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Research Submission

Diagnosis and Clinical Features of Trigemino-Autonomic Headaches

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Although severe short-lasting headaches are rare, they can be considered disabling conditions with a major impact on the quality of life of patients. These headaches can divided broadly in to those associated with autonomic symptoms, so called trigeminal autonomic cephalgias (TACs), and those with few or no autonomic symptoms. The TACs include cluster headache, paroxysmal hemicranias, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms as well as short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing syndrome. In all of these syndromes, half-sided head pain and ipsilateral cranial autonomic symptoms such as lacrimation or rhinorrhea are prominent. The paroxysmal hemicranias have, unlike cluster headaches, a very robust response to indomethacin, leading to a notion of indomethacin-sensitive headaches. The diagnosis of TACs is exclusively a clinical task. Because of the fact that cluster headache is strictly half-sided, typically involves the region around the eye and temple and often starts in the upper jaw, most patients first consult a dentist or ophthalmologist. No single instrumental examination has yet been able to define, or ensure, the correct diagnosis, or differentiate idiopathic headache syndromes. It is crucial that a trained neurologist sees these patients early so that management can be optimized and unnecessary procedures can be avoided. Although TACS are, in comparison to migraine, quite rare, they are nevertheless clinically very important for the neurologist to consider as they are easy to diagnose and the treatment is very effective in most patients.

Key words: trigeminal autonomic cephalgia, cluster headache, diagnosis, clinic, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, autonomic symptoms

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Although migraine, tension type headache, and even medication overuse headache are more common, it is important to recognize cluster headache (CH) and related cephalalgias because of the fact that the pain is truly excruciating and, because the symptoms are fairly stereotyped, relatively easy to diagnose. The differential diagnosis comprises intracranial pathologies that, together with the fact that treatment is very effective in most patients, make the correct diagnosis even more important. CHs have been identified as far back as the seventeenth century.[1] The pathophysiological background, however, has only started to become clear in recent decades. Current diagnostic guidelines are provided by the International Headache Society (IHS) classification criteria and are based primarily upon clinic-based patient populations. Clinically and pathogenically CH is distinct from other primary head pain syndromes, such as migraine. Because of the fact that CH shares most of the clinical features with a group of other headache types, these syndromes have been

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subsumed under the term "trigeminal autonomic cephalalgia." This term has been coined by Goadsby and Lipton[2] and is very useful in daily practice: it takes in a group of unilateral headaches which all have autonomic symptoms as part of their diagnosis, yet with distinct differences between them to allow specific treatment options. This review summarizes the clinical and diagnostic features of these syndromes. As the international classification of headaches changes over time, this review now includes hemicrania continua because this headache syndrome shares crucial clinical features with the TACs and is recognized as part of the TACs in the 2013 classification. Another headache entity, hypnic headache, shares the strong circadian rhythmicity of pain attacks with, eg, CH, but has no accompanying autonomic symptoms and is therefore not recognized in this group[3] or in this review.

SEARCH STRATEGY

A literature search was performed using the reference databases MEDLINE; the key words used were "cluster headache," "trigemino-autonomic headache," "TAC," "paroxysmal hemicrania," "SUNA," "SUNCT," and "Hemicrania continua" (last search in January 2013). All papers published in English or German were considered. Papers discovered by this search were reviewed, as were references cited therein. In addition, review books were considered.[4,5]

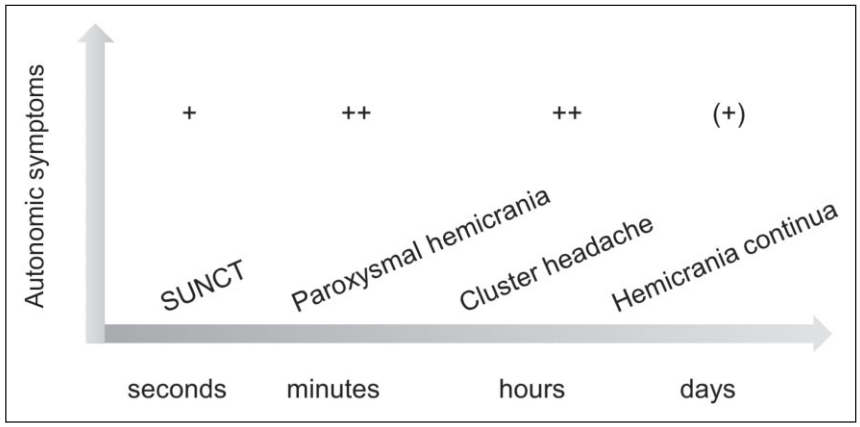
THE CLASSIFICATION

Goadsby and Lipton[2] were the first to propose the term "trigeminal autonomic cephalgias (TAC)" for a group of primary headaches with pain and autonomic involvement in the facial area of the trigeminal nerve. All these headache syndromes have 2 features in common: short-lasting, unilateral, severe headache attacks, and the accompaniment of typical autonomic symptoms. The clinical features of the TACs at presentation are highly characteristic when typical. To date, the following syndromes belong to the TACs:[6]

- episodic and chronic CH
- episodic and chronic paroxysmal hemicrania (PH)
- short-lasting unilateral neuralgiform headache attacks
- hemicrania continua

Why is it important to know and recognize all the different types of TAC, given that they are relatively rare? First, they are easy to recognize. Second, in most cases, a subclassification is possible and reasonable, as therapeutic regimen and response differ. For neurologists, despite the diagnostic challenges, the short-lasting primary headaches are important to recognize because of their excellent, but highly selective response to treatment. In 1997, Goadsby and Lipton documented a nosological analysis and definition of a group of short-lasting headache syndromes.[2] These PHs are characterized by frequent, short-lasting attacks of unilateral pain usually in the orbital, supraorbital, or temporal region. The pain is severe and associated with autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, and ptosis and eyelid edema.

Goadsby and Lipton divided these short-lasting primary headache syndromes into those exhibiting marked autonomic activation and those without autonomic activation. The Figure and Table 5 summarize a list of short-lasting headaches with autonomic symptoms. The former group comprises chronic and episodic PH, short-lasting unilateral neuralgiform headache attacks (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms [SUNA] and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT] syndrome), and CH.[6] These headache syndromes are compared with other short-lasting headache disorders, such as hypnic headache, and a chronic headache syndrome with milder autonomic features such as hemicrania continua. Recent imaging data, however, place hemicrania continua nearer to the TACs,[7] and future work will probably do the same with hypnic headache. Idiopathic stabbing headache, cough headache, exertional headache, sexual headache, and trigeminal neuralgia are not part of these syndromes as these short-lasting disorders have no autonomic component,[4,6] although all headaches, and even experimental trigeminal nociceptive input, if severe enough, may trigger some



Figure—Different headache types corresponding to length of headache duration, with the headaches with the shortest pain attacks listed on the left. The SUNA/SUNCT syndrome exhibits neuralgiform-like attacks lasting only seconds, paroxysmal hemicrania lasting between 10 and 20 minutes, and cluster headache usually presenting with attacks that last 1-2 hours, whereas hemicrania continua may last days or even months. The autonomic features are also distinct with cluster headache and paroxysmal hemicrania expressing the most symptoms and hemicrania continua may even exist without marked activation of the autonomic symptoms. SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

minor autonomic symptoms as part of the trigeminovascular reflex.[8,9]

CH

CH is certainly the most prominent and most common of the TACs and is considered one of the most severe pain syndromes in humans. Indeed, female patients have described each attack as being worse than childbirth.[10] Despite the fact that a recent health-related quality of life study in 56 patients suggested that CH has a marked functional consequence, even when appropriate treatments are used,[11] CH is still underdiagnosed and suboptimally managed in primary care.[12]

The diagnosis of CHs is exclusively a clinical task. The *International Classification of Headache Disorders*[6] uses explicit diagnostic criteria (see Table 1), which are "unambiguous, precise and with as little room for interpretation as possible." The fact that at least 14 synonyms for CH have been used in the past underlines the former lack of etiological understanding and importance of operational diagnostic criteria, hence explicit diagnostic criteria for research and clinical practice. CH, in its typical form, is unmistakable. However, no single instrumental examination is able to define or differentiate idiopathic headache

Table 1.—Diagnostic Criteria of Cluster Headache

A: At least 5 headache attacks fulfilling criteria B-D:
B: Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (when untreated).
C: Either or both of the following:
  1. at least 1 of the following symptoms or signs, ipsilateral to the headache:
     a) conjunctival injection and/or lacrimation
     b) nasal congestion and/or rhinorrhea
     c) eyelid edema
     d) forehead and facial sweating
     e) forehead and facial flushing
     f) sensation of fullness in the ear
     g) miosis and/or ptosis
  2. a sense of restlessness or agitation
D: Attacks have a frequency between 1 every other day and 8 per day for more than half of the time when the disorder is active
E: Not better accounted for by another ICHD-3 diagnosis.

Note: During part (but less than half) of the time-course of 3.1 Cluster headache, attacks may be less severe and/or of shorter or longer duration.
Episodic cluster headache: At least 2 cluster periods lasting 7 days to 1 year separated by pain free periods lasting ≥1 month.
Chronic cluster headache: Attacks occur for more than 1 year without remission or with remission < 1 month.
Probable cluster headache: Attacks fulfilling all but 1 criteria for cluster headache.

syndromes.[13] Nevertheless, in the clinical setting, the use of neuroimaging (cranial computerized tomography [CCT], magnetic resonance imaging [MRI], magnetic tomography [MR]-angiography, etc) in headache patients varies widely. Electrophysiological and laboratory examinations including examination of the cerebrospinal fluid are not helpful. For the initial diagnosis and in the case of an abnormal neurological examination, a cranial computerized tomography scan and a cranial MRI should be considered in order to exclude abnormalities of the brain.[14,15] Particularly in older patients, mass lesions or malformations in the midline have been described to be associated with symptomatic CH.[16,17]

CLINICAL APPEARANCE

CH prevalence is approximately 0.1% of the population and mostly affects men. The stereotypical attacks may strike up to 8 times a day, are relatively short-lived, and characterized by strictly unilateral severe head pain accompanied by autonomic phenomena.[6] Only in approximately 15% of cases is a side shift mentioned.[18] In contrast to migraineurs, cluster patients are restless and prefer to pace about or sit and rock back and forth. Some patients will exert pressure on the painful area with a hand over the affected eye and temple. Many will isolate themselves during the attack or leave the house to get into cold or fresh air. They may also become aggressive during an attack. The unilateral autonomic symptoms such as ptosis, miosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion only during the pain attack are ipsilateral to the pain, indicating parasympathetic hyperactivity and sympathetic impairment. In some patients, the signs of sympathetic paralysis (miosis and ptosis) persist indefinitely[19] but intensify during attacks. Sweating and cutaneous blood flow also increase on the painful side, particularly in areas of sympathetic deficit.[20] About 3% of all patients lack autonomic symptoms[21] and in rare cases sympathetic disturbances persist on the previously affected side of the face in patients whose CH has switched sides.[5] It seems that there is no typical form of pain in these syndromes. It may be throbbing, sharp, or stabbing, and this may even vary from bout to bout and indeed between attacks. The pain, although usually involving the ophthalmic division of the trigeminal nerve, may also involve any part of the head as well and very occasionally not involve the ophthalmic division at all.[22] Another clinical landmark of the syndrome is the circadian rhythmicity of the relatively short-lived (15-180 minutes) painful attacks. In the episodic form, attacks occur daily for some weeks followed by a period of remission of at least 2 weeks. About 15-20% of patients suffer from chronic symptoms (without remissions = chronic CH). On average, a cluster period lasts 6-12 weeks while remissions can last up to 12 months. The attacks occur regularly, and their timing seems to be related to the sleep-wake cycle. The most salient feature of CH is the reported seasonal variation and the clockwise regularity of the headache attacks.[23] Consequently, a whole range of circadian irregularities in hormone levels have been reported in CH patients.[24,25] While this circadian and circannual rhythmicity is characteristic of the episodic variant, little is known on rhythmicity in chronic CH. A recent case report regarding a secondary chronic CH showed evidence, even in the chronic form, of a distinct circadian and semicircannual rhythmicity over time.[26] Infra- and supra-annual (ie, cycles shorter or longer than 12 months) exacerbations over several weeks occurred independent from a 12-month cycle.

Such information is important for clinicians, as, depending on the level of activity of the disease, a preventative may be efficient at some times and not at others. This implies that missing effects of preventatives should not be misinterpreted as a failure – the prophylactic drugs may well be efficient again when the activity of the disease levels out again. In addition, a "clockwise" circadian rhythmicity of attacks and an individual circannual preponderance should be considered as hallmark for CH. Sjaastad[27] suggested that episodic cluster headache (ECH) and secondary chronic cluster headache (CCH) have only minute differences and display smooth transitions, while primary CCH is a separate entity lacking the criterion of clustered attacks. It is not clear whether that is true but primary chronic cluster seems to be more often medically intractable.[10] When chronic CH is unresponsive to medical treatments, it becomes a serious

problem and even surgical options may have to be considered.

DIFFERENTIAL DIAGNOSIS

All headache syndromes with short-lasting, unilateral, severe headache attacks, and typical autonomic accompanying symptoms (eg, PH and SUNA/SUNCT) need to be considered. The term SUNA was recently introduced to distinguish SUNCT attacks from very similar pain attacks with a different occurrence or distribution of autonomic symptoms during the pain. However, these syndromes differ in duration, frequency, and rhythmicity of the attacks[2] and in the intensity of pain and autonomic symptoms as well as treatment options (see Table 2). There are reports of aura in CH[28] and even a "hemiplegic cluster."[29] There seem to be some cases of CH without headache,[30] as well as the opposite: CH without autonomic symptoms[21,31] and even bilateral cases.[5] In a series of well-observed case reports presenting 3 atypical CHs, the authors suggests that as more cluster patients are seen by headache specialists, new forms of this well-defined primary headache syndrome will be identified.[32] However, the concept of trigemino-autonomic syndromes is certainly useful for clinicians seeking a pathophysiological understanding of the primary *neuro*-vascular headaches and allowing us to place the various treatments aimed at treating or preventing these headaches into context.

Although CH mostly affects the region of the eye and temple, it also very often starts in the upper jaw. This leads most patients to first consult a dentist or ophthalmologist. In 2004, 40% of those seen by a specialist other than a neurologist subsequently had an invasive procedure.[33] However, the more we know and understand about CH in the last 50 years, the larger the reduction in mean time to diagnosis. Bahra and Goadsby concluded that CH is certainly better recognized now than previously, although unacceptable delays still occur and many patients are not managed optimally early in their disease course.[33] Bahra and Goadsby also demanded that early neurologic referral is indicated in patients with a suspected diagnosis of CH so that management can be optimized and unnecessary procedures avoided.[33]

Table 2.—Comparison of Cluster Headache With Related Headache Syndromes

	Cluster Headache	Paroxysmal Hemicrania	SUNA/SUNCT Syndrome	Hemicrania Continua	Hypnic Headache
Epidemiology					
- Gender (Male : Female)	3:1	1:3	8:1	1:1,8	1,8:1
- Prevalence	0.9%	0.02%	very rare	rare	very rare
- Age of onset	28-30 years	20-40 years	20-50 years	20-30 years	40-70 years
Pain					
-Quality	boring, throbbing	boring	stabbing	pressing	pulsating
-Intensity	extremely high	high	moderate to high	moderate	moderate
-Localization	periorbital	orbital, temporal	orbital, temporal	unilateral, temporal	bifrontal, median
-Duration of attack	15-120 minutes	2-45 minutes	5-250 seconds	fluctuating, constant, with	30-120 minutes
-Frequency of attack	1-8/day	1-40/day	1/day bis 30/hour	superimposed attacks	1-2/day
Autonomic symptoms	++	++	+	(+)	–
Circadian rhythmicity	+	(–)	–	–	+
Alcohol trigger	++	(+)	(–)	–	–

*Modified from[7]
SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Table 3.—Diagnostic Criteria of Paroxysmal Hemicrania

A. At least 20 attacks fulfilling criteria B-E
B. Severe, unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes
C. At least one of the following symptoms or signs, ipsilateral to the pain:
   1. conjunctival injection and/or lacrimation
   2. nasal congestion and/or rhinorrhea
   3. eyelid edema
   4. forehead and facial sweating
   5. forehead and facial flushing
   6. sensation or fullness in the ear
   7. miosis and/or ptosis
D. Attacks have a frequency above 5 per day for more than half the time
E. Attacks are prevented absolutely by therapeutic doses of indomethacin
F. Not attributed to another ICHD-3 diagnosis

Table 4.—Diagnostic Criteria of Short-Lasting Unilateral Neuralgiform Headache Attacks

A. At least 20 attacks fulfilling criteria B-D
B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs or in a sawtooth pattern
C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
   1. conjunctival injection and/or lacrimation
   2. nasal congestion and/or rhinorrhea
   3. eyelid edema
   4. forehead and facial sweating
   5. forehead and facial flushing
   6. sensation or fullness in the ear
   7. miosis and/or ptosis
D. Attacks have a frequency of at least once a day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis

PH

Clinical Appearance.—PH was first described by Sjaastad and Dale[34] (for a review, see Dodick, 2004[35]) and is characterized by relatively short bouts of severe unilateral pain in the orbital and temporal area. PH is a rare condition, and although proper investigations are lacking, it is estimated that the PHs comprise about 3-6% of all the trigeminal autonomic cephalalgias. The age of onset is usually in the twenties, with a female predominance. The typical attack duration is 10-20 minutes, the typical attack frequency is >5 per day, but there are reports of between 1 and 40 attacks per day (see Table 3). Similar to CH, a chronic and an episodic form have been described, and the syndrome also conveys a distinctive temporal pattern.[36] The pain is associated with at least 1 autonomic symptom, such as ipsilateral conjunctival injection and tearing with nasal congestion and rhinorrhea. Typically described as a problem of women, this seems incorrect from a substantial cohort that has recently been reported.[37]

The syndrome is also characterized by complete response to indomethacin. Although this response is exceptional and long lasting, patients who develop gastrointestinal problems, notably peptic ulcer disease on indomethacin, are a substantial challenge. Some such patients have responded to cyclooxygenase II selective inhibitors, others seem to benefit from Gabapentin.

Differential Diagnosis.—Again, all headache syndromes with short-lasting, unilateral, severe headache attacks, and typical autonomic accompanying symptoms (eg, CH and SUNA/SUNCT) need to be considered. The hallmarks in differential diagnosis are the duration of the attacks and the complete response to indomethacin.

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS: SUNA AND SUNCT SYNDROME

Clinical Appearance.—Attacks of moderate or severe, strictly unilateral head pain lasting seconds to minutes, occurring at least once a day and usually associated with prominent autonomic symptoms come in 2 forms: either strictly with lacrimation and redness of the ipsilateral eye or with additional autonomic symptoms, or when 1 of the 2 mentioned are missing (see Table 4). If the 2 autonomic symptoms (lacrimation and redness of the ipsilateral eye) but no other autonomic symptoms are present, the syndrome is called *SUNCT* syndrome, otherwise it is called *SUNA*. SUNCT may be a subform of SUNA, although this requires further study. Until this is proven, each is classified as a separate subtype. SUNCT and SUNA are among the rarest idiopathic headache syndromes (although ideal epidemiological data are lacking) and are characterized by an extremely high frequency of

attacks (up to 200 attacks/day) with less severe pain but marked autonomic activation during attacks. Even though there are distinct clinical differences – such as the frequency and duration of attacks and the different approach to treatment – many of the basic features of SUNCT and SUNA – such as episodicity, autonomic symptoms, and unilaterality – are shared by other headache types, including CH and PH. This suggests a pathophysiological similarity to those syndromes and prompted the suggestion to unify them on clinical grounds as TACs. The paroxysms of pain usually last between 5 and 250 seconds, although longer, duller, interictal pains have been reported. Patients can have up to 30 episodes per hour, although it is more usual to have 5-6 per hour. The frequency may also vary in bouts. The conjunctival injection seen with SUNCT is often the most prominent autonomic feature and tearing may also be very obvious.

Differential Diagnosis.—The major differential diagnosis of short-lasting unilateral neuralgiform headache attacks is with trigeminal neuralgia. The most important clinical signs pointing toward SUNCT/SUNA and against trigeminal neuralgia include the prominent distribution of pain in the ophthalmic division of the trigeminal nerve, triggering of attacks from cutaneous stimuli and a lack of a refractory period to these triggers. In contrast to PH, there is no reproducible indomethacin effect in SUNCT/SUNA, and in contrast to CH, no important effect of oxygen, sumatriptan, or verapamil. For practical reasons, indomethacin should be tried in all extremely short-lasting headaches, before lamotrigine or carbamazepine is tried.

Hemicrania Continua.—Hemicrania continua is now recognized as belonging to the TAC group. Hemicrania continua is characterized by a continuous, unilateral headache that varies in intensity, waxing, and waning without disappearing completely.[38] The IHS definition states that the headache is side-locked, ie, does not change sides (see Table 5). Usually there are mild autonomic symptoms such as lacrimation, conjunctival injection, nasal symptoms, and ptosis/miosis, and the syndrome typically responds well to indomethacin.[6]

Hemicrania continua is sometimes misdiagnosed as half-sided tension-type headache or chronic migraine. Hemicrania continua is probably underdiagnosed, but the absolute requirement for an indomethacin effect is helpful in distinguishing it from other primary headaches. However, cases with bilateral pain have been reported,[22] and interestingly, nausea, photophobia, phonophobia, and cranial autonomic symptoms may arise with exacerbations. In general terms, the background pain of hemicrania continua is more severe than the interparoxysmal pain of the other TACs, and the worsenings in hemicrania continua are longer than the paroxysms of the other TACs.[22] This is particularly important in differentiating hemicrania continua from PH.

Table 5.—Diagnostic Criteria of Hemicrania Continua

A. Unilateral headache fulfilling criteria B-D
B. Present for >3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
   1. at least one of the following symptoms or signs, ipsilateral to the headache:
      a.) conjunctival injection and/or lacrimation
      b.) nasal congestion and/or rhinorrhea
      c.) eyelid edema
      d.) forehead and facial sweating
      e.) forehead and facial flushing
      f.) sensation or fullness in the ear
      g.) miosis and/or ptosis
   2. a sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of indomethacin
E. Not better accounted for by another ICHD-3 diagnosis

STATEMENT OF AUTHORSHIP

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REFERENCES

1. Eadie MJ. *Headache Through the Centuries*. New York: Oxford University Press; 2012.
2. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain*. 1997;120(Pt 1):193-209.
3. Evers S, Goadsby PJ. Hypnic headache: Clinical features, pathophysiology, and treatment. *Neurology*. 2003;60:905-909.
4. Olesen J, Tfelt-Hansen P, Welch K. *The Headaches*, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.
5. Sjaastad O, ed. *Cluster Headache Syndrome*. London: WB Saunders Company Ltd; 1992.
6. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia*. 2004;24:1-160.
7. Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. *Headache*. 2004;44:747-761.
8. Frese A, Evers S, May A. Autonomic activation in experimental trigeminal pain. *Cephalalgia*. 2003;23: 67-68.
9. May A, Goadsby PJ. The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cereb Blood Flow Metab*. 1999;19:115-127.
10. May A. Cluster headache: Pathogenesis, diagnosis, and management. *Lancet*. 2005;366:843-855.
11. D'Amico D, Rigamonti A, Solari A, et al. Health-related quality of life in patients with cluster headache during active periods. *Cephalalgia*. 2002; 22:818-821.
12. Geweke LO. Misdiagnosis of cluster headache. *Curr Pain Headache Rep*. 2002;6:76-82.
13. Sandrini G, Friberg L, Janig W, et al. Neurophysiological tests and neuroimaging procedures in non-acute headache: Guidelines and recommendations. *Eur J Neurol*. 2004;11:217-224.
14. Favier I, Haan J, Ferrari MD. Cluster headache: To scan or not to scan. *Curr Pain Headache Rep*. 2008;12:128-131.
15. Favier I, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalgias due to structural lesions: A review of 31 cases. *Arch Neurol*. 2007;64:25-31.
16. Hannerz J. A case of parasellar meningioma mimicking cluster headache. *Cephalalgia*. 1989;9:265-269.
17. Purdy RA, Kirby S. Headaches and brain tumors. *Neurol Clin*. 2004;22:39-53.
18. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache–clinical findings in 180 patients. *Cephalalgia*. 1983;3:21-30.
19. Drummond PD. Dysfunction of the sympathetic nervous system in cluster headache. *Cephalalgia*. 1988;8:181-186.
20. Drummond PD. Sweating and vascular responses in the face: Normal regulation and dysfunction in migraine, cluster headache and harlequin syndrome. *Clin Auton Res*. 1994;4:273-285.
21. Ekbom K. Evaluation of clinical criteria for cluster headache with special reference to the classification of the International Headache Society. *Cephalalgia*. 1990;10:195-197.
22. Goadsby PJ, Cittadini E, Burns B, Cohen AS. Trigeminal autonomic cephalalgias: Diagnostic and therapeutic developments. *Curr Opin Neurol*. 2008;21:323-330.
23. Waldenlind E, Drummond PD. Synthesis of cluster headache pathophysiology. In: Olesen J, Tfelt Hansen P, Welch KM, eds. *The Headaches*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:783-789.
24. Leone M, Attanasio A, Croci D, et al. Neuroendocrinology of cluster headache. *Ital J Neurol Sci*. 1999;20:S18-S20.
25. Goadsby PJ. Pathophysiology of cluster headache: A trigeminal autonomic cephalgia. *Lancet Neurol*. 2002;1:251-257.
26. Jurgens TP, Koch HJ, May A. Ten years of chronic cluster – attacks still cluster. *Cephalalgia*. 2010;30:1123-1126.
27. Sjaastad O. Cluster headache syndrome. In: Detchant LW, Warlow CP, eds. *Major Problems in Neurology*. London: WB Saunders; 1992:230-269.
28. Silberstein SD, Niknam R, Rozen TD, Young WB. Cluster headache with aura. *Neurology*. 2000;54:219-221.

29. Siow HC, Young WB, Peres MF, Rozen TD, Silberstein SD. Hemiplegic cluster. *Headache*. 2002;42:136-139.
30. Leone M, Rigamonti A, Bussone G. Cluster headache sine headache: Two new cases in one family. *Cephalalgia*. 2002;22:12-14.
31. Vigl M, Zebenholzer K, Wessely P. Cluster headache without autonomic symptoms? *Cephalalgia*. 2001;21: 926-927.
32. Rozen TD. Atypical presentations of cluster headache. *Cephalalgia*. 2002;22:725-729.
33. Bahra A, Goadsby PJ. Diagnostic delays and mismanagement in cluster headache. *Acta Neurol Scand*. 2004;109:175-179.
34. Sjaastad O, Dale I. Evidence for a new (?), treatable headache entity. *Headache*. 1974;14:105-108.
35. Dodick DW. Indomethacin-responsive headache syndromes. *Curr Pain Headache Rep*. 2004;8:19-26.
36. Sjaastad O, Apfelbaum R, Caskey W, et al. Chronic paroxysmal hemicrania (CPH). The clinical manifestations. A review. *Ups J Med Sci Suppl*. 1980;31:27-33.
37. Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: A prospective clinical study of 31 cases. *Brain*. 2008;131(Pt 4):1142-1155.
38. Sjaastad O, Spierings EL. "Hemicrania continua": Another headache absolutely responsive to indomethacin. *Cephalalgia*. 1984;4:65-70.