Chapter 89

Neurophysiology and Autonomic Dysfunction in Cluster Headaches

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NEUROPHYSIOLOGY OF CLUSTER HEADACHE

Neurophysiologic tools have been used to explore the function of central and peripheral neural pathways that may be involved in cluster headache (CH). Techniques include electroencephalography, evoked potentials, studies of threshold for nociceptive responses, and assessment of pain perception. In general, the neurophysiologic approach has shown that CH is associated with altered pain processing, not only in trigeminal circuits but also in other parts of the body.

ELECTROENCEPHALOGRAPHY AND EVOKED POTENTIALS

In an early electroencephalographic investigation, abnormal activity, generally focal activity, was identified between attacks in about 50% of cases with no further changes during the attack (24). More recently, evoked potential data have supported the notion of central nervous system involvement in CH. For example, the asymmetry of brainstem auditory-evoked potentials was greater in CH patients both during attacks and between attacks than in controls, presumably due to asymmetrical conduction in central acoustic pathways. In contrast, brainstem auditory-evoked potentials did not differ between controls and CH patients on lithium therapy (4). The amplitude of visual-evoked potentials was found to be reduced in the pain-involved hemisphere during the pain-free period (2), although another study failed to replicate this result (44). Somatosensory-evoked potentials to median nerve stimulation were recorded in CH patients during and between severe attacks induced by intravenous administration of 40 μg of histamine. During the attack, the amplitude of the N1–P2 complex was lower than in patients outside the attack and lower than in normal subjects (16), presumably because powerful pain modulation mechanisms were triggered during the attack.

Van Vliet et al. (63) recently investigated trigeminal somatosensory-evoked potentials in patients with episodic CH. Electrical stimuli were delivered to the corner of the mouth at three times the sensory threshold. Evoked potentials were delayed during bouts, particularly on the symptomatic side, consistent with a deficit in processing trigeminal sensations.

Blink Reflexes

The blink reflex is a trigeminofacial reflex obtained by electrical or mechanical stimulation of the supraorbital nerve. The reflex consists of two responses: an early ipsilateral response (R1) and a late bilateral response (R2). The R2 is a nociceptive reflex mediated by a polysynaptic circuit through the pons and lateral medulla (26). The amplitude of the R2 response to contralateral stimulation was found to be significantly lower on the symptomatic than asymptomatic side during bouts of CH (46).

The R2 component is modulated both by segmental and heterosegmental influences and can be inhibited by prior stimulation of the supraorbital nerve or a peripheral nerve (47). The recovery of the inhibited R2 response can be investigated by increasing the delay between the conditioning stimulus responsible for the inhibition and the supraorbital stimulus producing the R2 response. The recovery curve of R2 after paired supraorbital stimuli depends on the excitability of trigeminofacial circuits (43), whereas limb stimulation inhibits R2 by activating reticular pathways (62). In CH patients, the R2 recovered more rapidly on the symptomatic side after paired supraorbital stimuli (34), possibly reflecting sensitization in the spinal trigeminal complex. When index finger stimulation was used to condition the supraorbital stimulus, R2 recovery was more

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rapid bilaterally in CH patients than controls. The bilateral deficit in R2 inhibition may reflect hypoactivity of reticular nuclei due to reduced central opioid activity (34).

Corneal Reflex

To elicit the corneal reflex, constant current stimuli are delivered from a thin cotton thread soaked in saline solution, which floats in tear fluid on the cornea. The response is recorded from the orbicularis oculi muscles. The latency, amplitude, and duration of the corneal reflex were found to be normal in CH patients both during the active phase and in remission (51). However, during the active phase, the threshold of the corneal reflex was significantly reduced, suggesting an increased excitability of trigeminal nociceptive neurones or facial motor neurones. These findings support the notion of a reversible impairment in activity of the trigeminal pain control system during the active phase of CH (51).

Infratrochlear Nerve Stimulation

High-intensity transcutaneous electrical stimulation applied to the emergence of the infratrochlear nerve induces a constriction of the ipsilateral pupil that is slow in onset and long-lasting. Miosis, which is homatropine resistant, has been attributed to an antidromic activation of the iris sensory fibers (17). In CH sufferers during the active period, transcutaneous electrical stimulation of the infratrochlear nerve elicits normal pupillary constriction in the asymptomatic eye, whereas the response in the symptomatic eye is minimal (15). This observation suggests that repeated attacks of CH deplete neuropeptide stores in trigeminal nerve terminals. If so, miosis during CH attacks is unlikely to be due solely to local release of neuropeptides.

Nociceptive Flexion Reflex

The nociceptive flexion (RIII) reflex has been used to investigate the integrity of antinociceptive mechanisms in several pain conditions, including primary headaches (53). The RIII reflex is obtained by stimulating the sural nerve at the retromalleolar level and recording the response from the biceps femoris. The RIII reflex threshold was found to be lower on the symptomatic than nonsymptomatic side both during (52) and between bouts of CH (40), implying a persistent impairment of the pain control system on the symptomatic side of the body. This impairment was associated with a phase shift in the circadian rhythm of the RIII threshold during episodic bouts of CH and with an absence of circadian variation in patients with chronic CH (40). Thus, impairment of the pain control system in CH may be associated with periodic failure of the mechanisms involved in regulating biologic rhythms (40).

Pain Perception

The pain threshold to electrical stimulation of the cornea was found to be lower than normal during the active phase of CH, particularly on the symptomatic side (51). Pain perception is also altered in other parts of the body. For example, Procacci et al. (45) detected cutaneous and deep hyperalgesia to electrical and mechanical stimuli on the symptomatic side of the body in patients with episodic CH. Moreover, pain or paresthesiae during 10 minutes of limb ischemia appeared earlier, was more intense, and lasted longer on the symptomatic than nonsymptomatic side. Pain perception thresholds at symmetrical points on each side of the head and over the deltoid muscle were assessed with a pressure algometer both in episodic and chronic CH (3). Patients had lower pain pressure thresholds than controls at all sites during bouts and in remission, consistent with the hypothesis of altered pain processing in CH. In addition, pressure pain thresholds were lower on the symptomatic than nonsymptomatic side during bouts of episodic CH, possibly due to inflammation in symptomatic scalp tissues or to trigeminal sensitization.

AUTONOMIC DISTURBANCES IN CLUSTER HEADACHE

CH is associated with a range of local and more general autonomic disturbances. Local signs of parasympathetic overactivity such as lacrimation and nasal discharge often develop during attacks. Signs of ocular sympathetic paralysis (miosis and ptosis) also develop in some patients during attacks and persist interictally together with vasomotor and sudomotor signs of sympathetic deficit. Paradoxically, however, sweating increases on the painful side of the face during attacks, particularly in areas of sympathetic deficit. In patients with ocular and thermoregulatory signs of sympathetic deficit, the symptomatic parts of the face are supersensitive to adrenergic and cholinergic drugs. Furthermore, changes in blood pressure and heart rate suggest that disturbances in cardiovascular control may develop during attacks.

Opinions diverge over the source of these autonomic disturbances. According to some, autonomic dysfunction originates centrally in association with a hypothalamic disturbance that compromises inhibitory pain control mechanisms. Others hold that venous stasis or an inflammatory process in the cavernous sinus accounts for the cyclical pain and associated autonomic disturbances. Another possibility is that many of the autonomic disturbances are secondary to trigeminal discharge during attacks of CH.

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Disturbances in Blood Pressure and Heart Rate

Blood pressure typically increases whereas heart rate decreases during CH attacks (6). In addition, the variability of beat-to-beat changes in heart rate alters as the attack progresses. Two recent studies present a similar picture of the time course of these heart rate fluctuations. Tubani et al. (61) monitored heart rate continuously over 24 hours to capture one or more spontaneous attacks in seven patients. In each case, the high-frequency component of heart rate variability (mediated by parasympathetic activity) increased dramatically at the onset of the attack and returned toward baseline as the attack subsided. Conversely, the low-frequency component of heart rate variability (related to blood pressure and baroreflex control and mediated both by sympathetic and parasympathetic activity) dropped slightly at the onset of the attack, then rose toward the end of the attack. De Marinis et al. (6) investigated changes in heart rate variability during attacks in eight CH patients. The low-frequency component of heart rate fluctuations increased before the onset of headache (in parallel with a mild tachycardia) but then fell during the attack, whereas the high-frequency component increased as the attack progressed.

The mechanism of these disturbances in cardiovascular control is uncertain. Perhaps an increase in parasympathetic activity at the onset of the attack forms part of a normal baroreflex mechanism that attempts to reduce pain-evoked increases in blood pressure. Alternatively, activation of trigeminal depressor or oculocardiac reflexes might contribute to bradycardia. A sustained fall in arterial oxygen saturation precedes attacks of CH (32). Since heart rate increases in CH patients during oxygen deprivation (56), hypoxia before attacks could contribute to tachycardia before the onset of the headache.

To investigate whether a disturbance in sympathetic vasoconstrictor outflow might contribute to cardiovascular instability, Nordin et al. (42) recorded sympathetic traffic in the peroneal nerve during attacks of CH. Increases in blood pressure that corresponded with pulse-synchronous bursts of sympathetic activity indicated that an increase in sympathetic vasoconstrictor outflow to muscles contributed to the rise in blood pressure. This response is almost certainly secondary to pain, because the same relationship between bursts of sympathetic activity in the peroneal nerve and blood pressure was observed during eye pain induced by the instillation of soapy water (41). Pain or the anticipation of pain might also trigger transient tachycardia at the onset of attacks.

Cardiac arrhythmias develop during CH attacks in some patients (37), possibly in association with changes in autonomic balance (48). Alternatively, a change in breathing patterns during intense pain could evoke cardiac arrhythmias and contribute to changes in heart rate variability. Respiratory sinus arrhythmia during deep breathing, an index of vagal modulation of heart rate, does not change consistently during attacks of CH (30).

Cardiovascular reflexes generally do not differ from normal in CH patients during the headache-free interval. For instance, increases in heart rate, decreases in blood pressure, and changes in heart rate variability were found to be similar in patients and controls during head-up tilt (6,31). However, immersing the hand in ice-cold water for 5 minutes was found to provoke greater increases in blood pressure in patients than in controls (60), possibly due to pain or stress-induced sympathetic hyperactivity in CH patients. Furthermore, local vascular reflexes may be compromised in symptomatic tissues. For example, the Valsalva maneuver provokes greater increases in intraocular pressure on the symptomatic than asymptomatic side during bouts of CH, presumably due to a reduction in arterial tone of the orbital vasculature or impairment of venous drainage to the cavernous sinus (1).

Autonomic Innervation of the Face

The sympathetic supply of the face is regulated by activity in midbrain sites such as the hypothalamus and periaqueductal gray matter. Projections descend from brainstem nuclei through the intermediolateral cell column of the cervical and upper thoracic region of the spinal cord to synapse with neurons that supply the superior cervical ganglion. Postganglionic fibers that supply the periocular region form a nerve plexus around the internal carotid artery before following branches of the trigeminal nerve to the periphery. The rest of the face is supplied by postganglionic fibers that project from the caudal part of the superior cervical ganglion along the external carotid artery, hence bypassing potential intracranial sites of injury. Neurons in the cervical sympathetic pathway regulate vasoconstrictor tone in the facial skin (particularly the lips, nose, and ears), exocrine glands, and probably the major intracranial vessels. Cervical sympathetic activity also triggers active cutaneous vasodilation and facial sweating during heat stress and emotional reactions, and regulates pupillary dilation and tonic separation of the eyelids.

Parasympathetic neurons control local blood flow and glandular secretions around the eyes, nose, and mouth. A major function of the lacrimal, nasal, and salivary secretions is to wash away potentially harmful substances. These substances are identified by trigeminal neurons that form the afferent limb of trigeminal–parasympathetic secretory and vasodilator reflexes (27). The trigeminal–parasympathetic reflexes complement local neurogenic vasodilation and inflammation induced by release of vasoactive peptides from sensory nerves. Parasympathetic vasodilator fibers in the facial nerve also supply the proximal segments of large intracranial vessels (65). Trigeminal–parasympathetic vasodilation in these large

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intracranial vessels may work cooperatively with local neurogenic vasodilation to protect the brain from potentially harmful substances.

Ocular Disturbances

A lesion compromising the peripheral part of the ocular sympathetic pathway appears to be responsible for ocular sympathetic deficit in most CH patients. A central or preganglionic sympathetic lesion does not disrupt pupillary dilation to substances such as tyramine or hydroxyamphetamine, which release noradrenaline from the terminal projections of postganglionic sympathetic fibers. However, pupillary dilation is impaired in patients with a postganglionic sympathetic lesion and in CH patients with signs of ocular sympathetic deficit (13), presumably because the postganglionic sympathetic fibers are injured or dead.

Micieli et al. (38) reported that pupillary dilation in response to painful corneal stimulation was attenuated bilaterally in CH patients during the active phase of their headache cycle, particularly on the symptomatic side. The mydriatic response is mediated by sympathetic activation, whereas the miosis that follows this brief mydriatic response is mediated by parasympathetic activity or by the peripheral release of neuropeptides from sensory nerve terminals. Pupillary dilation in response to painful electrical stimulation of the sural nerve was also attenuated on the symptomatic side in CH patients during bouts (39), but did not differ from control values during the remission period between bouts. Presumably, a transient ocular sympathetic deficit prevented normal pupillary dilation to the sural nerve and corneal stimulation during bouts (38,39). Surprisingly, in asymptomatic CH patients *without* signs of ocular sympathetic deficit, bilateral pupillary dilation induced by painful stimulation of the neck was found to be *greater* than in controls (25). This fits with the idea of pain or stress-induced sympathetic hyperactivity in CH patients.

Tassorelli et al. (60) investigated pupillary responses to pain provoked by immersing the hand in ice-cold water. At baseline, pupil diameter did not differ between the symptomatic and asymptomatic sides or between patients and controls. In controls, an early mydriatic response during the first 30 seconds of the test was followed by pupillary constriction several minutes later. The early mydriatic response was similar in patients and controls, irrespective of whether patients were in the active phase or in remission. However, miosis did not develop in CH patients. Intramuscular injection of 0.4 mg of naloxone blocked miosis in controls but induced miosis in CH patients, indicating that CH is associated with altered opioid control of pupillary activity. Whether this opioid influence is of central or peripheral origin is uncertain, but it is tempting to conclude that a disturbance in central opioid release compromises inhibitory pain modulation and disrupts autonomic activity in CH patients.

The occasional presence of ocular sympathetic deficit on the asymptomatic side (8) or bilaterally in patients with CH (29) raises questions about the mechanism and site of lesion in these unusual cases. However, in the vast majority of CH patients, persistent signs of ocular sympathetic deficit on the symptomatic side seem to be due to dysfunction of postganglionic fibers.

Facial Flushing and Sweating

Thermoregulatory flushing and sweating are impaired on the symptomatic side of the forehead in CH patients with persistent signs of ocular sympathetic deficit (13), but, paradoxically, sweating and blood flow often increase in this region during attacks (12,57). This paradoxical response is probably due to cross-innervation of denervated blood vessels and sweat glands by parasympathetic lacrimal fibers. If so, the forehead should sweat when the eye waters, both during painful ocular stimulation and during attacks of CH. In accordance with this hypothesis, painful stimulation of the eye induced sweating and flushing on the sympathetically denervated side of the forehead in patients with a postganglionic lesion, including patients with CH (13). In contrast, sweating was symmetrical to eye pain in most patients with a central or preganglionic sympathetic lesion.

Like other patients with a postganglionic cervical sympathetic lesion (50), the forehead sweat glands of CH patients are supersensitive to cholinergic substances (55). Denervation may also induce vascular supersensitivity to sympathetic neurotransmitters and neuromodulators, which might contribute to vasodilation during attacks of CH in patients with cervical sympathetic deficit (7).

A preganglionic cervical or central sympathetic lesion usually interrupts sweating and releases sympathetic vasoconstrictor tone in the symptomatic upper limb (11,33). Thus, if a central lesion was responsible for cervical sympathetic deficit in CH, the lesion should also block sweating and vascular activity in the hand. However, sudomotor responses were symmetrical in the hands of patients with CH (11); thus, a central origin of cervical sympathetic deficit in CH seems unlikely.

Lacrimation, Nasal Secretion, and Salivation

In most cases the lacrimation, nasal stuffiness and nasal secretion that develop on the symptomatic side during attacks are probably secondary to primary trigeminal discharge, although release of sympathetic vasoconstrictor tone during attacks might also contribute to nasal stuffiness. Interruption of parasympathetic pathways in the greater superficial petrosal nerve prevents lacrimation

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during attacks (18), indicating that the trigeminal–parasympathetic lacrimal reflex (9,10) mediates this response. Neuropeptides released peripherally from trigeminal nerve endings might also play a minor role in this response (20). Unlike the sympathetic innervation of the face, trigeminal–parasympathetic reflexes function normally without evidence of denervation supersensitivity in CH patients (54).

Minor increases in sweating, lacrimation, and nasal secretion on the painless side during attacks of CH has prompted speculation that these responses are mediated by a central disturbance (58). When one side of the nose is pinched, corneal moisture increases substantially on the stimulated side (10); however, corneal moisture also increases slightly in the other eye, indicating minor crossover of the trigeminal–parasympathetic lacrimal reflex in the brainstem. This crossover probably accounts for the presence of minor lacrimation and other parasympathetic disturbances on the painless side during attacks of CH.

Salivation decreases on both sides of the mouth during attacks of CH (54), presumably because sympathetic activation in response to pain overrides reflex trigeminal–parasympathetic salivation due to trigeminal discharge. The sympathetic innervation of salivary glands follows branches of the external carotid artery and trigeminal nerve to the periphery, thus bypassing possible intracranial sites of injury.

Possible Mechanism of Autonomic Disturbances in Cluster Headache

As outlined above, CH is associated with cervical sympathetic deficit and with signs of central sympathetic and parasympathetic discharge during attacks. Most evidence points to a peripheral source of cervical sympathetic deficit in CH. Vasodilation of the internal carotid artery or swelling of the arterial wall in the carotid canal during attacks might injure the plexus of sympathetic fibers that follow the artery to the periphery (14). Alternatively, an inflammatory process in the cavernous sinus may compromise sympathetic fibers en route to the eye and forehead (21). Pain or anticipation of pain probably alters central sympathetic discharge and cardiovascular activity before and during attacks. Thus, discharge of a primary neural generator during attacks of CH could provoke central and local sympathetic disturbances.

Surgical treatments that target the trigeminal ganglion and nerve root usually block recurrent attacks of CH and associated parasympathetic activity (22), indicating that trigeminal–parasympathetic reflexes mediate these disturbances. It has generally been assumed that a peripheral source of pain (e.g., inflammation in the cavernous sinus) triggers parasympathetic activity. However, the persistence of parasympathetic disturbances with or without cyclical headaches in the occasional patient after trigeminal surgery (28,35,36) suggests that links between trigeminal and parasympathetic nuclei in the brainstem might also contribute to parasympathetic disturbances during attacks of CH. The occasional report of cyclical headaches without autonomic symptoms (64) and cyclical autonomic symptoms without headache (49) implies that the pain and autonomic disturbances of CH can be generated independently. Positron emission tomography studies have identified specific ipsilateral activation of the posterior hypothalamic gray matter during attacks of CH (5,59), suggesting that the hypothalamus is the primary generator of CH attacks. In particular, a hypothalamic disturbance may be responsible for the periodicity of attacks and cluster periods, for triggering pain, and for disturbances in autonomic and vascular control. Thus, a combination of direct hypothalamic discharge and secondary recruitment of trigeminal–parasympathetic reflexes could mediate parasympathetic disturbances during attacks of CH and related trigeminal–autonomic cephalalgias. As noted above, pain modulation is disrupted in CH patients, particularly during bouts. Presumably, this increases the likelihood of pain and trigeminal sensitization during hypothalamic discharge.

Although most autonomic disturbances are probably secondary to trigeminal nerve activity in CH, vascular instability might aggravate pain. For example, vasodilation or swelling of the internal carotid artery in the carotid canal could cause pain because of entrapment of sensory fibers that supply the arterial wall (23); alternatively, the swollen artery might compress the trigeminal ganglion directly (21,22). Head-down tilting increases the diameter of the common carotid artery and can induce headache and ocular sympathetic deficit during bouts of CH (19). These findings support the idea that dilation of the common carotid artery or distension of the arterial wall in the carotid canal is a source of pain and sympathetic disturbances during attacks.

The rapid escalation of pain from a niggling sensation to intense pain during attacks suggests that the pain-producing mechanism quickly builds upon itself, perhaps in a positive loop. For example, trigeminal activation might provoke local swelling of intracranial vessels and aggravate an inflammatory process that, in turn, intensifies trigeminal discharge and boosts vascular swelling and inflammation. This cycle may continue until the trigeminovascular response fatigues and pain subsides.

REFERENCES

1. Barriga FJ, Sanchez-del-Rio M, Baron M, Dobato J, Gili P, Yanguela J, et al. Cluster headache: interictal asymmetric increment in intraocular pressure elicited by Valsalva manoeuvre. *Cephalalgia* 2004;24:185–187.
2. Boiardi A, Carenini L, Frediani F, et al. Visual evoked potentials in cluster headache: central structures involvement. *Headache* 1986;26:70–73.

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3. Bono G, Antonaci F, Sandrini G, et al. Pain pressure threshold in cluster headache patients. *Cephalalgia* 1996;16:62–66.
4. Bussone G, Sinatra MG, Boiardi A, et al. Brainstem auditory evoked potential (BAEPs) in cluster headache (CH): new aspects for a central theory. *Headache* 1986;26:67–69.
5. Cohen AS, Goadsby PJ. Functional neuroimaging of primary headache disorders. *Curr Neurol Neurosci Rep* 2004;4:105–110.
6. de Marinis M, Strano S, Granata M, et al. Sympathetic-parasympathetic activation during spontaneous attacks of cluster headache: evaluation by spectral analysis of heart-rate fluctuations. *Cephalalgia* 1995;15:504–510.
7. Drummond PD. Autonomic disturbances in cluster headache. *Brain* 1988;111:1199–1209.
8. Drummond PD. Dissociation between pain and autonomic disturbances in cluster headache. *Headache* 1990;30:505–508.
9. Drummond PD. The mechanism of facial sweating and cutaneous vascular responses to painful stimulation of the eye. *Brain* 1992;115:1417–1428.
10. Drummond PD. Lacrimation and cutaneous vasodilatation in the face induced by painful stimulation of the nasal ala and upper lip. *J Auton Nerv Syst* 1995;51:109–116.
11. Drummond PD. The site of sympathetic deficit in cluster headache. *Headache* 1996;36:3–9.
12. Drummond PD, Lance JW. Thermographic changes in cluster headache. *Neurology* 1984;34:1292–1298.
13. Drummond PD, Lance JW. Pathological sweating and flushing accompanying the trigeminal lacrimal reflex in patients with cluster headache and in patients with a confirmed site of cervical sympathetic deficit: evidence for parasympathetic cross-innervation. *Brain* 1992;115:1429–1445.
14. Ekbom K, Greitz T. Carotid angiography in cluster headache. *Acta Radiol Diag* 1970;10:177–186.
15. Fanciullacci M, Fusco BM, Alessandri M, et al. Unilateral impairment of pupillary response to trigeminal nerve stimulation in cluster headache. *Pain* 1989;36:185–191.
16. Firenze C, Del Gatto F, Mazzotta G, et al. Somatosensory evoked potential study in headache patients. *Cephalalgia* 1988;8:157–162.
17. Fusco BM, Alessandri M, Campagnolo V, et al. Transcutaneous electrical stimulation applied to the infratrochlear nerve induces a homatropine-resistant miosis in humans. *Clin Sci* 1990; 78:457–462.
18. Gardner WJ, Stowell A, Dutlinger R. Resection of the greater superficial petrosal nerve in the treatment of unilateral headache. *J Neurosurg* 1947;4:105–114.
19. Hannerz J, Jogestrand T. Effects of increasing the intracranial blood volume in cluster headache patients and controls. *Cephalalgia* 1995;15:499–503.
20. Hardebo JE. The involvement of trigeminal substance P neurons in cluster headache. An hypothesis. *Headache* 1984;24:294–304.
21. Hardebo JE. How cluster headache is explained as an intracavernous inflammatory process lesioning sympathetic fibres. *Headache* 1994;34:125–131.
22. Hardebo JE. On pain mechanisms in cluster headache. *Headache* 1991;31:91–106.
23. Hardebo JE. Activation of pain fibers to the internal carotid artery intracranially may cause the pain and local signs of reduced sympathetic and enhanced parasympathetic activity in cluster headache. *Headache* 1991;31:314–320.
24. Hasan Z, Sjaastad O, Lundervold A. An electroencephalographic investigation of patients with cluster headache. *Clin Electroencephalogr* 1976;7:203–207.
25. Havelius U, Heuck M, Milos P, et al. Ciliospinal reflex response in cluster headache. *Headache* 1996;36:568–573.
26. Holstege H. Neuronal organization of the blink reflex. In: Paxinos G, ed. *The human nervous system*. London: Academic Press, 1990:287–296.
27. Izumi H. Reflex parasympathetic vasodilatation in facial skin. *Gen Pharmacol* 1995;26:237–244.
28. Jarrar RG, Black DF, Dodick DW, et al. Outcome of trigeminal nerve section in the treatment of chronic cluster headache. *Neurology* 2003;60:1360–1362.
29. Khurana RK. Bilateral Horner's syndrome in cluster type headaches. *Headache* 1993;33:449–451.
30. Kruszewski P. Respiratory sinus arrhythmia in cluster headache syndrome. *Headache* 1993;33:98–104.
31. Kruszewski P, Bordini C, Brubakk AO, et al. Cluster headache: responses to head-up tilt. *Headache* 1995;35:465–469.
32. Kudrow L. The pathogenesis of cluster headache. *Curr Opin Neurol* 1994;7:278–282.
33. List CF, Peet MM. Sweat secretion in man. V. Disturbances of sweat secretion with lesions of the pons, medulla and cervical portion of the cord. *Arch Neurol Psychiatry* 1939;42:1098–1127.
34. Lozza A, Schoenen J, Delwaide PJ. Inhibition of the blink reflex R2 component after supraorbital and index finger stimulations is reduced in cluster headache: an indication for both segmental and suprasegmental dysfunction? *Pain* 1997;71:81–88.
35. Matharu MS, Goadsby PJ. Persistence of attacks of cluster headache after trigeminal nerve root section. *Brain* 2002;125:976–984.
36. Maxwell RE. Surgical control of chronic migrainous neuralgia by trigeminal ganglio-rhizolysis. *J Neurosurg* 1982;57:459–466.
37. Micieli G, Cavallini A, Bosone D, et al. Imbalance of heart rate regulation in cluster headache as based on continuous 24-h recordings. *Clin Auton Res* 1993;3:291–298.
38. Micieli G, Tassorelli C, Ruiz L, et al. The trigemino-pupillary response in cluster headache. *Cephalalgia* 1993;13:338–342.
39. Micieli G, Magri M, Sandrini G, et al. Pupil responsiveness in cluster headache: a dynamic TV pupillometric evaluation. *Cephalalgia* 1988;8:193–201.
40. Nappi G, Sandrini G, Alfonsi E, et al. Impaired circadian rhytmicity of nociceptive reflex threshold in cluster headache. *Headache* 2002;42:125–131.
41. Nordin M, Fagius J. Effect of noxious stimulation on sympathetic vasoconstrictor outflow to human muscles. *J Physiol (Lond)* 1995;489:885–894.
42. Nordin M, Fagius J, Waldenlind E. Sympathetic vasoconstrictor outflow to extremity muscles in cluster headache. Recordings during spontaneous and nitroglycerin-induced attacks. *Headache* 1997;37:358–367.
43. Penders C, Delwaide PJ. Physiologic approach to the human blink reflex. In: Desmedt JE, ed. *New developments in electromyography and clinical neurophysiology*, vol 3. Basel: Karger, 1973:649–657.
44. Polich J, Aung M, Dalessio DJ. Pattern-shift visual evoked responses in cluster headache. *Headache* 1987;27:446–451.
45. Procacci P, Zoppi M, Maresca M, et al. Lateralisation of pain in cluster headache. *Pain* 1989;38:275–278.
46. Raudino F. The blink reflex in cluster headache. *Headache* 1990;30:584–585.
47. Rossi A, Scarpini G. Gating of trigemino-facial reflex from low-threshold trigeminal and extratrigeminal cutaneous fibres in humans. *J Neurol Neurosurg Psychiatry* 1992;53:121–135.
48. Russell D, Storstein L. Cluster headache: a computerized analysis of 24 h holter ECG recordings and description of ECG rhythm disturbances. *Cephalalgia* 1983;3:83–107.
49. Salvesen R. Cluster headache sine headache: case report. *Neurology* 2000;55:451.
50. Salvesen R. Innervation of sweat glands in the forehead. A study in patients with Horner's syndrome. *J Neurol Sci* 2001;183:39–42.
51. Sandrini G, Alfonsi E, Ruiz L, et al. Impairment of corneal pain perception in cluster headache. *Pain* 1991;47:299–304.
52. Sandrini G, Antonaci F, Lanfranchi S, et al. Asymmetrical reduction of the nociceptive flexion reflex threshold in cluster headache. *Cephalalgia* 2000;20:647–652.
53. Sandrini G, Arrigo A, Bono G, et al. The nociceptive flexion reflex as a tool for exploring the pain control system in headache and other pain syndromes. *Cephalalgia* 1993;13:21–27.
54. Saunte C. Autonomic disorders in cluster headache, with special reference to salivation, nasal secretion and tearing. *Cephalalgia* 1984;4:57–64.
55. Saunte C, Russell D, Sjaastad O. Cluster headache: on the mechanism behind attack-related sweating. *Cephalalgia* 1983;3:175–185.
56. Shen JM, Schaanning J. Cluster headache: pulse rate changes evoked by hyperoxia and hypoxia. *Headache* 1994;34:79–82.
57. Sjaastad O, Saunte C, Russell D, et al. Cluster headache: the sweating pattern during spontaneous attacks. *Cephalalgia* 1981;1:233–244.

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58. Sjaastad O, Saunte C, Fredriksen TA. Bilaterality of cluster headache. An hypothesis. *Cephalalgia* 1985;5:55–58.
59. Sprenger T, Boecker H, Tolle TR, et al. Specific hypothalamic activation during a spontaneous cluster headache attack. *Neurology* 2004;62:516–517.
60. Tassorelli C, Micieli G, Osipova V, et al. Combined evaluation of pupillary and cardiovascular responses to cold pressor test in cluster headache patients. *Cephalalgia* 1998;18:668–674.
61. Tubani L, Baratta L, Giorgino F, et al. Heart rate variability in cluster headache. *Ann Ital Med Int* 2003;18:42–46.
62. Valls-Solé J, Cammarota A, Alvarez R, et al. Orbicularis oculi responses to stimulation of nerve afferents from upper and lower limbs in normal humans. *Brain Res* 1994;650:313–316.
63. Van Vliet JA, Vein AA, Le Cessie S, et al. Impairment of trigeminal sensory pathways in cluster headache. *Cephalalgia* 2003;23:414–419.
64. Vigl M, Zebenholzer K, Wessely P. Cluster headache without autonomic symptoms? *Cephalalgia* 2001;21:926–927.
65. Zhu BS, Blessing WW, Gibbins IL. Parasympathetic innervation of cephalic arteries in rabbits: comparison with sympathetic and sensory innervation. *J Comp Neurol* 1997;389:484–495.