe known to man. Although diagnosed less frequently than migraine and tension-type headaches, CH is nonetheless an important clinical entity, particularly given our evolving understanding of its actual epidemiology, pathophysiology, current diagnostic criteria and treatment approaches. We carried out a systematic review through the United States National Library of Medicine (PUBMED) by using the search term "cluster headache" and the results were narrowed to manuscripts published in the last ten years with subsequent reference searches and verification of source data. This article presents a review of the current understanding of the most important aspects of CH, with emphasis on mechanisms and treatment approaches.

Keywords: Cluster; Headache; Review

RESUMO

A cefaleia em salvas (CS) é a cefaleia trigêmino-autonômica cuja dor é considerada uma das mais intensas conhecidas pelo homem. Apesar de ser diagnosticada com menor frequência do que migrânea e cefaleia do tipo tensional, a CS é de fato uma entidade clínica importante, principalmente pelo nosso progresso na compreensão de sua real epidemiologia, fisiopatologia, critérios diagnósticos atuais e abordagens terapêuticas. Nós realizamos uma revisão sistemática através da United States National Library of Medicine (PUBMED) usando o termo "cluster headache" e os resultados foram reduzidos aos manuscritos publicados nos últimos dez anos com subsequente busca das referências e verificação das fontes de informação. Este artigo apresenta uma revisão da compreensão atual dos principais aspectos da CS, com ênfase nos mecanismos e abordagens terapêuticas.

Palavras-chave: Cefaleia; Salvas; Revisão

INTRODUCTION

Cluster headache (CH) is a debilitating condition with recurrent unilateral attacks of excruciating pain and cranial autonomic features.[1] Among the most severe pain known to man, it has considerable impact on social functioning and quality of life.[2] Effective therapies are available, but unlikely to be prescribed as it remains underdiagnosed.[3]

HISTORY

Some authors label Nicolaes Tulp as the first to describe a headache resembling CH in 1641, although lacking some of the current diagnostic criteria.[4] The first historical description to fulfill the International Headache Society (IHS) diagnostic criteria of episodic CH (ECH) was published in 1745 by van Swieten.[5]

The unique features of CH have been more recognized since the nineteenth century, under various eponyms and nicknames: in 1878, "hemicrania angioparalytica";[6] in 1913, "erythroprosopalgia";[4] in 1926, "periodic migrainous neuralgia", which was changed to "ciliary neuralgia" in 1936;[7] "erythromelalgia of the head" in 1939, which was renamed to "histaminic cephalalgia" and "Horton's headache" in 1952.[6] IHS International Classification of Headache Disorders (ICHD) also includes "greater superficial petrosal neuralgia" and "hemicrania neuralgiformis chronica".[1] "Sphenopalatine neuralgia" and "vidian neuralgia" are not sufficiently validated as distinct entities,[1] justifying classification as CH.[6]

The name CH was used for the first time in 1952 by Kunkle et al. to emphasize the typical recurrence pattern of the pain[8] and its clinical description was broadened in 1958, being widely accepted henceforth.[9] In 1962, the IHS included the term CH among the "vascular headaches of migraine type".[10] First published in 1988[11] and revised in 2004,[1] ICHD included diagnostic criteria gleaned from observations, studies and consensus.

EPIDEMIOLOGY

The prevalence, incidence and distribution of CH in the general population is uncertain because most studies taken as reference applied inconsistent diagnostic criteria and used biased methods to investigate a very large sample.[4]

Prior to the ICHD era, a questionnaire was used to find a prevalence of 92/100,000 18-year-old Swedish men in 1977.[12] Past medical records of neurological, ophthalmological and otorhinolaryngological services were reviewed with a questionnaire to find a prevalence of 69/100,000 in San Marino between 1970 and 1984.[13]

The first population-based study on CH to use the IHS diagnostic criteria revised the medical records of patients from Olmsted County, USA, between 1979 and 1981 to find an overall incidence of 9.8/100,000/year (men 15.6; women 4.0).[14] Their follow-up study looking at years 1989-1990 showed a decrease in the overall incidence to 2.07/100,000/year (men 4.25).[15] San Marino follow-up study applied the previous methodology with the IHS diagnostic criteria to find a prevalence of 56/100,000 between 1985 and 1999 with an estimated incidence of 2.5/100,000/year.[16] These studies are biased because less than half of patients seek medical care.[12,17-18]

Published in 2008, a meta-analysis pooled the data from almost all epidemiological study on CH, despite their biases, and obtained a lifetime prevalence of 124/100,000 and 1-year prevalence of 53/100,000.[19]

A retrospective chart review has shown that African-American women develop CH more commonly than African-American men (25% and 17.4%).[20] Methodological issues have affected other studies with non-caucasian populations: Nigeria and China were studied prior to ICHD era; lay health care workers were used in Ethiopia; and a relatively small sample of the Malaysian population was studied.[19]

Published in 1997, a review of 482 patients referred to a headache center for CH showed that the male:female (M:F) ratio was declining with time, from a ratio of 6.2:1 prior to 1960 to 2.1:1 between 1990 and 1995.[21] In 2002, similar findings were published after observing 554 patients between 1963 and 1997.[22] Contradictorily, a patient sample obtained prospectively find a constant low ratio over the decades of 2.5:1[23] and a meta-analysis showed an overall ratio of 4.3:1.[19]

Studies have reported a mean age of onset of CH between 29.6[16] and 35.7[17] years, some with no statistical difference between genders,[3] others with lower age of onset for women compared to men (29.2 and 40.5 years).[17] Women seem to have a bimodal peak of onset of CH in the third and fifth decades, whereas men appear to have a single peak of onset in the third decade.[20] ECH is more common in both genders, affecting at least 80% of patients, while chronic CH (CCH) is rare, having been reported in only 4-20% of patients.[22,24] A meta-analysis showed a higher M:F ratio in CCH compared to ECH (15:1 and 3,8:1), and an overall ECH to CCH ratio of 6:1.[19] The mean age of onset of CCH for women is higher than it is for men (50.8 and 31.8 years) with M:F ratio reversal with age of onset after 50 years (0.6:1).[22] CH in children is rare.[25]

PATHOPHYSIOLOGY

The first hypotheses on CH were based on the vascular theory that oriented studies toward the trigeminal-vascular system (TVS). Innervation of encephalic blood vessels and meninges is mostly provided by fibers from the trigeminal ganglion,[26] containing calcitonin gene-related peptide (CGRP),[27] nitric oxide[28] and others vasodilators. Nociceptive stimulation activates neurons in the trigeminal nucleus caudalis (TNC), which project to multiple subcortical and cortical regions.[29] The activated trigeminal pain pathways play a major role in the modulation and experience of pain.[26] Although TVS is actually activated in CH, with increased CGRP in jugular veins during attacks,[27] it is not specific and whether it is cause or consequence is not clear.

Later, the autonomic features of CH have oriented the studies toward the trigeminal-autonomic reflex (TAR), generated when a stimulation of the TVS results in a rebound activation of the parasympathetic outflow via the facial nerve.[30] TAR releases acetylcholine and vasoactive intestinal peptide (VIP), important regulators of lacrimation and vasodilatation.[31] Believed to be a normal physiological response to pain because it occurs in migraine[32] and can be elicited even in healthy volunteers

with experimental trigeminal pain,[33] its intensity correlates with the severity of pain.[26] Despite the activation of TAR in CH, with increased VIP in jugular veins during attacks,[34] increased prevalence of autonomic features points to further autonomic dysfunctions.

Recently, the circadian rhythmicity of CH has oriented the studies toward the hypothalamus. The suprachiasmatic nucleus (SCN) controls the biological clock, projecting luminosity information to the pineal gland where melatonin is produced in a circadian rhythm to act satisfactorily.[26] CH reduces the melatonin production until its nocturnal peak disappears,[35] altering biological rhythms and decreasing its additional analgesic effect related to gabaergic reinforcement,[36] calcium modulation[37] and prostaglandin synthesis inhibition.[38] Occasional hypersexuality, hyperphagia[39] and laboratory evidence of perturbations in the hypothalamic-pituitary axis[35,40] suggest hypothalamic dysfunction beyond the SCN. Functional neuroimaging studies have shown an activation of the ipsilateral posterior hypothalamus during CH attacks[41] with neuronal loss or dysfunction,[42] while structural neuroimaging studies demonstrated an increase in the gray matter volume of the same hypothalamic area in CH patients.[43]

Hypothalamus receives connections from the frontal cortex and projects them to brainstem areas that have been implicated in the modulation of pain.[44] The posterior hypothalamus contains connections to the TNC,[45] to the parasympathetic[46] and sympathetic[47] systems that modulate TVS and TAR. It produces excitatory neuropeptides orexins A and B with orexin-A demonstrating equal affinity for orexin receptors 1 and 2, while orexin-B has a 10-fold higher affinity for receptor 2.[26] Activation of these receptors has been shown to differentially modulate inputs to the TNC,[48] where receptor 1 elicits an antinociceptive effect and receptor 2, whose gene (HCRTR2) 1246G>A polymorphism has been associated with increased risk of CH,[49] elicits a pronociceptive effect. The orexinergic system in the posterior hypothalamus is modulated by the SCN,[26] which explains how a dysfunctional biological pacemaker can originate periodic attacks of trigeminal pain with prominent autonomic features and endocrine abnormalities.

CLINICAL ASPECTS

Studies have shown that CH attacks usually lasts between 15 minutes and 3 hours, which helps to differentiate it from migraine. The pain is recurrent with a frequency from one every other day to eight per day. Usually described as a very severe unilateral orbital pain, it may be located in other areas within the first trigeminal branch territory.[23,50] The duration, frequency, severity and localization of attacks were included in the ICHD diagnostic criteria due to their marked constancy.[1] However, about 15% of patients had attacks lasting less than 15 minutes or more than 3 hours,[50] the pain sometimes extends to other trigeminal branches territories or even the occipito-cervical region, and at least 15% of patients experience a change of attack side during their clinical course,[23] which is notably common in CCH with 50.8% of side shift.[51]

CH pain rises and ends abruptly, often leaving patients asymptomatic between attacks. There may be a continuous discomfort on the affected side in severe CCH or ECH with numerous daily attacks.[52] The presence of cluster peaks around solstices[53] and dramatic regularity of timed attacks on day or during sleep (circannual and circadian rhythmicity) are not included in the ICHD diagnostic criteria because they are not seen in all patients. Ipsilateral autonomic signs are another distinctive feature of CH with parasympathetic hyperactivity and sympathetic hypoactivity[54] included in the ICHD diagnostic criteria. A sense of restlessness or agitation is so typical of a CH attack,[55] only approximately 3% of patients can lie still during a bout,[56] that it was accepted as an alternative criterion when the autonomic signs are subtle or even absent in up to 7% of patients.[50,54]

Other relevant features of CH include few recognized triggers such as alcohol, smoking, nitrates, increase in body heat, hypoxia and napping, which occur only during cluster periods. Symptoms generally attributed to migraine without aura can be observed in approximately 50% of patients, whilst up to 14% of patients report aura symptoms, with transient visual, motor or sensory disturbances preceding an attack.[23] Nausea and vomiting are more common in women with CH than men (46.9% and 17.4%)[20] and auras have been reported in 20% of patients with CCH.[52] Patients with CH and visual symptoms have been reported since 1972,[57] but the first four cases of hemiplegic cluster were published only thirty years later, in 2002.[58]

Graham[59] was the first to notice that some patients have a leonine facies with broad head and reddish thick furrowed brows and cheeks. Rare case reports have described patients with "CH sine headache".[60] Increased prevalence of obstructive sleep apnea (OSA),[61,62] patent foramen ovale[63] and right-to-left shunt64 has been reported in patients with CH. OSA prevalence in CH patients has ranged between 58.562 and 80.64%[61] with

some reports of benefit of continuous positive airway pressure to patients suffering from both conditions.[62,65] However, activation of temperature-sensitive neurons in the preoptic/anterior hypothalamus suppress the activity of the airway dilator muscles and diaphragmatic muscle during non-rapid eye movement sleep,[66] suggesting that OSA and CH are parallel processes generated in different areas of the hypothalamus.[67]

Early studies on smoking in CH were conducted on a small number of patients with similar high prevalence until 1990, when changing habits in the population determined a sustained decrease in the prevalence of smoking.[68] An Italian cohort demonstrated that the increased propensity of CH patients to smoking remained almost unaltered through time:[69] the prevalence of smoking in Italy in 1975 and in 1993 was 53.2% and 35% for men, and 16.3% and 19.2% for women; whereas the prevalence of smoking in CH patients before 1990 and after 1990 was 89.4% and 87.8% for men, and 56.5% and 57.1% for women. Two small case series hypothesized that smoking may impact the perpetuation and onset of CH.[70,71]

When compared with a group of matched patients with tension-type headache (TTH), ECH patients showed a higher frequency of anxiety disorders (23.8%) during the year preceding the onset of headaches and significantly greater anxiety scores during the clinical episode than TTH patients (4.8%).[72] Studies demonstrated that ECH patients presented impaired neuropsychological evaluations on verbal memory, visuospatial memory and executive performance.[72,73] Those studies have shown that this cognitive decline was not related to a mood disorder and not statistically different from those presented by patients with migraine[73] or TTH.[72] Further studies confirm that all cognitive impairments in CH are transient, mild, and do not relevantly contribute to morbidity.[74]

DIAGNOSIS

ICHD diagnostic criteria:[1]

A. At least five attacks fulfilling B through D.

B. Severe or very severe unilateral orbital, supra-orbital and/or temporal pain lasting 15 to 180 minutes if untreated.

C. Headache is accompanied by at least one of the following: ipsilateral conjunctival injection and/or lacrimation; ipsilateral nasal congestion and/or rhinorrhea; ipsilateral eyelid edema; ipsilateral forehead and facial sweating; ipsilateral miosis and/or ptosis; a sense of restlessness or agitation.

D. Attacks have a frequency from one every other day to eight per day.

E. Not attributed to another disorder.

Additional ICHD diagnostic criteria for ECH and CCH:[1]

A. All fulfilling criteria A through E of CH.

B. At least two cluster periods lasting from 7 to 365 days and separated by pain free remissions of > 1 month (for ECH); Attacks recur for > 1 year without remission periods or with remission periods lasting < 1 month (for CCH).

A review of 56 cases of symptomatic trigeminal autonomic cephalalgias (TACs) found a wide range of both intracerebral and extracerebral cranial and cervical lesions and diseases that could be associated with them, and a abnormal neurological examination required additional neuroimaging in almost all reports.[75] A first attack suggestive of CH and all atypical cases must always be thoroughly investigated, but when the history is so typical with numerous periods, attacks and without interictal neurological deficits, complimentary investigation is not mandatory.

Differential diagnosis includes migraine, other TACs, trigeminal neuralgia (TN) and hypnic headache (HH). Migraine attacks are longer,[1] sometimes bilateral, with female preponderance, with prostration and quietness, and triggered by hormonal and dietary triggers other than alcohol.[23] Other TACs differs from CH by the shorter length and higher frequency of their attacks or absolute response to at least 150 mg of indomethacin.[1,23] TN attacks are briefer and more frequent, rarely affecting the first trigeminal branch territory, with female preponderance, trigger zones and without autonomic signs.[1,76] HH affects elderly patients with exclusively sleep attacks, usually bilateral, diffuse and without autonomic signs.[1] When CH symptoms are associated or overlapped with another headache, such as cluster-migraine[77] and cluster-tic,[78] the patient should receive a medication efficient for both conditions. Overlap between attack duration in TACs is expected,[1] but some overlap in treatment response among the TACs has emerged[79] and some clinical overlap includes coexistence of CH and chronic or episodic paroxysmal hemicrania (EPH),[80] CH and hemicrania continua,[81] and a case of EPH with seasonal variation similar to CH.[82]

TREATMENT

CH treatment can be divided in abortive, transitional and preventive.[56] The goal is to suppress attacks and to

maintain remission over the expected duration of the cluster period.[56,83]

First option for the abortive therapy of CH: pure oxygen inhalation via a non-rebreathing facial mask with a flow rate of at least 7 l/min over 15 minutes.[83] It is the safest method available, supported by a Cochrane review[84] and a randomized controlled trials (RCT),[85] which suggested that normal pressure oxygen therapy was likely to be effective in up to 78% of the cases. Although subcutaneous injection of sumatriptan 6 mg is the most effective medication for the abortive therapy in up to 75% of all patients,[56,83,86] should only be considered for patients without cardiovascular risk. Alternatives include nasal sprays of sumatriptan 20 mg or zolmitriptan 5 mg with slower onset, but being able to treat more attacks in a day.[83] Subcutaneous octreotide 100 mcg and oral zolmitriptan 5-10 mg can be tried with some efficacy,[83,86] while intranasal lidocaine 4-10%, ergotamine,[86] oral olanzapine 2.5-10 mg and suppositories of chlorpromazine or indomethacin[56] lack RCTs and they should be reserved to intractable CH attacks.

Without adequate RCTs about transitional therapy,[83,86] review of open studies and case series has confirmed the clinically well known efficacy of corticosteroids given under different short course regimens in up to 80% of all CH patients.[87] Dihydroergotamine has also been considered for a more laborious transitional therapy at daily intramuscular injections of 1 mg for a week or intravenous infusion of 1 mg twice or thrice a day for 3 days. Naratriptan 2.5 mg or frovatriptan 2.5 mg have been proposed as more tolerable with oral administration of one tablet twice a day for a week.[56]

Verapamil is the first choice in preventive therapy for CH, at a daily dose of at least 240 mg.[56,83,86] It can be used with other abortive and preventive medications for CH safely,[64] although serial electrocardiograms are recommended during titration[56,83,86] and should probably be monitored due to eventual PR prolongation during maintenance therapy.[88] Lithium 300-900 mg,[56,83,86] melatonin 10 mg, topiramate 50-400 mg,[56,83] methysergide 4-8 mg, pizotifen 3 mg,[83] intranasal capsaicin, and intranasal civamide[83,86] are drugs of second choice with decreasing level or recommendation. Other third choice agents have been reported to be effective: baclofen, valproate,[56,83,86] gabapentin, transdermal clonidine, leuprolide,[56,86] tizanidine,[86] mycophenolate, clomiphene, and testosterone.[56]

Interventional therapy includes greater occipital nerve (GON) blockade,[56,83,86,89] botulinum toxin (BTX) injections,[83,86,89] radiofrequency (RF) thermocoagulation, GON stimulation,[56,83] and hypothalamic stimulation. [56,83] GON injections have recently been shown to be efficacious,[89] either using an anesthetic alone or associated with steroids,[56,89] a good alternative to both abortive and transitional therapies.[56] BTX injections in some muscles ipsilateral to the pain have shown only limited success in CCH patients.[89] RF thermocoagulation of the trigeminal ganglion is the most commonly used surgical technique, among the best options for pain relief with only approximately 30% of procedure failure.[56] GON stimulation has been studied in 8 patients with refractory CCH and it may take up to 5 months to show any effect, suggesting more central than peripheral neuromodulation.[56,90] Stimulation of the posterior inferior hypothalamus ipsilateral to the pain is now established as a treatment for selected refractory cases of CCH and almost every patient has had a remarkable reduction in CH frequency.[56,91] As of 2009 April, 54 patients have been submitted to hypothalamic stimulation and 50% to 75% of CCH patients eligible to improvement evaluation, as the response may take weeks to months, were pain free or almost pain free.[91]

CONCLUSION

A rare disease when compared to migraine and TTH, CH gets less attention from private initiatives and public healthcare policies. Improvement in the management of CH should ultimately affect the quality of life of patients suffering from it.

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