History of cluster headache

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Abstract
Objective: To summarise the history of cluster headache evolving concepts and growing insights.

Background: Excruciating pain, activation of the parasympathetic nervous system, and circadian rhythmicity characterise cluster headache attacks.

Results: We find the oldest descriptions of patients suffering from the disorder in case reports of the 17th and 18th centuries. Only in the 19th and early 20th centuries did physicians start hypothesizing its cause. Initially, many researchers suspected the origin of the pain in peripheral nerves or blood vessels. However, eventually, they understood that the cause of the disease lies in the brain. In 1998, Positron emission tomography studies revealed increased activity of the posterior hypothalamus, whose role remains incompletely understood. Only recently have researchers realised that being diseased implies more than dysfunction. Recent studies analysed the consequences of cluster headache for each patient. Many struggle to deal with the disorder even in the absence of pain.

Conclusion: Physicians have been aware of this type of pain for at least 300 years. Only when researchers studied pathological anatomy and physiology did knowledge accrue. A more comprehensive picture of the disease severity emerged when they also considered its consequences.

Keywords
histaminic cephalalgia, history of headaches, neurology, pain, primary headache, trigeminal autonomic headache

Introduction
Cluster headache (CH) attacks are excruciating and often occur at night. Their hallmarks are unilateral pain and autonomic dysfunction that manifests as rhinorrhoea and reddening and tearing of one eye in almost all patients. Besides, most patients are restless, some self-harm, or even consider suicide. The end of the attack usually comes after 40–90 minutes and allows resting. – Only for some time, though, as the symptoms recur; studies indicate an average attack frequency of one to two per day.

The episodic form of the disorder is most common. Untreated patients suffer attacks for 6–8 weeks on average (so-called ‘bouts’). Then, they enter a remission period that may last for years. The chronic form affects about 10% of the patients who are never free of pain for more than 3 months.

There is a genetic predisposition for CH. Hence, men and women must have always suffered from this disorder. However, only recently have physicians come to see the syndrome as a separate disease. Its low point-prevalence might have slowed the insight. Yet, we will see that precise observation is hardly a unique feature of the 20th or 21st century. Doctors have been aware of this pain for a long time. What did change is the conceptualisation of the term ‘disease’ and the means to deal with it.

This article follows the disorder through the centuries focusing on evolving concepts and growing insights.
The evolving concept of disease

Case reports of the 17th and 18th centuries contain the earliest descriptions of CH. At that time, this genre of medical writing already had a long tradition. Its roots lie in Egyptian papyri from about 1600 BC. During the 4th century BC, Hippocrates also collected vast patient records. He focused on facts; emotions and mental states were less relevant to him. – He likely intended to deduce the prognoses of future patients. Later, Galen, a Greek physician born in the 2nd century AD, took notes as well. But, after him, European physicians stopped publishing their experiences for centuries. 19,20

Only in the late Renaissance did European physicians resume sharing their experiences. 19 We find examples of patients likely suffering from CH among their notes. For instance, two authors reported patients with headaches that occurred at fixed times. The first was the Dutch physician Nicolaas Tulp (1593–1674) in his ‘Observationes Medicæ’ (published in 1641). The second was Thomas Willis (1621–1675) in his book ‘De Anima Brutorum’ (published in 1672). 21 None of them provided enough information to confirm the diagnosis.

At that time, the humoral doctrine dominated medical reasoning. However, during that century, thinkers and physicians like Francis Bacon (1561–1626), Thomas Sydenham (1624–1689), and Robert Boyle (1627–1691) promoted a new mindset. 22,23 Their ideas would lead to the advent of empiricism. Sydenham said diseases are ‘to be reduced to certain and determinate kinds, with the same exactness as we see it done by botanic writers in their treatises of plants’. 24 This approach favoured the elaborate case descriptions published in the following century.

Francisco Suárez de Rivera (1686–1751?) was the personal physician to King Philip V and, later, King Ferdinand VI of Spain. In 1726, he published his ‘Teatro de la Salud o Experimentos Médicos’. One chapter described a nun with unilateral headache attacks above one eye and in the cheekbone. Ipsilateral tearing and restlessness accompanied the pain, which had circadian and circannual rhythmicity. 25

Gerard van Swieten (1700–1772) was the personal physician to Empress Maria Theresa and the founder of the Vienna School of Medicine. In 1745, he published his ‘Commentaria’, which would become a popular medical textbook. It contains the description of a middle-aged man with left-sided headaches. The ipsilateral eye teared and reddened during the attacks that occurred with circadian rhythmicity. 26,27

The detail-richness of these case reports witnesses proficient observation skills. 20,25–27 Today’s readers with basic knowledge about headache disorders will infer the diagnosis. – However, none of the authors bothered about diagnoses. At that time, physicians did not always group symptoms together and define them as a disease. Instead, ‘symptoms and signs were themselves diseases’. 28 Sydenham had taught interpreting constellations of symptoms as syndromes with similar prognoses.

The understanding of disease advanced under the influence of Giovanni Battista Morgagni (1682–1771) and Marie François Bichat (1771–1802). 23,24,28 Being diseased now implied bearing a tissue lesion. The patients and their individual complaints lost some importance. This new perspective seems unsuited to fostering an understanding of primary headaches. However, understanding of the term ‘disease’ soon developed further, and knowledge about headache disorders grew.

In the late 19th century, scientists started studying physiology. Diseases were now understood as due to dysfunction, and this view provided novel means to speculate about their origin. 28 At that time, scientists viewed migraine as a vascular headache. 29 However, before applying this idea to CH, they followed another path.

Insights into the pathophysiology

Neuralgia as the cause of the pain

Moritz Heinrich Romberg (1795–1873) was a physician and professor at the Friedrich Wilhelm University in Berlin. He published the book ‘Lehrbuch der Nervenkrankheiten’ in 1840. 23 It reports a type of headache that he called ‘ciliary neuralgia’ and seems to match what we now call CH. 30 Besides unilateral pain, it comprises a ‘contracted pupil’, unilateral photophobia, lacrimation, and eye reddening. However, there is no mention of circadian rhythmicity.

Romberg’s name for the disorder suggests the pain origin in a peripheral nerve. Others shared that view.

At the beginning of 20th century, several authors reported patients with symptoms resembling CH. In 1908, Greenfield Sluder (1865–1928) published the description of a headache he called ‘lower half headache’. 31,32 It comprised pain in the eye, upper jaw, and teeth and sometimes rhinorrhea and lacrimation. He suspected an implication of the sphenopalatine ganglion because of the symptom constellation. 31 However, he might have described a variant of the disorder; although the pain during CH attacks may occur in the lower half of the head, it is more common in the upper half. 33

In 1926, the London-based neurologist Wilfred John Harris (1869–1960) published his book ‘Neuritis and Neuralgia’. It discusses subtypes of an entity he referred to as ‘migrainous neuralgia’. 34,35 It lumps together different headaches, some of which may be a CH as we understand it. 34 However, his classification does not conform to our present understanding. Neither subcategory of the migrainous neuralgia corresponds to CH.

In one patient with ‘periodic migrainous neuralgia’, he observed the ‘cluster phenomenon’. It comprises daily attacks for some weeks that eventually disappear and later recur. Another subtype of the entity was ‘ciliary neuralgia’ – the same name Romberg had chosen almost 1 century
ago. One patient in this group had miosis and ptosis during the attacks.34,35

Harris Vail described a ‘Vidian neuralgia’ in 1932 that also resembles what we now call CH.36

The hypothesis of peripheral nerves being the cause of the pain persisted for many years. In 1988, Moskowitz thus suspected the ‘pathophysiological focus’ in the cavernous sinus.37 The reason was the close vicinity of fibres originating in the ophthalmic and maxillary divisions of the trigeminal nerve, and the superior cervical ganglion as well as fibres passing through the sphenopalatine ganglion. Several case reports describing CH mimics have since reported an affection in this location.38–42 However, in patients with (idiopathic) CH, there generally seems to be no abnormality.43,44

The references to the pain as neuralgia from different authors indicate that they presumed an implication of peripheral nerves.45 Consequentially, some physicians attempted to soothe the pain by treating peripheral nerves.46

Sluder provided pain relief by injecting cocaine or alcohol into the sphenopalatine ganglion.47 Harris proposed infiltrating the infraorbital nerve or the trigeminal ganglion.39 In 1947, Gardner and co-workers sectioned the petrosal nerve.48 Much later, others cut the trigeminal nerve root and the auriculotemporal nerve.49–50 In 1984, steroid blockades of the greater occipital nerve were introduced as prophylaxis.51 Not all researchers reporting these methods provided precise information on therapeutic success but generally indicated a good response in most of their patients.

More recently, electric stimulation of the sphenopalatine ganglion and the occipital nerve proved helpful to large proportions of patients with refractory chronic cluster headache.52,53

Nevertheless, peripheral nerves are unlikely to be the sole cause of the disorder, given the inconsistent successes of these approaches. However, the infiltrations and stimulations may have reduced the attacks by modulating central pain perception.54 Modulation of pain perception could also explain how stimulation of the vagus nerve reduced the attack frequency in some patients.55

Interest in the vagus nerve in relation to headaches had grown following the case report of a patient with intractable epilepsy published in 2002.56 His migraine frequency starkly decreased following the invasive stimulation of his vagus nerve. In 2005, Mauskop reported two patients whose chronic CH also responded to this treatment.57 However, more extensive studies followed only after the advent of non-invasive stimulation.

Even during the early 20th century, not all researchers assumed neuralgia to cause this type of pain. Others suspected an implication of the blood vessels.

The trigeminal-vascular system

Robert Paul Bing (1878–1956) was a professor in Basel, Switzerland,23 and in 1913, he published the first edition of his book ‘Lehrbuch der Nervenkrankheiten’.58 In it, he described an entity that he called ‘erythropsopoparlalgia’. The disorder resembles what we understand as CH today. Besides pain, his description included Horner’s syndrome and conjunctival hyperaemia. Bing even reported a higher prevalence in men. The name alludes to erythromelalgia because he assumed similar pathophysiology. He believed that dysfunction of the sympathetic nervous system caused vasodilation that led to pain.59

His emphasis on vasodilation anticipated Horton’s view of the pain as a ‘new syndrome of vascular headache’.59

Together with MacLean and Craig, Bayard Taylor Horton (1895–1980) published a detailed description of CH. Initially, they called it ‘erythromelalgia of the head’; Horton later preferred ‘histaminic headache’.60 They reported several patients with similar symptoms and presented a detailed clinical picture. It included unilateral pain, lacrimation, rhinorrhea, skin tenderness, circadian rhythmicity, and male predominance. Besides, they mentioned that the pain often occurred at night.61

Horton reported that some attacks had triggers, such as alcoholic beverages.60 He also found that subcutaneous injection of histamine could induce attacks in patients but never in controls. Histamine was one of only two vasodilating agents known at that time.62

Because epinephrine injections aborted the attacks, he deduced the presence of vasodilation. Further supporting this hypothesis, he relieved the pain by compressing the carotid artery. In 1970, Ekbom and Greitz confirmed the vasodilation with a carotid angiography during the attacks.63 It is likely that the deficit in sympathetic innervation is due to a vasodilation-related compression of the autonomous nerve fibres.

Bing, Sluder, Harris, and others were credited as the first describers of CH.26,64 However, Horton was the first to reach higher levels of awareness. Now, the search for an effective treatment began.

Horton believed that repeated histamine injections desensitise and lead to pain freedom, and initially, many physicians followed his therapeutic approach.62 However, they soon doubted that histamine was specific and effective.64,65 Later authors suspected that the end of the bout rather than the treatment stopped the pain in his sample.64 However, at that time, Horton did not know about the periodic occurrence of the attacks yet.

Harris may have treated some patients with ergotamine. But in 1947, Ekbom used it systematically to abort and prevent attacks of what he called ‘Harris-Horton disease’. Ergotamine had been known as a vasoconstrictor since the 19th century. The British ear, nose and throat surgeon Edward Woakes (1837–1912) recommended using it to treat migraine in 1868.66,67 However, in CH, both ergotamine and dihydroergotamine acted slowly and often did not lead to pain freedom.62 Thus, further treatment options were needed.
Alvarez and Mason had reported a headache relief – mostly of migraine attacks – through oxygen inhalation in 1941. It is unknown what made them consider this treatment approach. Horton promoted its use for ‘histaminic headache’ in 1952. However, the success rate of oxygen monotherapy was low, so he recommended a combination with ergotamine.\textsuperscript{58,69} Although oxygen at a sufficiently high concentration and flow (12–15 l/min, 100\% oxygen) is still a standard acute therapy, its mechanism is incompletely understood.\textsuperscript{70–72}

In 1952, Horton also treated some patients with corticosteroids but found the result unsatisfactory. Other physicians had more success but reported that its effect did not outlast the treatment.\textsuperscript{73–75} The mechanism of action is unknown; Shapiro reviews possible explanations for the effect.\textsuperscript{73}

In 1947, the Swedish Neurologist Karl-Axel Ekbom (1907–1977) highlighted the periodic nature of the disorder.\textsuperscript{23,64} Because of his observation of long remission periods, Kunkle et al. suggested the name ‘Cluster Headache’ in 1952.\textsuperscript{76,77} However, whether it was a disorder in its own right or a migraine variant remained unsettled.

In 1970, Lance and Anthony found that the two disorders have little in common save vasodilation.\textsuperscript{46} They detailed that, for instance, patients with CH tend to flush during the attacks, and migraine patients often pale. Scintillating scotomas are rare in CH but not in migraine. The sex distribution, the attack duration, and the recurrence pattern also differ. Besides, family history is scarce in CH, and histamine levels do not rise in migraine. They concluded that the two disorders differ both clinically and biochemically.

Around that time, two Headache classifications were published. One was the ‘ad hoc’ classification (1962), the other was the first edition of the International Headache Classification (1988). Both included CH as separate entities\textsuperscript{78,79}; the latter distinguished between an episodic and a chronic variant, as Ekbom had suggested in 1971.\textsuperscript{80}

At that time, researchers still suspected the cause of the disorder in the blood vessels. Hypothesising the occurrence of vasospasms, Meyer and Hardenberg tested a novel drug. In 1983, they were the first to investigate verapamil and find a reduction in the attack frequency.\textsuperscript{81,82} Later trials confirmed its positive effect; today it is the prophylaxis of choice.\textsuperscript{83} However, vasospasms are unlikely to occur during attacks. Thus, the mechanism of action of verapamil is incompletely understood. Animal experiments suggest a reduction of central sensitisation that may help prevent attacks.\textsuperscript{82,84–86}

The insights that vasoconstrictive agents could end migraine attacks, and that stimulation of serotonin receptors induced vasoconstriction, led to the development of a specific 5-hydroxytryptamin agonist. The first one became known as sumatriptan.\textsuperscript{87} Studies confirmed its positive effect on CH attacks in the late 1980s and early 1990s.\textsuperscript{88,89} Triptans are still a first-line acute therapy.\textsuperscript{90}

Calcitonin gene-related peptide (CGRP) was discovered in the 1980s. Soon its vasodilatory effect and increased concentration during migraine attacks became known. Promptly, researchers suspected an implication in CH, too.\textsuperscript{91,92}

In 1994, Goadsby and Edvinsson reported its elevated concentration in the jugular vein during attacks.\textsuperscript{93} Later, Snoer et al. suggested higher CGRP levels in episodic CH than in chronic.\textsuperscript{94} This finding suggests that CGRP plays a more critical role in episodic than chronic CH. It may also explain why antagonising its effect prevents attacks in the former, not the latter.\textsuperscript{95,96}

Later, researchers suspected that a specific reflex arc modulated the release of CGRP.

The trigeminal autonomic reflex

During the 1970s and 1980s, it became apparent that CH was not a one-of-a-kind disease. Gradually, researchers discovered other types of headaches that bore similarities. Sjaastad and co-workers described Chronic Paroxysmal Hemicrania in 1974,\textsuperscript{97} Hemicrania Continua in 1984,\textsuperscript{98} and Short-lasting, Unilateral Neuralgiform Headache Attacks with Conjunctional Injection, Tearing, Sweating, and Rhinorrhea (SUNCT) in 1989.\textsuperscript{99} These pain types share the co-occurrence of unilateral pain and autonomic symptoms. They differ from CH in their attack frequency and duration. Besides, the distinctive feature of the former two is that indomethacin at adequate doses prevents the attacks entirely and indefinitely.

Only in 1997 did Goadsby and Lipton subsume these types of pain as trigeminal autonomic cephalgias (TAC).\textsuperscript{100} In 1998, the second edition of the International Headache Classification included that name and, in addition, proposed another yet undescribed subtype in the appendix – Short-lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms (SUNA). The reason for suggesting this subtype was that the diagnostic criteria of SUNCT seemed too narrow.

The diagnosis of SUNCT required the presence of both conjunctival injection and tearing, which was not always the case, according to the authors’ experience.\textsuperscript{101} In 2005, Volcy et al. were the first to report a patient with SUNA.\textsuperscript{102}

Based on the co-occurrence of pain in the area supplied by the trigeminal nerve and the ipsilateral autonomic symptoms, Goadsby and Lipton suspected that the trigeminal autonomic reflex was central to this group of disorders.\textsuperscript{103} Its afferents run in the trigeminal nerve and synapse in the caudal nucleus of the trigeminal nerve. Efferent fibres emanate in the superior salivatory nucleus, pass through the facial nerve and the sphenopalatine ganglion, and increase parasympathetic activity. Consequences are lacrimation, conjunctival injection, nasal congestion, and dilation of the ophthalmic and carotid arteries.\textsuperscript{103} The latter likely causes...
compression of sympathetic nerve fibres, leading to Horner’s syndrome and, in some cases, Harlequin syndrome.103–105

The increased parasympathetic innervation modulates nociception in trigeminal nerve endings, releasing neurotransmitters, such as the vasoactive intestinal polypeptide.103 Thus, the reflex arc is not just an epiphenomenon but relevant to the pathophysiology of the attacks.103 Accordingly, researchers soon modulated the activity of the ganglion through electric stimulation and achieved pain relief and a reduction in the attack frequency in many patients.106 Others successfully infiltrated the sphenopalatine ganglion, using, in contrast to Sluder (see above), onabotulinumtoxin A.107,108

Let it be emphasised that unilateral and bilateral cranial autonomic symptoms may occur during migraine attacks as well.109,110 However, in migraine, they appear during the attack rather than at its beginning.111 At any rate, autonomic symptoms are not specific to one group of headaches.

While the hypothesis of the implication of the trigeminal autonomic reflex in CH became widely accepted, questions remained – mainly whether the brain or a peripheral mechanism triggers its activation.112 Studies published in 2018 showed that stimulation of neither the afferent nor the efferent arm of the reflex suffices to elicit attacks.112–114 Consequently, the brain plays a crucial role.

**Hypothalamic involvement**

Research on the treatment of bipolar disorder popularised lithium in the late 1940s and early 1950s.115 In 1977 and 1978, the periodicity of CH attacks was one reason that led researchers to investigate the efficacy of the drug as prophylaxis for that disease as well.116,117 Lithium has since become a standard therapy.90

Researchers already knew since the 1970s that the hypothalamus stored most of the brain’s lithium,118 and in 1987, Kudrow speculated that the circannual rhythmicity of the bouts might be due to hypothalamic dysfunction.119 Studies reporting altered hormone concentrations supported that hypothesis.118,120 However, it took some more years to confirm the implication of the hypothalamus.

Attempts to image brain function during CH attacks using single-photon emission computed tomography (SPECT) in 1976 and 1980 yielded inconsistent results.121,122 In 1998, May and co-workers investigated cerebral blood flow during an attack using positron emission tomography (PET).123 They found an increased blood flow in the posterior parts of the ipsilateral hypothalamus in addition to the expected increases in the thalamus, cingulate, and insular cortex. Given the role of the hypothalamus in circadian rhythmicity, they suspected that the hypothalamus was the ‘primum movens in the acute cluster attack’.124,125 In 1998, Malick and Burstein found a trigemino-hypothalamic tract that signals – amongst others – nociceptive stimuli.124,125 This connection might be the anatomical foundation for the interaction of the hypothalamus and the trigeminal nerve.

A study by Yang et al. published in 2015 further supports the hypothesis that the hypothalamus is critical in the pathophysiology of CH.126 The authors reported altered functional connectivity of the hypothalamus and other cortical areas in patients with episodic CH. Consequently, a ‘pain modulation network’ may be implicated in the pathophysiology of the disease. Further studies support this idea.127–129

Leone and co-workers reported the first successful implantation of deep brain stimulation (DBS) electrodes into the posterior hypothalamus in 2001. Their patient had suffered from refractory chronic CH, and his attacks disappeared 48 hours after the activation of the stimulation.130 However, later reports of other patients indicated a more extended time until treatment response and variable successes.131,132 Moreover, voxel-based analysis suggested that stimulation of the trigemino-hypothalamic tract prevented attacks – not the stimulation of the hypothalamus.133 Thus, the posterior hypothalamus unlikely harbours the attack trigger.

Not only CH attacks comprised an activation of the posterior hypothalamus. Later research found it also in SUNCT, paroxysmal hemicrania, and hemicrania continua.134–137 Thus, this area must be relevant to the disorder.

In 2010, Montagna et al. published their hypothesis about the role of the posterior hypothalamus.138 They explained that the pain during CH attacks felt inescapable; it resembled pain elicited by the activation of A-delta fibres. Thus, the ictal restlessness could reflect a fight-or-flight reaction coordinated by the hypothalamic defensive system.138 Thus, the increased metabolic activity in the posterior hypothalamus may be due to a defensive reaction.

Still, the hypothalamus remains a likely candidate for the ‘primum movens’.84 It is left for future research to explore its role in detail.

**Genetic insights**

Towards the end of the 20th century, researchers published the first reports of monozygotic twins suffering from CH.139–141 Deeming the repeated random occurrence of a sporadic disorder in twins unlikely, they raised the possibility of a genetic factor. Subsequent studies added weight to this hypothesis, reporting the familial occurrence of CH and thus suggested a novel approach to investigating the disorder.12,142–148

The studies on familial CH found that having a first-degree relative and – to a lesser extent – a second-degree relative with CH implied an elevated risk of getting the disorder. They estimated that between 2.3% and 20% of CH patients have a positive family history.12,143,148

Accordingly, researchers suspected that CH might be a genetic disease in these cases. However, there was some disagreement about the inheritance. Russell et al. deduced
from their data an autosomal dominant gene with incomplete penetrance. Conversely, De Simone et al. reported a family in whom they observed an autosomal recessive pedigree.

The inheritance pattern of familial CH remains unsettled. Later studies analysed candidate genes and usually included all patients in their sample – not just those with familial CH.

Among the first were Shimomura and co-workers, who indicated a possible implication of the mitochondrial genome in one patient. However, two subsequent studies were unable to replicate this finding. Thus, a causal relationship between CH and the mutation is less likely.

Because of its implication in familial hemiplegic migraine, some researchers analysed CACNA1 but found no connection to CH. Similarly, no polymorphism of the nitric oxide synthase genes seemed relevant to the pathophysiology of the disorder.

Interest in hypocretin grew among researchers investigating CH when its accumulation in cells of the posterior and lateral hypothalamus became known. In 2004, Rainero et al. reported an association of a polymorphism (rs2653349) of the hypocretin receptor 2 gene with CH. A meta-analysis combining the results of three studies confirmed that this polymorphism modulates the risk for CH. Thus, the polymorphism is not a causative mutation but rather a modifier of genetic susceptibility.

Other researchers focused on CLOCK genes because of their implication in circadian rhythmicity. After some negative results, one study reported an association of a polymorphism (rs12649507) with CH. While this polymorphism seems implicated in regulating sleep duration, its relevance to CH is unknown.

A third polymorphism (rs1126671) thought to modify the risk of CH concerns the ADH4 gene implicated in the metabolism of alcohol. However, a subsequent study did not reproduce this finding.

More recent studies moved away from investigating single candidate genes and towards genome-wide analyses. In 2021, Harder et al. and O’Connor et al. reported the results of two genome-wide association studies comprising large samples. They identified seven genetic loci – four of which were identical in the two studies – associated with the disease. However, they detected none of the polymorphisms deemed relevant in previous research.

The findings of these studies are merely a starting point for further research. Currently, their role in the pathophysiology of CH is unknown.

The burden of disease

In the middle of the 20th century, the understanding of ‘disease’ changed again. At that time, some authors questioned the singular importance of lesions and dysfunctions. As similar complaints could have different or multiple causes, Henry Cohen emphasised in 1943 that ‘there are no diseases, only disease’. In 1967, John G. Scadding conceptualised the term as a deviation from the norm that placed an individual ‘at a biological disadvantage’.

Feinstein found that physicians often ‘ignored all the clinical distinctions of a patient’s illness’. In his book called ‘clinical judgement’, published in 1967, he discussed that comorbid conditions were one such distinction. One disease could place an individual at a biological disadvantage regarding the occurrence of another disease. Little was known at that time about the comorbidities of CH.

Symonds indicated in 1956 that three of his patients suffered from anxiety. Still, systematic studies of comorbidities followed only much later. In 1999, Jorge et al. reported an association of CH with anxiety. Further studies found an increased prevalence of depression, agoraphobia, and suicidal ideation. In 1992, Levi and co-workers reported an elevated smoking prevalence among patients with CH. Other researchers confirmed the finding and added that most patients’ parents had already smoked. In 2007, Donnet et al. found that cannabis consumption was also more common in patients with CH than in the general population.

Comorbidities were not the only aspect that received increasing attention. Broadening the understanding of the term ‘disease’ further, researchers became interested in the consequences of being diseased. Of course, physicians had never equated diseases with dysfunction; they had always been aware of their consequences, too. However, they had not yet systematically studied the issue.

During the early modern period, many writers of case reports had a penchant for drama that contrasted Hippocrates’ laconic style. There are examples in Suárez de Rivera’s and van Swieten’s case reports cited above. The former highlighted the extent of the restlessness mentioning that ‘six other Nuns cannot hold [the patient], due to her strength during the pain episodes’. Van Swieten emphasised the intensity of the pain, reporting that the patient ‘nearly went mad’.

Later authors also were conscious of the distress inflicted by the attacks. For example, Horton’s account of patients sleeping in a sitting position suggests hypnophobia, which only much later entered medical literature. In 1947, Ekbom reported self-harming behaviour during attacks and added, ‘Reactions to pain of this kind are not common among the calm Swedish people’.

In the 1990s, the first study addressed and attempted to measure patients’ quality of life with CH. More research followed in the next decade. They found that the in-bout period had a tremendous negative impact on the quality of life.

When researchers focused on other aspects of the burden of disease, it became apparent that many patients struggle to deal with the disorder even in the absence of pain; some
try to hide it from others or engage in avoidance behaviour.180 In addition, the disorder results in high direct and indirect costs.181

The significant disease burden uncovered by these studies persists despite the therapeutic advances of the past century. Hence, major unmet therapeutic needs remain.

Conclusion

This article highlighted the essential stages in our understanding of CH. Table 1 provides an overview of the discussed milestones. Of course, it could not appreciate every researcher’s merit. Every progress has many contributors.

Physicians have been aware of this type of pain for at least 300 years; we do not know who first saw a patient with CH. Only when researchers studied pathological anatomy and physiology did knowledge accrue. A more comprehensive picture of the disease severity emerged when they also considered its consequences.

The history of CH does not end here. Our understanding and therapeutic strategies will evolve further – as will medicine. We expect the development of new medications and strategies that reduce the disease burden. There is still a lot to do.

Table 1. Overview of the milestones in the history of cluster headache.

| Year | Milestone |
|------|-----------|
| 1641 | Nicolaas Tulp describes a headache with circadian rhythmicity. |
| 1672 | Thomas Willis reports of a headache with circadian rhythmicity. |
| 1726 | Francisco Suárez de Rivera publishes case report of a nun with unilateral headache, ipsilateral tearing and restlessness that occurred with circadian and circannual rhythmicity. |
| 1745 | Gerard van Swieten publishes a report of a man with left-sided headaches, ipsilateral tearing, and restlessness that had circadian rhythmicity. |
| 1840 | Romberg describes “ciliary neuralgia” that is characterised by unilateral facial pain, photophobia, eye reddening, and lacrimation. |
| 1908 | Sluder reports ‘lower half headache’ that he treated with infiltrations of the sphenopalatine ganglion. |
| 1913 | Bing publishes a description of ‘erythromelalgia’ that resembles what we understand today as cluster headache. |
| 1926 | Harris presents cases with a disease called ‘migrainous neuralgia’ that likely contains some patients of cluster headache. He suggests infiltrating the infraorbital nerve and the trigeminal ganglion. |
| 1932 | Vail reports the ‘Vidian neuralgia’. |
| 1937 | Horton et al. report patients with ‘erythromelalgia of the head’. |
| 1941 | Horton suggests the name ‘histaminic headache’ and histamine desensitisation as prophylaxis. |
| 1947 | Ekbom promotes Ergotamine as an acute treatment. |
| 1947 | Gardner et al. propose treating the disorder by sectioning the petrosal nerve. |
| 1952 | Horton attempts to treat patients with corticosteroids but reports limited success. |
| 1952 | Horton recommends oxygen inhalation as an acute treatment. |
| 1952 | Kunke et al. suggest the name ‘cluster headache’. |
| 1962 | The “ad hoc” headache classification contains cluster headache as a separate type of headache. |
| 1970 | Ekbom and Greitz confirm the presence of vasodilation during the attacks. |
| 1974 | Sjaastad and co-workers report the first case of paroxysmal hemicranias. |
| 1977 | First study confirming the efficacy of lithium as a prophylactic treatment |
| 1983 | First report of verapamil preventing attacks |
| 1984 | First report of steroid blockades of the occipital nerve |
| 1984 | Sjaastad and co-workers report the first case of Hemicrania continua |
| 1987 | Kudrow speculates that hypothalamic dysfunction could explain the circannual rhythmicity. |
| 1988 | The first edition of the International Headache Classification recognises cluster headache as a distinct type of headache. It distinguishes an episodic and a chronic form. |
| 1989 | Publication of the first study confirming the efficacy of sumatriptan as an acute treatment |
| 1989 | Sjaastad and co-workers report the first case of SUNCT |
| 1992 | Levi et al. establish that smoking is a common comorbidity in patients with CH. |
| 1993 | Kirkpatrick et al. publish a case series indicating that sectioning the trigeminal nerve prevents attacks in many patients. |
| 1994 | Goadsby and Edvinsson report increases CGRP concentrations during cluster headache attacks |
| 1994 | Solomon et al. report a markedly decreased quality of life in patients with cluster headache. |
| 1997 | Goadsby and Lipton hypothesise that the trigeminal autonomic reflex is central to the pathophysiology of cluster headache. |
| 1997 | Goadsby and Lipton propose the name ‘trigeminal autonomic cephalgia’. |
| 1998 | May and co-workers report increased perfusion of the posterior hypothalamus during the attacks. |
| 2001 | Leone and co-workers perform the first deep brain stimulation and implant the electrodes into the posterior hypothalamus. |
| 2005 | Volcy et al. publish the first report of SUNA. |
| 2019 | Monoclonal antibodies directed against CGRP fail to prevent attacks in patients with episodic cluster headache. |
| 2020 | Monoclonal antibodies directed against CGRP fail to prevent attacks in patients with chronic cluster headache. |

CGRP – calcitonin gene-related peptide. SUNA – short-lasting Unilateral Neuralgiform headache attacks with cranial autonomic symptoms, SUNCT – short-lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating, and rhinorrhoea.
Key Findings

- The first case reports of patients with cluster headache appeared in the 17th and 18th centuries.
- Only in the 19th century did physicians start hypothesising about the cause of the pain. First, they suspected neuralgia and then a vascular headache. Towards the end of the 20th century, knowledge of the trigeminal autonomic reflex and altered brain activity accrued.

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