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COMMENTARY

Cluster Headache is Still Lurking in the Shadows

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ABSTRACT

Cluster headache, apart from its legendary reputation as the most violent headache that can exist, suffers from an average 60-month delay in diagnosis. The simplicity of the clinical manifestations, although dramatic, makes this delay inexplicable. The education of emergency department physicians and various specialists not specifically dedicated to headaches allows cluster headache to remain in a lurking position with flourishing periods of disease that are often unpredictable in both onset and disappearance. Older drugs have always shown high efficacy but also an equally high rate of adverse events, often discouraging their appropriate use. The availability of a new drug class such as monoclonal antibodies for calcitonin gene-related peptide or its receptor ($CGRP_{(r)}$), which have already been efficient for migraine, shows a jeopardized geography of access in the world, and this favors the progression of the episodic form into chronic and of the chronic into refractory.

Keywords: Calcitonin gene-related peptide; Cluster headache; Education; Galcanezumab; Refractory chronic cluster headache; Verapamil

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Key Summary Points

Cluster headache is a quasi-rare disorder affecting 1 in 500 of the general population and still represents an unresolved challenge today.

The pathogenesis of cluster headache is currently based on the derangement of the interactions existing between the trigeminovascular leading to the release of specific neuropeptides like calcitonin gene-related peptides (CGRP) and pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38).

The treatment of cluster headache acute attacks still revolves around drug aged 30 years like subcutaneous sumatriptan.

The preventive treatment of cluster headache is based on the availability of galcanezumab, but this option is geographically limited to the US.

In those countries where galcanezumab is not available, verapamil at high dosage is still used with success but its use is limited by its cardiovascular risks.

The social and economic burden of this disease is high, therefore it is important to spread the use of CGRP monoclonal antibodies for all patients everywhere.

DIGITAL FEATURES

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CLUSTER HEADACHE, THE CINDERELLA AMONG THE PRIMARY HEADACHES

Despite all the remarkable efforts to raise awareness of cluster headache (CH), it still represents an unresolved challenge today, penalizing this scant group of patients that shows a prevalence of 1 in 500 of the general population, an inheritance that presents a risk from 5 to 18 times for first-degree relatives and from 1 to 3 for second-degree relatives of having the same pathology [1], with family history rate calculated at 6.27% [2]. The simplicity of its clinical profile is contrasted by the fact that the diagnosis is made with an average delay of 5 years from the first appearance of the attacks, and the correct therapeutic approach is administered only to a minority of these patients [3]. As a natural consequence of these discrepancies in health care, this population of CH patients shows a high ratio of sickness absence benefits and greater access to disability pensions [4].

The pathogenesis of this disease is, at the current state of knowledge, based on the derangement of the complex interactions existing between the trigeminovascular system activating the trigeminal-autonomic reflex, leading to the release of specific neuropeptides like calcitonin gene-related peptides (CGRP) and pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38), and its interactions with a deranged (putative) hypothalamic control center [5, 6]. Further multiple basic and clinical research approaches have added important information on the role of neurosteroids, neuroimaging and neurophysiology data, sleep disorders, and psychiatric comorbidities in this still not completely clear pathophysiological picture of CH [7–10].

One of the well-known criticalities in the treatment of CH is the aged drugs used for the control of the brutal attacks and for the suppression of the active and thriving phases of the disease or its prevention [11, 12]. However, the lightning-fast speed of the activation phases, with crises that reach the maximum in intensity and daily frequency in 24–72 h, requires a fast-track assistance path from the emergency

department to the hospital structures and the specialists dedicated to it, in order to prevent the disease from reaching its highest clinical expression and therefore a possible delayed response to therapy [13–15].

Beyond this criticality, it has recently been highlighted that the transition from randomized control trials (RCTs), which offer a mathematical view of drugs applied to a specific pathology, should be weighed against the flexibility of clinical practice as observed by real-world evidence (RWE) data [16]. The sum of all these criticalities has in fact brought to the clinical researchers' attention the entity of refractory chronic cluster headache (RCCH) [17], which will hopefully find a place in the next revision of the International Classification of Headache Disorders, the 4th.

The paucity of therapeutic approaches towards CH has over time stimulated researchers to reapply innovative therapies already used in migraine, such as neurostimulation and botulinum toxin with RWE, unfortunately far from the original results of the RCTs [18, 19].

OLD AND NOVEL TREATMENTS FOR CH

Acute treatment of CH is based on subcutaneous sumatriptan and oxygen, the transitional treatment on the use of corticosteroids, and the preventative one on the use of verapamil [5]: this pharmacological approach is more than 30 years old.

Unfortunately, the problems for CH do not end here because only part of these suffering patients can take advantage of a new therapy that has been extended from migraine also to CH in the USA and immediately abates the crises. In fact, on February 28, 2020, the European Medicines Agency (EMA) rejected the approval of galcanezumab (100 mg × 3/monthly subcutaneously) for the prevention of episodic and chronic cluster headache, a highly effective therapy currently available in USA after the Food Drug and Administration approval [20–23]. There is hope today for a reassessment by EMA after the publication of ongoing studies on RWE.

Meanwhile, given the dramatic nature of the clinical picture and the extreme violence of the painful attacks, scientific journals continue to dedicate little space to CH, not only because of its relative rarity, but especially because the medical world has a lack of knowledge on CH.

Just to give an example, among the currently available preventative therapies, verapamil at high dosage (360 mg and more up to 720 mg/day) offers good efficacy [24]. Unfortunately, a possible adverse event an occur as the atrioventricular block produces an underdosage in clinical practice with a lack of efficacy.

Last but not least, recent valuable estimates of the direct and indirect costs of episodic and chronic CH in the specific setting of a tertiary headache center confirmed the high economic impact of CH on both the National Health System and patients [25].

Therefore, we must reiterate the strong need for extended clinical-diagnostic points for CH jointly to a better education to pharmacological management, in order to improve the status of this neglected patients' population [26].

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