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CLUSTER HEADACHE- SUICIDE HEADACHE: PATHOGENESIS, DIAGNOSIS, AND MANAGEMENT

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Abstract: Cluster headache is a primary headache disorder characterized by recurrent, strictly unilateral attacks of severe orbital or temporal pain, accompanied by ipsilateral cranial autonomic symptoms. Despite being clinically well defined for more than two centuries, its pathophysiology remains incompletely understood. Recent advances implicate trigeminovascular activation and hypothalamic dysfunction, particularly disturbances in circadian rhythm regulation, as central mechanisms. Functional imaging consistently demonstrates hypothalamic activation during cluster attacks and in related trigemino-autonomic cephalalgias, supporting a shared neurobiological basis. Diagnosis is clinical, guided by International Classification of Headache Disorders (ICHD) criteria, although neuroimaging may be warranted to exclude secondary causes. Acute management relies on subcutaneous sumatriptan and high-flow oxygen, with intranasal lidocaine and dihydroergotamine as adjuncts. Preventive therapy is essential to reduce attack frequency; verapamil remains the cornerstone, with lithium, corticosteroids, methysergide, and calcium channel blockers as additional options. Overall, evidence highlights the hypothalamus as a pivotal structure in cluster headache pathogenesis and a potential target for future therapies.

Key words: Cluster headache; trigemino-autonomic cephalalgia; hypothalamus; circadian rhythm; trigeminovascular system; functional imaging; verapamil; lithium; preventive therapy; acute management.

MAIN PART

Introduction

Cluster headache represents a distinct primary headache disorder characterized by excruciating unilateral pain, typically localised in the orbital or periorbital region, and consistently associated with ipsilateral autonomic manifestations. The condition exhibits a strong circadian pattern, with attacks occurring at predictable times of the day and recurring in cyclical bouts, separated by periods of remission in the majority of affected individuals. These headaches frequently arise 1–2 hours after sleep onset or in the early morning and often demonstrate seasonal clustering, implicating hypothalamic involvement in the underlying mechanism. As a result, traditional vascular theories have been supplanted by recognition of neurovascular processes as the central contributors. Familial aggregation further suggests a genetic predisposition in certain populations. Advances in neuroimaging have broadened understanding of the pathophysiology and have even enabled therapeutic interventions such as hypothalamic deep brain stimulation. While many patients respond favourably to current treatments, a subset remains refractory. Encouragingly, diagnostic delays have decreased in recent years, likely due to increased awareness of the syndrome and more effective therapeutic approaches.

Clinical Features

Patients frequently describe cluster headache as one of the most severe forms of pain known, often using vivid and distressing metaphors to convey its intensity. Female patients have reported that the pain surpasses that of childbirth. Attacks are typically brief (15–180 minutes) yet intensely debilitating and may occur up to eight times daily. They are strictly unilateral and are invariably accompanied by cranial autonomic symptoms, including lacrimation, conjunctival injection, rhinorrhoea, nasal obstruction, ptosis, and miosis. These features are almost always ipsilateral to the pain and are

attributed to parasympathetic hyperactivity alongside sympathetic dysfunction. In some cases, signs such as miosis and ptosis may persist between attacks.

In contrast to migraineurs, individuals with cluster headache exhibit marked restlessness, often pacing, rocking, or applying pressure to the affected region. Many seek relief through exposure to fresh or cold air, while others isolate themselves due to irritability and aggression during attacks. Although rare, approximately 3% of patients present without autonomic symptoms, and a small proportion experience persistent sympathetic disturbances even after side-shifts of the pain.

The disorder occurs in episodic and chronic subtypes. Episodic cluster headache, the most prevalent form, manifests as daily attacks lasting weeks to months, followed by remission periods that may extend up to a year. Chronic cluster headache, defined by an absence of remission exceeding one month for at least one year, poses significant management challenges, with surgical interventions considered for medically intractable cases.

Epidemiology and Genetics

Cluster headache is considerably less prevalent than migraine, affecting fewer than 1% of the population. It shows a marked male predominance, with the episodic form accounting for 80–90% of cases. Bouts may involve one to eight attacks per day, persisting for weeks to months, while remission phases remain symptom-free. Chronic cluster headache may present de novo or evolve from the episodic form.

One of the most frequent concerns expressed by patients is whether, similar to migraine, cluster headache tends to diminish with advancing age. Until recently, evidence addressing this question was largely anecdotal, but larger epidemiological investigations have begun to clarify the issue. Overall, findings suggest that the natural history of the disorder includes a tendency for symptom reduction over time.

The most comprehensive epidemiological study to date examined approximately 550 individuals with both episodic and chronic cluster headache across a follow-up period exceeding three decades (1963–1997). Results revealed a decline in the predominance of male cases, with a higher male-to-female ratio observed among patients whose onset occurred before 1970 compared to those with onset after that year. Notably, the relative proportion of episodic to chronic forms remained stable. Current prospective data indicate that the condition is around three times more frequent in men than in women, although clinical presentation appears identical across sexes. It has been hypothesised that hormonal influences and environmental lifestyle factors may contribute to the observed rise in female cases after 1970. Additionally, improved recognition and acceptance of the disorder among physicians may partly explain the increasing number of diagnoses in women.

Medical histories of affected patients often highlight a relatively high prevalence of head trauma or concussion, although establishing a direct causal relationship remains problematic. Furthermore, nearly 85% of patients with chronic cluster headache are long-term cigarette smokers. Interestingly, cessation of smoking does not alter the disease course, raising the possibility that chronic nicotine exposure may act as a trigger in genetically susceptible individuals.

Prior to the 1990s, cluster headache was rarely regarded as an inherited condition. However, subsequent reports, including cases among monozygotic twins and evidence of familial clustering in approximately 7% of families, point towards a genetic contribution. This familial occurrence corresponds to a 14-fold increased risk among first-degree relatives and a two-fold increase among second-degree relatives. A large study involving 186 index cases and 624 first-degree relatives documented a positive family history in 11% of patients. Although the precise inheritance pattern could not be established, segregation analyses have suggested autosomal dominant transmission in some families, while other findings support recessive or multifactorial inheritance models.

The variability in age of onset, which can range from childhood (7 years) to late adulthood (over 80 years), complicates the differentiation between affected and unaffected individuals in genetic analyses.

Nevertheless, the significantly increased familial risk provides strong evidence for a hereditary component in at least a subset of cases. Despite this, no definitive molecular genetic markers have been identified to date. Given the paroxysmal nature and circadian/seasonal rhythmicity of the disorder, future genetic research is likely to focus on candidate genes regulating ion channels and biological clock mechanisms.

Epidemiological data indicate that symptoms often diminish with age, though longitudinal evidence remains limited. Large-scale studies spanning several decades reveal a decreasing male-to-female ratio in incidence, particularly after 1970, possibly reflecting both biological influences (such as hormonal or environmental factors) and heightened diagnostic recognition among women.

Pathophysiology

Although the clinical features of cluster headache have been well described for over two centuries, the precise mechanisms underlying the disorder remain incompletely understood. Significant progress has been achieved in the past decade, yet the pathophysiology continues to present unresolved questions. Any explanatory model must account for three cardinal characteristics of the syndrome: the trigeminal distribution of pain, the ipsilateral cranial autonomic manifestations, and the circadian or episodic recurrence of attacks. The traditional vascular hypothesis, which attributed the disorder to inflammation within the cavernous sinus involving trigeminal and sympathetic fibres, has now been largely replaced by concepts emphasising central neurovascular processes. Severe unilateral pain appears to arise from activation of the ophthalmic division of the trigeminal nerve, while cranial parasympathetic outflow from the facial nerve is thought to mediate the associated autonomic features such as lacrimation and rhinorrhoea.

Autonomic Features

Autonomic dysfunction in cluster headache is complex. Sympathetic impairment, producing miosis and ptosis, is thought to reflect neuropraxia of postganglionic fibres. Current theories suggest at least three potential sources for the autonomic manifestations: (1) central dysregulation linked to hypothalamic dysfunction, (2) trigeminal-parasympathetic activation leading to vasodilation or perivascular oedema within the carotid canal and secondary compression of sympathetic fibres, and (3) direct consequences of trigeminal discharge. Some evidence indicates that parasympathetic overactivity alone could account for ocular sympathetic deficits. A minority of patients (approximately 3%) do not experience autonomic symptoms, and there are reports of family members with both symptomatic and asymptomatic presentations. Rarely, pain and autonomic features may occur independently. Nevertheless, the prototypical attack is strictly unilateral and accompanied by prominent ipsilateral autonomic disturbances.

The relapsing–remitting nature of the disorder, its seasonal variation, and the regularity of attacks suggest a central role of the biological clock. Endocrine studies lend support to hypothalamic involvement: reduced plasma testosterone concentrations, impaired responses to thyrotropin-releasing hormone, and multiple circadian irregularities have been observed in affected individuals. Melatonin, a key circadian marker, demonstrates blunted nocturnal peaks and, in some cases, complete loss of rhythmicity. These findings implicate the suprachiasmatic nuclei of the hypothalamus, which regulate circadian function via retinal input, as a likely generator or trigger of cluster headache attacks.

Functional Imaging

Neuroimaging has provided compelling evidence for hypothalamic involvement. Positron emission tomography (PET) studies have consistently demonstrated activation of hypothalamic grey matter during both spontaneous and nitroglycerin-induced attacks. Such findings indicate that the hypothalamus acts in a permissive or triggering capacity rather than being merely a secondary response to trigeminal nociception.

Cluster headache belongs to the group of trigemino-autonomic cephalalgias (TACs), which also include paroxysmal hemicrania and short-lasting unilateral neuralgiform headache with conjunctival

injection and tearing (SUNCT). Although these syndromes share overlapping features, they can typically be distinguished by clinical course and therapeutic responsiveness. Functional imaging suggests partial overlap in activation patterns among these conditions, raising the possibility of shared pathophysiological substrates within the hypothalamus and trigeminovascular system.

Neuroimaging in Related Syndromes

Functional MRI studies of patients with SUNCT have consistently identified hypothalamic activation in regions closely adjacent to those implicated in cluster headache. Similar activation has also been reported in atypical trigemino-autonomic headache presentations. These findings reinforce the concept that TACs represent a spectrum of disorders unified by hypothalamic dysfunction, with variations in neuronal modulation or trigeminovascular involvement determining their clinical differences.

Hemicrania continua, another unilateral headache associated with autonomic features, demonstrates both similarities and distinctions. Although classically excluded from TACs due to its continuous nature and indomethacin responsiveness, neuroimaging has revealed activation not only in the posterior hypothalamus but also in brainstem structures such as the dorsal rostral pons, substantia nigra, and pontomedullary junction. This pattern reflects its clinical phenotype, which overlaps with both TACs and migraine. Collectively, such imaging data support the view that primary headache syndromes can be differentiated based on their distinct neuroanatomical activation signatures. However, an unresolved question remains whether these patients' brains are structurally normal, or whether subtle anatomical abnormalities contribute to disease expression.

Diagnosis

The diagnosis of cluster headache is made solely on clinical grounds. According to the International Classification of Headache Disorders (ICHD), explicit diagnostic criteria are employed, designed to be precise and leave minimal scope for subjective interpretation. The fact that more than a dozen synonyms for cluster headache have historically been in use highlights both the earlier uncertainty surrounding its etiology and the importance of standardized diagnostic guidelines for research and clinical practice. In its classic presentation, cluster headache is usually unmistakable. However, no single instrumental or laboratory test can definitively establish or distinguish idiopathic headache syndromes.

Despite this, in clinical practice, the application of neuroimaging techniques such as cranial CT, MRI, or MR angiography in headache patients shows considerable variability. Ancillary tests—including electrophysiological studies and cerebrospinal fluid analysis—are generally not informative. For initial diagnostic evaluation, especially in patients with neurological abnormalities on examination, cranial CT or MRI is advisable to exclude secondary causes, such as intracranial masses or midline malformations, which have occasionally been associated with symptomatic cluster headache, particularly in elderly individuals.

Differential Diagnosis

The revised ICHD classification groups cluster headache within the broader category of trigemino-autonomic cephalgias. Disorders in this group share two defining features: severe, short-lasting, unilateral headache episodes coupled with characteristic cranial autonomic manifestations. These syndromes differ, however, in the temporal pattern, frequency, and periodicity of attacks, as well as in the intensity of pain, the degree of autonomic involvement, and their respective therapeutic approaches.

Although cluster headache typically follows a well-defined pattern, atypical presentations have been reported. These include cluster attacks associated with aura, hemiplegic variants, headache-free episodes with autonomic symptoms, and conversely, cases with headache but absent autonomic signs. Even bilateral manifestations, though rare, have been documented. Case reports describing unusual variants suggest that as more patients are evaluated by headache specialists, novel subtypes of this primary headache disorder may be identified.

Overall, the concept of trigemino-autonomic syndromes provides clinicians with a valuable framework for understanding the pathophysiological basis of neurovascular headaches. It also contextualizes the selection of both acute treatment strategies and long-term preventive interventions.

Acute Therapeutic Approaches

In an open retrospective trial, intravenous administration of 1 mg dihydroergotamine over a 3-day period was reported to be effective in terminating severe cluster headache attacks. The use of ergotamine for short-term prophylaxis has also been investigated. Suppository formulations, however, require a relatively long latency before therapeutic onset; nevertheless, a 2 mg dose administered in the evening has been recommended to prevent nocturnal cluster episodes.

Intranasal lidocaine has also been explored as a treatment option. Application of 1 mL of a 4–10% solution on the side of pain, with the patient's head reclined at 45° and rotated 30–40° toward the affected side, has demonstrated efficacy in roughly one-third of patients. The mechanism of action is believed to involve blockade of the sphenopalatine fossa. This approach was originally inspired by earlier observations that cocaine could abort cluster headache attacks, prompting debate about whether its therapeutic effect derived from anesthetic properties rather than psychotropic ones.

Prioritization of Acute Therapy

Given the abrupt onset and rapid intensification of pain, subcutaneous sumatriptan remains the first-line treatment. Oral formulations are generally inadequate because of their slow absorption and delayed onset. Inhaled oxygen constitutes the second standard therapeutic option. Compared with these, topical lidocaine is less reliable and often inconsistent in efficacy. Nevertheless, because of its safety profile and ease of self-administration, every patient is advised to attempt lidocaine therapy at least once, particularly considering that cluster attacks may occur up to eight times per day.

Preventive Pharmacotherapy

Preventive treatment is crucial in cluster headache management. Because patients may experience multiple daily attacks, excessive reliance on abortive strategies risks overtreatment and toxicity. The primary objective of prophylaxis is to suppress recurrent episodes and sustain remission throughout the anticipated cluster period. Therapy should be tailored to the individual. In episodic forms, medication is discontinued at the end of the cycle, whereas in chronic cases, tapering every other month helps assess the ongoing need for treatment.

Verapamil is the cornerstone of preventive therapy. Doses of 240–320 mg per day are widely regarded as first-line treatment for both episodic and chronic cluster headache. Although randomized controlled evidence is limited, clinical trials suggest verapamil is at least as effective as lithium, with a faster onset of benefit. In refractory cases, daily doses above 720 mg may be required; typically, treatment should be escalated gradually, with increments of 80 mg every 3 days, up to 480–720 mg before considering therapy unsuccessful. ECG monitoring is mandatory because of potential cardiac adverse effects such as bradycardia and conduction disturbances. Other side-effects include edema, gastrointestinal complaints, constipation, and mild headache. Both immediate-release and extended-release formulations are effective, though no direct comparative trials exist. Corticosteroids (prednisone 30–100 mg or dexamethasone 2–4 mg daily) may be combined during the first two weeks of therapy to bridge the latency before verapamil achieves full efficacy. Nimodipine has shown promise in small open studies.

Lithium has also been employed at doses of 600–1500 mg daily in more than 20 open-label studies. Response rates were as high as 78% in chronic and 63% in episodic cluster headache, though placebo-controlled trials did not confirm efficacy in the episodic form. In a head-to-head double-blind crossover trial, lithium and verapamil demonstrated comparable benefit, with verapamil showing faster therapeutic action and better tolerability.Lithium therapy requires close monitoring of serum levels (0.6–1.2 mmol/L) and regular assessment of renal, hepatic, and thyroid function. Adverse effects

include tremor, renal impairment, and thyroid dysfunction. Given its narrow therapeutic index, lithium is generally reserved for chronic cases when other options are ineffective or contraindicated.

Methysergide has been proposed primarily for episodic cluster headache. Open studies report benefit in 20–73% of patients, typically at doses ranging from 4–8 mg per day, titrated upward to a maximum of 12 mg. The active metabolite methylergometrine necessitates caution when used with other ergot derivatives or triptans. While short-term side effects include nausea, abdominal pain, cramps, and edema, long-term administration is restricted to 3–4 months due to risks of retroperitoneal and pulmonary fibrosis.

Corticosteroids are another widely used preventive option, though robust randomized controlled trials are lacking. Multiple open studies consistently confirm their effectiveness in rapidly suppressing cluster attacks, often serving as bridging therapy until longer-acting preventives take effect. Typical regimens include prednisone 60–100 mg daily for 5 days, followed by gradual tapering of 10 mg per day. Approximately 70–80% of patients respond favorably. Both oral and intravenous routes have been shown effective, and in some cases continuous administration is required for attack control.

CONCLUSION

Cluster headache is a distinct and debilitating primary headache syndrome with characteristic clinical, neurobiological, and chronobiological features. Advances in neuroimaging and circadian biology have clarified the role of hypothalamic dysfunction in its pathophysiology, while trigeminovascular activation accounts for pain and autonomic manifestations. Although diagnosis is clinical, structured criteria from the ICHD ensure reliability and comparability across research and practice. Acute therapies such as subcutaneous sumatriptan and oxygen provide rapid relief, whereas preventive regimens—particularly verapamil—are essential to control attack frequency and disease burden. Emerging evidence from related trigemino-autonomic cephalalgias underscores a shared pathophysiological framework, positioning the hypothalamus as a promising therapeutic target. Continued integration of clinical observation, neuroimaging, and pharmacological research will be crucial for improving outcomes in this disabling disorder.

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