CLUSTER HEADACHE: A REVIEW

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Abstract

There is growing interest in biomedical literature over the past few years regarding Cluster headache, this underdiagnosed primary headache that is the most common of Trigeminal Autonomic Cephalalgias. This review provides the essentials to diagnose and treat Cluster headache, which presents most often with a typical head pain accompanied with ipsilateral autonomic nervous system features that constitute the episodic and chronic form of the disease. Important lifestyle risk factors and scales to assess the impact in sufferers' quality of life are reviewed alongside with a synopsis of the pathophysiology background. Furthermore, we highlight the improvements made in early diagnosis due to the growing awareness of healthcare providers and the evolving therapeutic repertoire that includes nowadays a monoclonal antibody and a handheld neuromodulation device amongst traditional agents.

Key words: cluster headache, pain, autonomous nervous system, early diagnosis, treatment

Cluster headache (CH) is a unique clinical syndrome amongst the primary headaches, classified as a Trigeminal Autonomic Cephalalgia (TAC). It presents with attacks of severe or excruciating unilateral head pain combined with ipsilateral autonomic nervous system symptoms, causing ictal restlessness and agitation and significant disability to the sufferers [1]. The natural course of the disease in its episodic form (eCH) consists of bouts, that last weeks or even months, followed by pain free periods, whereas its chronic form (cCH) attacks come in longer periods, unremitting for more than a year and in many cases, long term. In cluster headache, stereotypical attacks of rather short-lasting pain sometimes tend to group predominantly at evening hours, following a bizarre chronobiology of Circadian rhythm [1, 2]. Although it is considered a 'rare' disease, compared to the other primary headaches, it affects nearly 1/1000 people, more prevalent to men (3,6:1 ratio) with an age of onset at around 20 up to 50 years old [3,4]. The underlying pathophysiology and the inheritance pattern are not yet fully understood, while treatment consists mainly of non-specific agents and only recently monoclonal antibodies targeting calcitonin gene related peptides (CGRP) have been studied [17]. Despite its striking characteristics, CH remains underdiagnosed and mistreated by physicians, sometimes for years or even decades [5,9].

The 3rd edition of the International Classification of Headache Disorders (ICHD-3) defines intensity of CH pain as severe or very severe when left untreated; strictly unilateral, affecting orbital, supraorbital or temporal sites [1]. Pain intensifies rapidly within 5 to 10 minutes and may last 15 to 180 minutes leaving the sufferer exhausted and vulnerable to another episode [1, 3, 4, 18]. During the pain the recumbent position is most certainly not preferred and unlike patients with migraine, pacing, sitting, or even seeking physical activity and exposure to cold are preferred by patients, as are perceived to relieve the pain [18]. The number of episodes range from once every other day to eight times a day and attacks are accompanied with at least one of the following symptoms or signs ipsilateral to the headache: lacrimation, conjunctival injection, nasal congestion followed by rhinorrhea. Less commonly, forehead and facial sweating, redness and a sense of fullness in the ear. Signs of miosis, ptosis and/or eyelid edema suggesting ipsilateral to pain Horner syndrome may accompany [1-4, 18]. At least five episodes with the above characteristics are required to diagnose CH based entirely on the clinical features, unless they are accounted for by another ICHD-3 diagnosis [1]. The dissemination of bouts in time, when recorded in headache diaries, helps categorize CH forms and demonstrates that the vast majority of patients suffer from eCH, while around 10% from cCH. Chronic cluster headache may start de novo or develop from the episodic form, while some patients with cCH may remit to the episodic form [1-4, 18].

Past medical history of head trauma and social habits such as smoking (>20 cigarettes/day), high alcohol (50-100g/day) and caffeine intake (5-7 cups/day) have been recognized more commonly than expected among CH patients, but the significance is not clarified [6]. A late age of onset combined with longer course of the disease which consists of more than one cluster bout per year or longer lasting

cluster bouts followed by shorter remission periods and more frequent sporadic attacks are well known predisposing factors for relapsing to cCH. On the other hand, use of prophylactic treatment has been shown to favor swinging back into eCH [5, 6].

Several studies hitherto have tried to shed light to the mystery of why this so unique clinical syndrome remains underdiagnosed for so long [5, 7, 9]. Delays in diagnosis are present worldwide and vary from country to country with the mean time to correct diagnosis in UK estimated in 2,6 years, in Spain 4,6 years, in Italy and East European countries 5,3-6,4 years, while data report that the median time in Greece was 1 year (range 0-7) only when the diagnosis made after the 2010. Before 2000, patients waited patiently for a median time of 13 years (range 0-45) [5,9]. Migraine, trigeminal neuralgia and sinusitis were amongst the common misdiagnoses made by general practitioners, ENT specialists, ophthalmologists, dentists or even neurologists or neurosurgeons [5,9]. Overall, in Greece patients with CH were shown to have consulted a median number of 2-5 clinicians before the correct diagnosis, while even neurologists missed the diagnosis in a notable 40% of the patients evaluated [5]. Nowadays, increasing information shared on the internet, social media, podcasts and patient groups have raised awareness about the disease, leading to a considerable number of cases of self-diagnosis by the sufferers. Early onset of the disease, side sifts between or within bouts, location of pain in "atypical" areas such as in the jaw, cheek, lower teeth or ear, presence of photophobia, absence of restlessness and absence of autonomic features may lead to this diagnostic delay [5, 9]. In some cases, the nature of the disease per se, and mainly the short-lasting attacks that tend to cluster and may disappear for quite some time from bout to bout could explain why some patients do not seek promptly expert care. Nonetheless, mis- or late diagnosing leads to mistreated patients that may use over-the-counter medications with poor response or use inappropriate substance, such as illicit drugs. In real life, a whole range of alternative remedies are almost always inadequate to handle the pain caused by cluster headache and without expert supervision, futility seizes the patients that experience the detrimental effects of the condition in their socioeconomic aspects of their life as years pass by [5, 9].

Quality of life (QoL) and Disability surveys using scales have evaluated the impact of the disease in daily activities and mental health [14, 15]. Only rather recently (2016) the Cluster Headache quality of life scale (CHQ) was published. It contains 28 items addressing the restriction of activities, impact on mood and interpersonal relationships, anxiety, and lack of vitality while previous studies failed as they were hospital- based rather than population- based and not sensitive to clinical changes [15]. Although patients underwent surgical procedures for CH that alleviated pain and reduced weekly attacks, QoL improvements were not statistically significant [14]. Absence of CH-guided Disability scales obliges researchers to use either generic or migraine-specific assays like the Migraine Disability Assessment (MIDAS) and the Headache Impact Test (HIT-6) which are short questionnaires that address the negative impact of headache the past 3 months and 4 weeks, respectively [13, 14]. Either one shares its own faults given the fact that a bout may last for only a month and MIDAS requires a long recall period of symptoms. HIT-6 score >60 reflects the severity and the need for treatment though its 3rd question: *"When you have a headache, how often do you wish you could lie down?"* is clearly not designed for the CH patients [13, 14].

Apart from identifying common environmental factors among the sufferers, the understanding of CH pathophysiology may help unmask any genetic predisposition. Recent systematic reviews suggest that while the majority of the cases are sporadic, 6,3% appear to be familial and first-degree relatives of CH patients encounter 5-18 times higher risk of developing this disorder compared to the general population. Studies evaluating single nucleotide polymorphisms (SNPs) and genome- wide association studies (GWAS) revealed the role of HCRTR2 and GNB3 gene-containing SNPs but none of them were significantly associated with CH [10, 11, 12].

The circannual periodicity of the attacks points for a pathophysiological involvement of hypothalamus, the location of first order autonomic neurons who mediate sleep-wake cycles via the suprachiasmatic nucleus. Imaging studies genuinely show the activation of ipsilateral hypothalamic gray matter during the attacks but it is enigmatic how hypothalamus contributes to the pathophysiology [10, 11, 12]. Another culprit is thought to be the trigemino- autonomic reflex which is elicited via efferent neurons of the superior salivatory nucleus that synapse in spheno-palatine ganglion (SPG) and the facial nerve supplying parasympathetic innervation to cranial vasculature and glands [10]. The trigeminal nerve serves as the afferent branch to converge at the trigeminal ganglion (TG) and project back to the trigeminal nucleus caudalis (TNC). Whenever this reflex activates, neuropeptides like CGRP, vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP/ADCYAP1) increase in cranial blood stream [10, 11, 12]. CGRP and its receptors are found in abundance in the central nervous system, especially the posterior Hypothalamus, the trigeminovascular system and the Aδ-, C- fibers involved in pain perception [17]. Presence of CGRP in the TNC alters neuronal activity lowering the activation threshold,

thus contributing to the nociception of pain [17]. PACAP on the other hand greatly increases CGRP release in lamina I/II of TNC, propagating pain [10]. Neurogenic inflammation is the result of vasodilation, plasma protein extravasation, glial and mast cell activation in an unclear hypothalamus mediated response that supports both the periodicity and the profound autonomic activation during the pain [10, 11, 12].

Cluster headache symptoms are not always benign and primary. Ekbom's classic observation of CH symptoms in patients with ipsilateral internal carotid artery stenosis contributed to rule out this secondary headache [8]. In the following years, a large number of pathologies have been associated with secondary cluster headache and a thorough investigation is usually warranted at first appearance of cluster headache symptoms [19].

Treatment of CH is traditionally divided into three categories: acute, bridging and preventive therapies [3, 7]. First presented in a study of 1985, the well-established (level A evidence) use of high-flow (12L/min) concentrated oxygen when provided through a non-rebreather mask can usually terminate the attack within 20 minutes [16]. Recent data from the largest CH survey performed hitherto, updated the effectiveness that reaches up to 44% for "completely effective" result, although there are reported implications regarding the difficulty in obtaining the particular treatment as it is hard to find (apart from the hospitals) and not always compensated for home use by the insurance companies [16]. Comparable effectiveness is shown with 6mg subcutaneous injection of sumatriptan, a serotonin receptor agonist for 5-HT1B and 5-HT1D, completely relieves symptoms in 43% of patients within 15 minutes [3, 7, 16]. Zolmitriptan 5mg nasal spray (level A),10 mg nasal spray (level A) and sumatriptan 20gm nasal spray (level B) can be a plausible alternative to injections wherever this formulation is available. Dihydroergotamine intramuscular injection and cafergot/ergotamine tablets shared intermediate effectiveness and intermediate side effects. Intranasal capsaicin or lidocaine and the newest entry of intranasal ketamine appear safe but of limited effectiveness acute treatment choices [3, 7, 16]. Last but not least, opioids were only 8% "completely effective" and around 50% "completely ineffective", crystallizing that they are a non -viable solution for CH [16].

Bridging therapies consist of short-term interventions that focus on rapidly decreasing the frequency of a sufferer's attacks when a bout starts, regarding the long-term preventive methods require some more time. Oral steroids are traditionally initiated in a tapering dose, while suboccipital nerve block with injected steroids (level A evidence) can be an alternative when systematic use of steroids is contraindicated [3, 7, 16]. Sphenopalatine ganglion (SPG) block with suprazygomatic alcohol solution or radiofrequency ablation (RF) are not widely used nowadays [16].

Preventive therapies aim to reduce the frequency and the severity of pain in the long run and they are used in combination with acute and bridging techniques. Verapamil, a calcium channel blocker that acts in vascular smooth muscle, promotes vasodilation and presents effectiveness in doses ranging 240-960mg per day. Vradycardia, constipation and leg oedema are the main usual side effects [3, 7, 16]. Second- line agents with a lesser potential for efficacy and noteworthy adverse effects, are lithium, used in doses ranging 600-1500mg per day and topiramate [3, 7, 16]. CGRP monoclonal antibody galcanezumab was the first agent in this modern category of preventive treatments to be approved only for episodic CH, when 300mg of subcutaneous injection once monthly proved effectiveness and met safety criteria. Eptinezumab, another CGRP monoclonal antibody, is currently being tested for eCH and cCH [17]. Although IgG antibodies do not cross the brain blood barrier in large amounts, they can still affect the trigeminal ganglion which is left outside BBB and postulate a possible mechanism of action [17]. Devices used for preventive reasons in refractory CH are the non- invasive vagus nerve stimulator (nVNS) and an implantable neuromodulator of the SPG. Deep Brain Stimulation (DBS) of the posterior hypothalamus, especially in the refractory chronic CH, aligns with the suspected pathophysiology of CH, but the relevant studies had to halt [16].

This concise essay was conducted to provide the theoretical background needed to diagnose and treat Cluster Headache, the most common trigeminal-autonomic cephalalgia. Open questions during the clinical evaluation about the nature and the duration of pain, followed by sneaky, closed- type questions about the presence of autonomic symptoms and the mysterious clustering of the attacks followed by pain free periods, will finally unravel this stereotypical deliberating headache that causes significant disability to the sufferers. Exclusion of secondary headaches is most often needed for atypical cases, depicting the brain and its vasculature. Early onset bridging therapy and acute / abortive medication alongside with a long-lasting preventive agent is the mainstay for treatment. The need for psychological support in chronic pain syndromes and lifestyle modifications are "preventive strategies" themselves and should be broached to the patients, pointing out the importance of alcohol avoidance, the thorough management of comorbidities and sleep hygiene Important notice should be given to the patient's adherence to the treatment due to the common phenomenon of medication overuse which can be overthrown by close monitoring via headache diaries and an empathic listener- medical expert. The grow-

ing interest of healthcare providers to acknowledge the key features of the disease pledge to an early diagnosis, with better outcomes and prevention of the chronic form of the disease which is even more disabling and difficult to treat.

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