

Persistence of attacks of cluster headache after trigeminal nerve root section

Manjit S. Matharu and Peter J. Goadsby

Headache Group, Institute of Neurology, University College London, UK

Correspondence to: Professor Peter J. Goadsby, Institute of Neurology, Queen Square, London WC1N 3BG, UK
E-mail: peterg@ion.ucl.ac.uk

Summary

Cluster headache is a strictly unilateral headache that occurs in association with cranial autonomic features. We report a patient with a trigeminal nerve section who continued to have attacks. A 59-year-old man described a 14-year history of left-sided episodes of excruciating pain centred on the retro-orbital and orbital regions. These episodes lasted 1–4 h, recurring 2–3 times daily. The attacks were associated with ipsilateral ptosis, conjunctival injection, lacrimation, rhinorrhoea and facial flushing. From 1986 to 1988, he had trials of medications without any benefit. In February 1988, he had complete surgical section of the left trigeminal sensory root that shortened the attacks in length for 1 month without change in their frequency or character. In April 1988, he had further surgical exploration and the root was found to be completely excised; post-operatively, there was no change in the symptoms. From 1988 to 1999, he had a number of medications, including verapamil and indomethacin, all of which were ineffective. Prednisolone 30 mg orally daily rendered the patient completely pain free. Sumatriptan 100 mg orally and 6 mg subcutaneously aborted the attack after ~45 and 15 min, respectively. He was completely anaesthetic over the entire left trigeminal distribution. Left corneal reflex was absent. Motor function of the left trigeminal

nerve was preserved. Neurological and physical examination was otherwise normal. MRI scan showed a marked reduction in the calibre of the left trigeminal nerve from the nerve root exit zone in the pons to Meckel's cave. An ECG-gated three-dimensional multi-slab MRI inflow angiogram was performed. No dilatation was observed in the left internal carotid artery during the cluster attack. Blink reflexes were elicited with a standard electrode and stimulus. Stimulation of the left supraorbital nerve produced neither ipsilateral nor contralateral blink reflex response. Stimulation of the right supraorbital nerve produced an ipsilateral response with a mean R2 onset latency of 36 ms and a contralateral response with a mean R2 onset latency of 32 ms. Lack of ipsilateral vessel dilatation makes the role of vascular factors in the initiation of cluster attacks questionable. With complete section of the left trigeminal sensory root the brain would perceive neither vasodilatation nor a peripheral neural inflammatory process; however, the patient continued to have an excellent response to sumatriptan. The case illustrates that cluster headache may be generated primarily from within the brain, and that triptans may have anti-headache effects through an entirely central mechanism.

Keywords: trigeminal autonomic cephalgia; sumatriptan; trigeminocervical; cluster headache; migraine

Abbreviations: MRA = MRI inflow angiogram; ROI = regions of interest

Introduction

It is a basic tenet of the current understanding of headache that the pain is in some way generated by cranial nociceptors with the role of the brain to interpret, modulate and respond to afferent nociceptive traffic (Olesen *et al.*, 2000). Although centrally produced pain, such as that seen with thalamic lesions, is a well-accepted entity, this is a smaller part of the whole in terms of the clinical load of pain. Similarly, headache is not generally considered to be generated in the CNS without a

peripheral input. In contrast, clinicians accept many aspects of the acute attack of primary neurovascular headaches, migraine and cluster headache to occur without any abnormality in the periphery (Goadsby *et al.*, 2002). Consider photophobia, seen in both migraine (Headache Classification Committee of The International Headache Society, 1988) and cluster headache (Bahra *et al.*, 2002); there is no suggestion that the sun burns brighter. Moreover, there are well-characterized cases of

headache arising in the brain, such as in epileptic events (Young and Blume, 1983; Siegel *et al.*, 1999), or as migraine-like headaches being generated from stimulation of brainstem regions (Raskin *et al.*, 1987; Veloso *et al.*, 1998) or local brainstem lesions (Haas *et al.*, 1993; Goadsby, 2002). Could the generation of headache from the CNS be more important than has hitherto been considered?

Broadly, headache may be classified as primary, where the headache syndrome is the core disorder; and secondary, where the pain is generated from some described locus, such as a brain tumour or infection (Headache Classification Committee of The International Headache Society, 1988). This is an uncomfortable distinction if the peripheral vessels generate the pain. The patient to be described challenges the view that the pain signal generator need necessarily be peripheral in primary neurovascular headache. Our patient has chronic cluster headache, an unremitting severe pain syndrome marked by discrete attacks accompanied by symptoms such as lacrimation, conjunctival injection or nasal congestion, and underwent a complete trigeminal sensory nerve root section. Cluster headache has been considered to be due to peripheral vascular change (Ekbom and Greitz, 1970; Waldenlind *et al.*, 1993), or indeed a vascular or inflammatory process within the cavernous sinus (Moskowitz, 1988; Hardebo, 1994). Recent imaging data suggest an important involvement of the posterior hypothalamic grey matter in the active period as a central locus of dysfunction (May *et al.*, 1998a, 1999a, 2000) and thus a CNS locus for the disorder. A further key question in primary headache arises from the development and clinical use of triptans, serotonin 5-HT_{1B/1D} agonists, in migraine (Ferrari, 1998) and cluster headache (The Sumatriptan Cluster Headache Study Group, 1991). These compounds were developed as cranial vasoconstrictors (Humphrey *et al.*, 1990), but it has become clear in experimental models that these compounds inhibit peripheral neuronal (Moskowitz and Cutrer, 1993) and trigeminal nucleus activation (Goadsby, 2000). The current patient presents a unique opportunity to reconsider some fundamental aspects of cluster headache pathophysiology and the site of action of treatments.

Clinical case

A 59-year-old left-handed man presented with a 14-year history of intermittent, daily headaches. There was no prior history of headache or any obvious precipitant at onset.

Current clinical picture

The patient described strictly left-sided episodes of excruciating, sharp pain centred on the retro-orbital and orbital regions, forehead and temple. These episodes

lasted between 1 and 4 h, recurring 2–3 times daily. The attacks were associated with ipsilateral ptosis, conjunctival injection, lacrimation, rhinorrhoea and facial flushing. He denied nausea, vomiting, photophobia, phonophobia or osmophobia. Movement had no effect on the pain. There were no aura symptoms. Alcohol triggered an attack within half an hour. Once or twice a day he had attacks of purely cranial autonomic symptoms without any accompanying pain. Left-sided conjunctival injection, lacrimation and rhinorrhoea occurred concurrently for 15–120 min, although these symptoms are milder in intensity than during an episode of pain. Also independently of the pain episodes, he had sharp stabbing pains in the left eye or upper lip 3–4 times a day, with each episode lasting a few seconds, consistent with idiopathic stabbing headache.

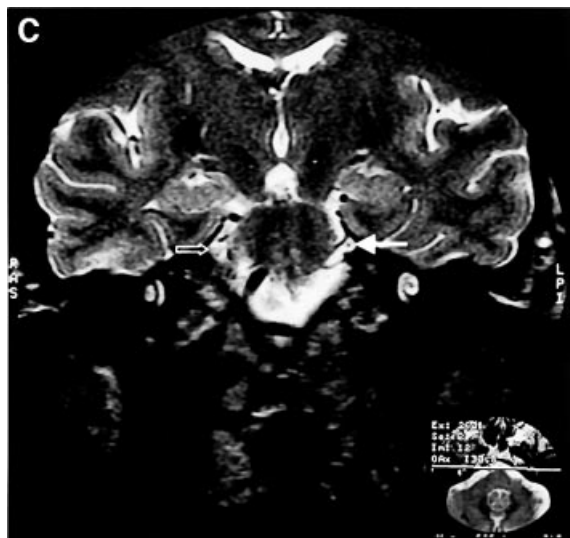
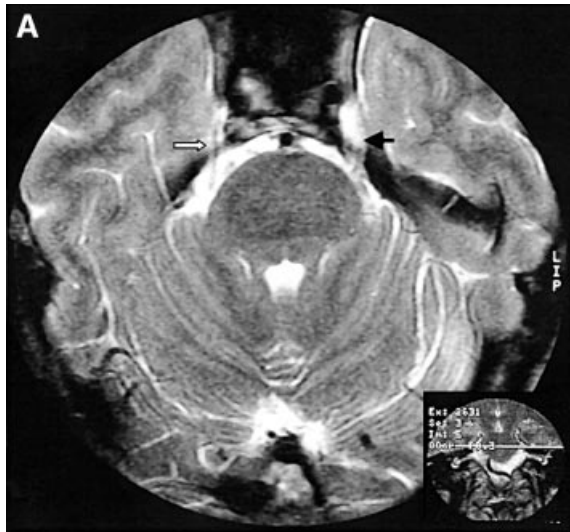
Previous history

His headaches began in 1986. Over a 2-year period he had trials of propranolol, amitriptyline, lithium, methysergide, isometheptene and ergotamine tablets and suppositories, all without any benefit as preventatives, or for the acute attacks. In February 1988, he had a complete surgical section of the left trigeminal sensory root. This led to the attacks being reduced in length for 1 month without any change in the severity or character of the symptoms. In April 1988, a further surgical exploration of the left trigeminal sensory root was performed as the symptoms had continued. The sensory root was found to be completely excised. Post-operatively, there was no change in the symptoms. Thereafter, he had trials of sodium valproate 1.8 g daily, verapamil 120 mg tds, pizotifen 1.5 mg tds, cyproheptadine 4 mg qds, indomethacin 75 mg tds, naproxen, diclofenac, mefenamic acid 500 mg as required, nortriptyline, dothiepin 175 mg daily, clonazepam 0.5 mg bd, carbamazepine 100 mg tds, vigabatrin 2 mg bd, gabapentin 900 mg daily, azathioprine 50 tds, nifedipine 10 mg bd, acetazolamide 500 mg bd, high-flow rate oxygen, intranasal lignocaine drops and zolmitriptan 2.5 mg, all of which had no effect. In addition, he had further trials of lithium 800 mg daily and methysergide 2 mg tds that were limited by side effects, but there was improvement in the symptoms.

In the past medical history, he twice had renal colic. On both occasions he had spontaneously passed a renal stone. There was no family history of headaches. He was a non-smoker. He ceased drinking alcohol with the onset of the headaches.

Physical examination

On examination, he was completely anaesthetic over the entire left trigeminal distribution. The left corneal reflex was absent. Motor function of the left trigeminal nerve was preserved. Neurological and physical examination



was otherwise normal. Routine haematological and biochemical screening was normal.

An MRI scan showed a marked reduction in the calibre of the left trigeminal nerve from the nerve root exit zone in the pons to Meckel's cave, and evidence of previous posterior fossa craniectomy (Fig. 1). No other abnormality was identified.

Successful treatments

Prednisolone 30 mg daily rendered the patient completely pain free; he had been taking short courses of prednisolone 2–3 times annually since 1990. Sumatriptan 100 mg orally and 6 mg subcutaneously aborted the attack after ~45 and 15 min, respectively; this had been the mainstay of his treatment since 1995.

Physiological observations

Magnetic resonance angiography

An ECG-gated three-dimensional multislab MRI inflow angiogram (MRA) with a repetition time (TR) of 39 ms, 32 mm slab thickness, an effective slice thickness of 1 mm and a flip angle of 25° was performed, using a Siemens MAGNETOM Vision scanner operating at 2 T. The MRA was performed using a transverse section through the extracranial portion of the internal artery just distal to the carotid bifurcation. The patient had a scan at rest and after a nitroglycerine-induced attack of acute cluster headache. The entire three-dimensional data set was processed with maximum intensity projections. Using the integrated software (Siemens calculation tool), regions of interest (ROI) were drawn around the vessels identified as the internal carotid arteries on either side. The absolute values for vessel diameter (cm²), blood flow (cm³/s), and mean and peak velocity (cm/s) were calculated. The haemodynamic changes in the vessels between conditions

Fig. 1 (A) Axial fast spin echo T₂-weighted MRI through the trigeminal nerve. The right trigeminal nerve (white arrow) is seen in continuity from the root entry zone at the pons to Meckel's cave. The left Meckel's cave is expanded, reflecting previous surgery. The left trigeminal nerve (black arrow) is seen in continuity from the root entry zone to the entrance of Meckel's cave, where it is truncated and cut off. A small calibre nerve is seen medially within Meckel's cave, consistent with the preserved motor root. (B) Coronal fast spin echo T₂-weighted MRI through the pontine cistern, showing the normal and symmetrical calibre of the trigeminal nerves just proximal to the root entry zone. (C) Coronal fast spin T₂-weighted MRI through the entrances to the Meckel's caves. The right trigeminal nerve (black arrow) has a normal calibre. Note the marked reduction in the calibre of the left trigeminal nerve (white arrow), consistent with the preserved motor root.

are expressed as a percentage change from the rest to pain condition.

Blink reflexes

Blink reflexes were elicited with a standard electrode. This is a parallel assembly with two stimulation surfaces 25 mm apart, positioned over the left supraorbital nerve. The following stimulus parameters were used: monopolar square wave, duration 0.5 ms, interstimulus interval 12–18 s (pseudorandomized); current intensity 10 mA, six sweeps. EMG recordings were obtained from bilateral surface electrodes placed infraorbitally (different) and at the root of the nose (indifferent), acquisition bandwidth 1 Hz–1 kHz; digitization: sampling rate 2.5 kHz, sweep length 150 ms. PC-based offline analysis was performed with custom-written software. Recordings were obtained bilaterally stimulating first from the left side then from the right side.

Results

Magnetic resonance angiography

The resting vessel area of the internal carotid was symmetrical comparing the ipsilateral and contralateral sides. No change in vessel area ipsilateral to pain was observed during acute cluster headache.

Blink reflexes

Stimulation of the left supraorbital nerve produced neither an ipsilateral nor contralateral blink reflex response (Fig. 2A and B). Stimulation of the right supraorbital nerve produced an ipsilateral response with a mean R2 onset latency of 36 ms (Fig. 2C) and a contralateral response with a mean R2 onset latency of 32 ms (Fig. 2D).

Discussion

This patient with cluster headache was treated by trigeminal sensory root section, with denervation of the structures proposed to generate the pain; he continued to have attacks. If the denervation was complete, then, by definition, the structures innervated by this nerve, the cranial vessels and other intracranial pain-producing structures, such as the dura mater, must be unnecessary to the perception of the pain. This clinical therapeutic experiment suggests that only the brain pathways are required for cluster headache, at least once the condition is established. Furthermore, the therapeutic outcome with sumatriptan establishes that this triptan can act within the CNS to block cluster headache without any necessary peripheral input. It is of additional interest that his shorter lasting attacks, which are probably idiopathic stabbing headache, also continued, again suggesting their generation in the CNS.

The patient's headache syndrome before the operation, from his account, and certainly by his current history, fulfils

standard criteria for chronic cluster headache (Headache Classification Committee of The International Headache Society, 1988). He has been resistant to most treatments; chronic cluster headache is often a therapeutic challenge (Olesen and Goadsby, 1999). He has a typical response to oral corticosteroids and his current attacks are indistinguishable clinically from typical cluster headache. There is no neuropathic component to the pain, suggesting that it is not simply a response to nerve injury. Trigeminal neuropathic pain, as seen after injury, is more usually persistent and is difficult to confuse with typical cluster headache. Moreover, there is not a single case report in which there is triptan responsiveness to trigeminal neuropathic pains. Indeed, for atypical facial pain, sumatriptan has been reported to be ineffective in a controlled trial (Harrison *et al.*, 1997). It is notable that his problems are the same now as they were after the surgery, which argues against plastic changes in the nervous system being the sole explanation for his problems.

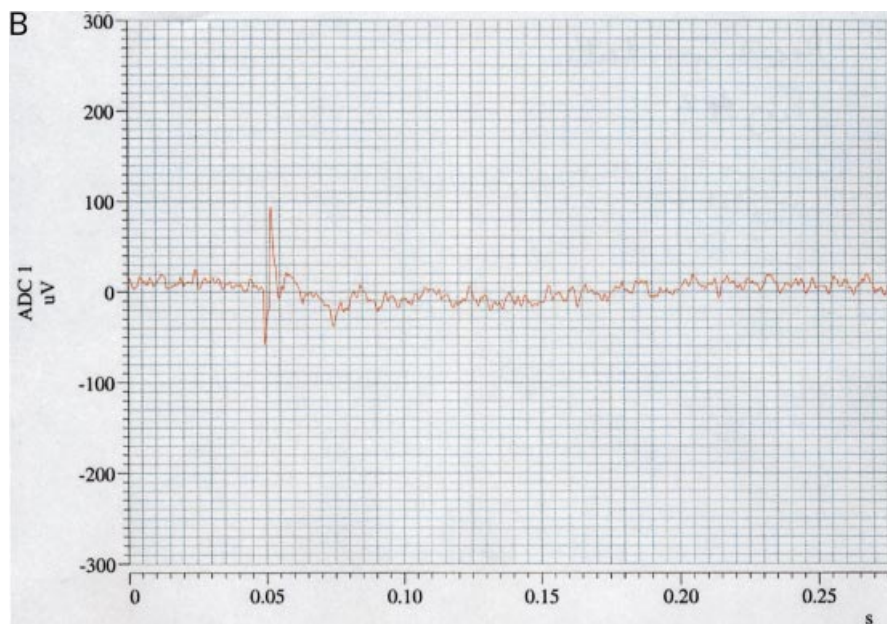
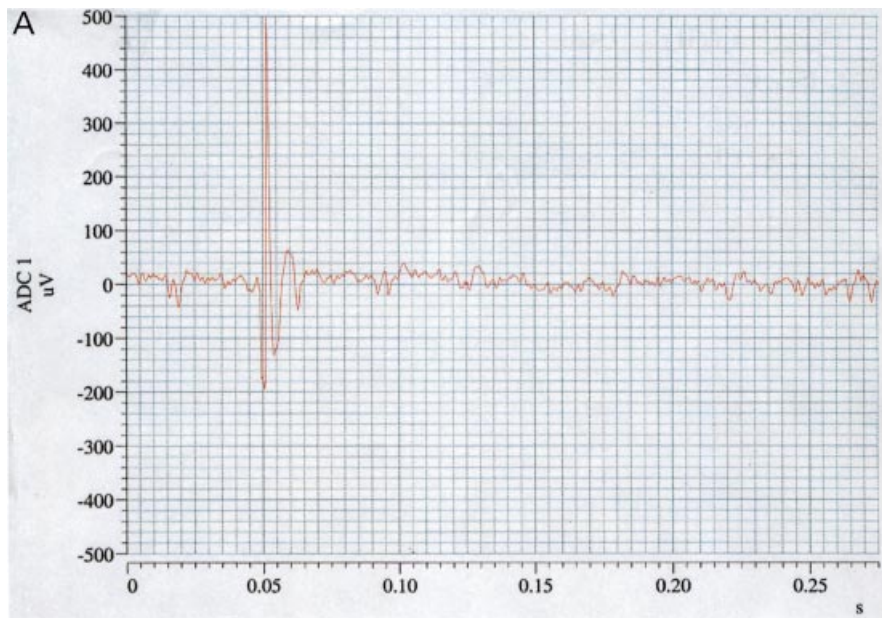
Is it possible that the nerve was not cut? Certainly it must be possible without post-mortem confirmation that the nerve is intact. However, it is remarkable that the patient was re-explored with confirmation of the section and has the predicted clinical findings of a dense anaesthesia ipsilateral to the section, as well as clear findings on brain imaging of the nerve, and an absent blink reflex. The absence of both an ipsilateral and contralateral blink reflex response when stimulating the left (lesioned) side clearly demonstrates absence of the afferent arc (first division of the trigeminal nerve) of the blink reflex. The normal ipsilateral and contralateral responses when stimulating on the right demonstrate both a normal right-sided afferent arc and a normal right and left efferent (facial nerve) pathways. There is some suggestion in the literature that trigeminal root section is curative for cluster headache (Kirkpatrick *et al.*, 1993). However, given the fact that cluster headache by its nature can have long remissions, it could not be concluded that an initial amelioration after root section reflected the long-term outcome. Indeed, it is clear from this published series that some patients remain with their attacks (O'Brien *et al.*, 1999). Some patients with cluster headache even after trigeminal nerve block with local anaesthetic can experience nitrate triggering of their attacks (O'Brien *et al.*, 1999), as our patient does. This may be due to a central triggering effect of nitrates rather than the traditional peripheral effect.

Could other pathways have been involved? Hardebo (1994) has suggested a role for the VIIth cranial nerve for nociceptive transmission in cluster headache. Anatomical evidence suggests a limited role for the facial (VIIth) nerve providing afferent information from the head (Boudreau *et al.*, 1977). In humans, this is limited to the ear and some skin around it (White and Sweet, 1955). Direct evidence of dural or substantial cranial vessel innervation from those nerves is lacking. Indeed, Cushing (1904) noted that after total extirpation of the trigeminal ganglion, there was ipsilateral dural insensitivity. Moreover, patients with a dull headache associated with placement of a CSF drain, probably a low

CSF pressure headache (Mokri *et al.*, 1997), would only complain of pain contralateral to the extirpation. Another possibility would be some involvement of branches of C₂, which projects into the caudal trigeminal nucleus. After trigeminal root section in primates, Denny-Brown and Yanagisawa (1973) showed that substantial areas of cutaneous facial input could be re-activated after intravenous strychnine injection. In this patient, the functional re-innervation would have to be for non-cutaneous pain structures only. This is possible, but unlikely. Finally, there is evidence for crossed trigeminal innervation from cranial

vessels in experimental animals (Edvinsson *et al.*, 1993); indeed, for non-human primates; there is functional anatomical evidence using Fos immunohistochemistry (Hoskin *et al.*, 1999). The crossover occurs in the brainstem so, as an example, the right carotid artery may project to the right and left trigeminal nucleus caudalis and on to the thalamus. However, there is no evidence that the contralateral vessel has *peripherally* crossed innervation, which would be needed to explain the findings in this case on a peripheral basis.

In addition to the clinical observations, MRAs were conducted at rest and during cluster headache. It has been



known for some years that the internal carotid artery dilates during acute cluster headache (Ekbom and Greitz, 1970; Waldenlind *et al.*, 1993). Indeed, there is pooling of PET tracer in the region of the cavernous sinus (May *et al.*, 1998a,

2000) that corresponds to internal carotid dilatation (May *et al.*, 1999b). Similarly, pooling of PET tracer (May *et al.*, 1998b) and internal carotid dilatation of 17% (May *et al.*, 2000) is reported after injection of the pain-producing

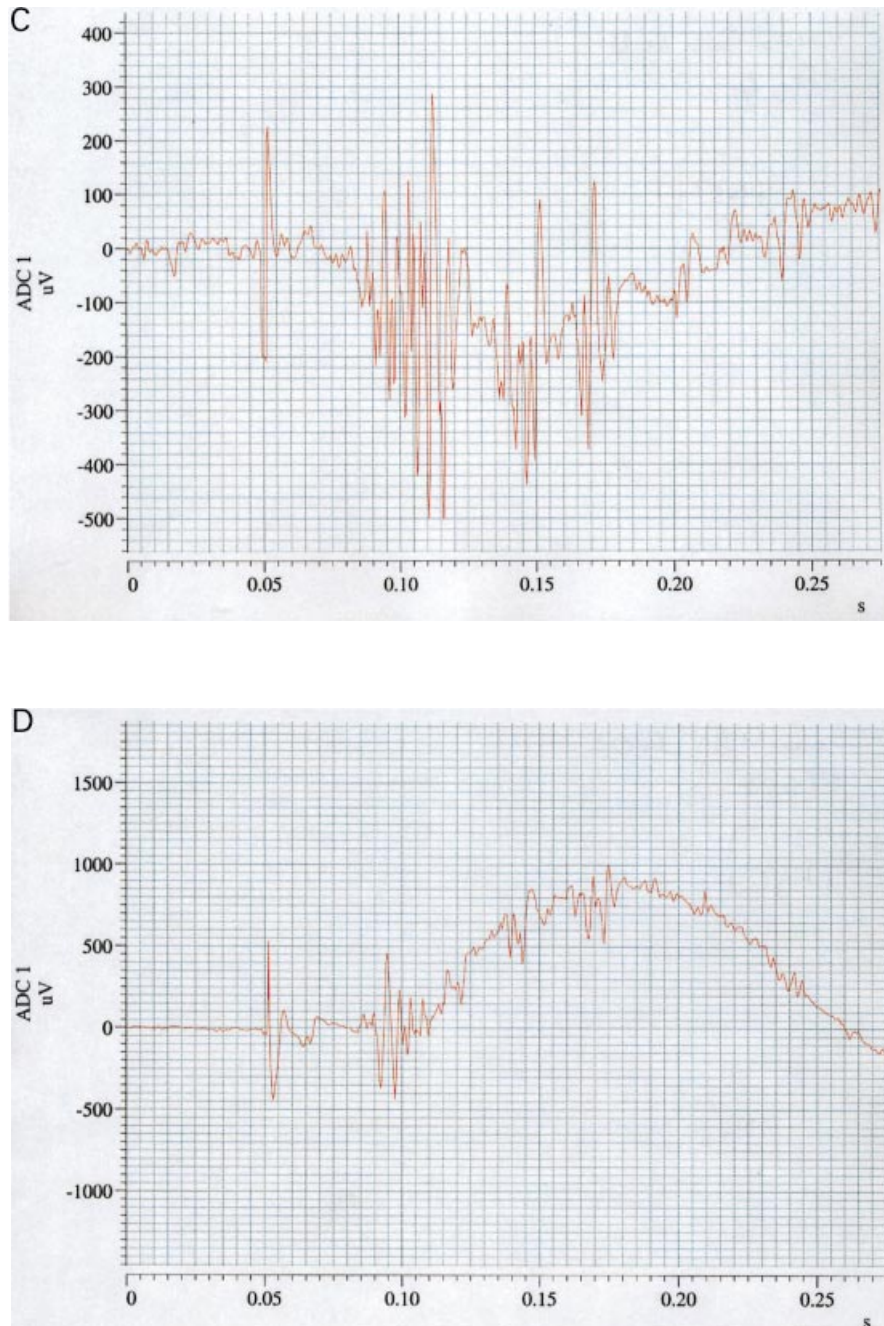


Fig. 2 (A) Stimulation of the left supraorbital nerve, recording ipsilaterally. A stimulus artefact is noted at 5 ms, but no blink reflex. (B) Stimulation of the left supraorbital nerve, recording contralaterally. A stimulus artefact is noted at 5 ms, but no blink reflex. (C) Stimulation of the right supraorbital nerve, recording ipsilaterally. The R2 component of the blink reflex is clearly demonstrated, with EOG artefact thereafter. Note the change in EMG gain. (D) Stimulation of the right supraorbital nerve, recording contralaterally. The R2 component of the blink reflex is clearly demonstrated, with EOG artefact thereafter.

substance capsaicin into the forehead. There is no dilatation in this patient. It has been suggested that the vasodilatation in cluster headache is due to activation of the trigeminal-autonomic (parasympathetic) reflex (May and Goadsby, 1999). It is remarkable that this dilatation is not seen here, lending physiological support to the notion that the sensory root has indeed been sectioned. The fact that the patient still has cranial autonomic symptoms, such as lacrimation, suggests that this pathway can be activated from the brain without the reflex trigeminal connection. A similar phenomenon, cranial autonomic symptoms without pain, has been demonstrated after percutaneous radiofrequency ganglio-rhizolysis (Maxwell, 1982). Certainly there is evidence in experimental animals for a direct pathway from hypothalamus to superior salivatory nucleus (Spencer *et al.*, 1990), the latter containing the pre-ganglionic cell bodies of the cranial autonomic outflow. We have seen isolated autonomic activation in the cohort of cluster headache patients we have managed in recent years, and this phenomenon is reported in another trigeminal-autonomic cephalgia, paroxysmal hemicrania (Bogucki *et al.*, 1984; Pareja, 1995).

Another vexed issue in primary headache is the site of action of anti-migraine compounds. This issue has exercised the headache community in the last decade (Humphrey and Goadsby, 1994) with the development of the triptans. Triptans are serotonin-5HT_{1B/1D} agonists (Goadsby, 2000), which are specific treatments of migraine (Ferrari *et al.*, 2001) and cluster headache (The Sumatriptan Cluster Headache Study Group, 1991) with no general anti-pain or even facial pain (Harrison *et al.*, 1997) properties. Sumatriptan was developed as a selective constrictor of large extracerebral vessels that was designed to have no significant CNS actions (Humphrey *et al.*, 1990). In experimental animals, it can be shown that blood-brain barrier disruption is required for the trigeminal inhibitory effect of sumatriptan (Kaube *et al.*, 1993; Shepherd *et al.*, 1995). Other more brain-penetrant triptans, such as naratriptan (Goadsby and Knight, 1997; Cumberbatch *et al.*, 1998), rizatriptan (Cumberbatch *et al.*, 1997), eletriptan (Goadsby and Hoskin, 1999) or zolmitriptan (Goadsby and Hoskin, 1996), act to inhibit trigeminal neurones in experimental animals, and trigeminal nucleus neurones may be inhibited by local microiontophoresis of triptans (Storer and Goadsby, 1997) or ergots (Lambert *et al.*, 1992). Taken together, these data suggest that one mechanism of action of triptans might be direct inhibition of the trigeminal second order synapse (Goadsby, 2000).

The patient described has an excellent clinical response to sumatriptan in the absence of either cranial vessels or the peripheral nerve as a target for the intervention. This patient demonstrates, given that the clinical picture is as it seems, that triptans, certainly sumatriptan, can act solely through central inhibition of trigeminal neurones. This does not suggest that the peripheral actions are not adjunctive, but does suggest a possible pre-eminence for the brain site of action. The patient's results predict that an appropriate neurally active compound will be efficacious in cluster headache. Whether

such a compound would also have acute anti-migraine actions is a further crucial question.

In summary, we present a patient with typical chronic cluster headache who had an ipsilateral trigeminal nerve sensory root section. This procedure denervates the ipsilateral cranial vessels and dura mater but neither stopped his attacks, nor affected their treatment. In the absence of a post-mortem, one cannot be completely sure of the root section; however, after two operations, and with a dense trigeminal sensory loss, this patient presents a profound clinical and therapeutic conundrum. His picture challenges conventional wisdom and demands consideration of the brain mechanisms in primary headache as, perhaps, pre-eminent. Primary headache probably requires the head, peripheral structures but at least due consideration to central processing and mechanisms is likely to be fundamental to understanding primary neurovascular headaches.

Acknowledgements

The authors wish to thank Drs Holger Kaube and Nicola Giffin for carrying out the blink reflex study, and Dr Catriona Good for reviewing the MRI. The work reported has been supported by the Migraine Trust and the Wellcome Trust. M.S.M is a Migraine Trust Research Fellow. P.J.G. is a Wellcome Trust Senior Research Fellow.

References

- Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study in 230 patients with diagnostic implications. *Neurology*. 2002; 58: 346–61.
- Bogucki A, Szymanska R, Braciak W. Chronic paroxysmal hemicrania: lack of a pre-chronic stage. *Cephalalgia* 1984; 4: 187–9.
- Boudreau JC, Oravec J, White TD, Madigan C, Chu S-P. Geniculate neuralgia and facial nerve sensory systems. *Arch Otolaryngol* 1977; 103: 473–81.
- Cumberbatch MJ, Hill RG, Hargreaves RJ. Rizatriptan has central antinociceptive effects against durally evoked responses. *Eur J Pharmacol* 1997; 328: 37–40.
- Cumberbatch MJ, Hill RG, Hargreaves RJ. Differential effects of the 5HT_{1B/1D} receptor agonist naratriptan on trigeminal versus spinal nociceptive responses. *Cephalalgia* 1998; 18: 659–63.
- Cushing H. The sensory distribution of the fifth cranial nerve. *Johns Hopkins Hosp Bull* 1904; 15: 213–32.
- Denny-Brown D, Yanagisawa N. The function of the descending root of the fifth nerve. *Brain* 1973; 96: 783–814.
- Edvinsson L, MacKenzie ET, McCulloch J. Cerebral blood flow and metabolism. New York: Raven Press; 1993.
- Ekbom K, Greitz T. Carotid angiography in cluster headache. *Acta Radiol Diagn (Stockh)* 1970; 10: 177–86.
- Ferrari MD. Migraine. [Review]. *Lancet* 1998; 351: 1043–51.

- Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT_{1B/1D} agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; 358: 1668–75.
- Goadsby PJ. The pharmacology of headache. [Review]. *Prog Neurobiol* 2000; 62: 509–25.
- Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. *Cephalalgia*. In press 2002.
- Goadsby PJ, Hoskin KL. Inhibition of trigeminal neurons by intravenous administration of the serotonin (5HT)_{1B/D} receptor agonist zolmitriptan (311C90): are brain stem sites a therapeutic target in migraine? *Pain* 1996; 67: 355–9.
- Goadsby PJ, Hoskin KL. Differential effects of low dose CP122,288 and eletriptan on fos expression due to stimulation of the superior sagittal sinus in the cat. *Pain* 1999; 82: 15–22.
- Goadsby PJ, Knight Y. Inhibition of trigeminal neurons after intravenous administration of naratriptan through an action at the 5-hydroxytryptamine (5HT_{1B/D}) receptors. *Br J Pharmacol* 1997; 122: 918–22.
- Goadsby PJ, Lipton RB, Ferrari MD. Migraine: current understanding and management. *N Engl J Med* 2002; 346: 257–70.
- Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. *Headache* 1993; 33: 452–55.
- Hardebo JE. How cluster headache is explained as an intracavernous inflammatory process lesioning sympathetic fibers. *Headache* 1994; 34: 125–31.
- Harrison SD, Balawi SA, Feinmann C, Harris M. Atypical facial pain: a double-blind placebo-controlled crossover pilot study of subcutaneous sumatriptan. *Eur Neuropsychopharmacol* 1997; 7: 83–8.
- Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988; 8 Suppl 7: 1–96.
- Hoskin KL, Zagami A, Goadsby PJ. Stimulation of the middle meningeal artery leads to Fos expression in the trigeminocervical nucleus: a comparative study of monkey and cat. *J Anat* 1999; 194: 579–88.
- Humphrey PP, Goadsby PJ. Controversies in headache. The mode of action of sumatriptan is vascular? A debate. [Review]. *Cephalalgia* 1994; 14: 401–10.
- Humphrey PP, Feniuk W, Perren MJ, Beresford IJ, Skingle M, Whalley ET. Serotonin and migraine. [Review]. *Ann NY Acad Sci* 1990; 600: 587–98.
- Kaube H, Hoskin KL, Goadsby PJ. Inhibition by sumatriptan of central trigeminal neurones only after blood–brain barrier disruption. *Br J Pharmacol* 1993; 109: 788–92.
- Kirkpatrick PJ, O'Brien MD, MacCabe JJ. Trigeminal nerve section for chronic migrainous neuralgia. *Br J Neurosurg* 1993; 7: 483–90.
- Lambert GA, Lowy AJ, Boers P, Angus-Leppan H, Zagami AS. The spinal cord processing of input from the superior sagittal sinus: pathway and modulation by ergot alkaloids. *Brain Res* 1992; 597: 321–30.
- Maxwell RE. Surgical control of chronic migrainous neuralgia by trigeminal gangliorhizolysis. *J Neurosurg* 1982; 57: 459–66.
- May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. [Review]. *J Cereb Blood Flow Metab* 1999; 19: 115–27.
- May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. *Lancet* 1998a; 352: 275–8.
- May A, Kaube H, Buchel C, Eichten C, Rijntjes M, Juptner M, et al. Experimental cranial pain elicited by capsaicin: a PET study. *Pain* 1998b; 74: 61–6.
- May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med* 1999a; 5: 836–38.
- May A, Buchel C, Bahra A, Goadsby PJ, Frackowiak RS. Intracranial vessels in trigeminal transmitted pain: a PET study. *Neuroimage* 1999b; 9: 453–60.
- May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. *Neurology* 2000; 55: 1328–35.
- Mokri B, Piepgras DG, Miller GM. Syndrome of orthostatic headaches and diffuse pachymeningeal gadolinium enhancement. *Mayo Clin Proc* 1997; 72: 400–13.
- Moskowitz MA. Cluster headache: evidence for a pathophysiologic focus in the superior pericarotid cavernous sinus plexus. [Review]. *Headache* 1988; 28: 584–6.
- Moskowitz MA, Cutrer FM. Sumatriptan: a receptor-targeted treatment for migraine. *Annu Rev Med* 1993; 44: 145–54.
- O'Brien MD, Kirkpatrick PJ, McCabe JJ. Trigeminal nerve section for chronic migrainous neuralgia. In: Olesen J, Goadsby PJ, editors. Cluster headache and related conditions. *Frontiers in headache research*, Vol. 9. Oxford: Oxford University Press, 1999. p. 291–5.
- Olesen J, Goadsby PJ. Cluster headache and related conditions. *Frontiers in headache research*, Vol. 9. Oxford: Oxford University Press; 1999.
- Olesen J, Tfelt-Hansen P, Welch KMA. The headaches. 2nd edn. Philadelphia: Lippincott Williams & Wilkins; 2000.
- Pareja JA. Chronic paroxysmal hemicrania: dissociation of the pain and autonomic features. *Headache* 1995; 35: 111–13.
- Raskin NH, Hosobuchi Y, Lamb S. Headache may arise from perturbation of brain. *Headache* 1987; 27: 416–20.
- Shepherd SL, Williamson DJ, Williams J, Hill RG, Hargreaves RJ. Comparison of the effects of sumatriptan and the NK1 antagonist CP-99,994 on plasma extravasation in dura mater and c-fos mRNA expression in trigeminal nucleus caudalis of rats. *Neuropharmacology* 1995; 34: 255–61.

Siegel AM, Williamson PD, Roberts DW, Thadani VM, Darcey TM. Localized pain associated with seizures originating in the parietal lobe. *Epilepsia* 1999; 40: 845–55.

Spencer SE, Sawyer WB, Wada H, Platt KB, Loewy AD. CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. *Brain Res* 1990; 534: 149–69.

Storer RJ, Goadsby PJ. Microiontophoretic application of serotonin (5HT)_{1B/1D} agonists inhibits trigeminal cell firing in the cat. *Brain* 1997; 120: 2171–7.

Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med* 1991; 325: 322–6.

Veloso F, Kumar K, Toth C. Headache secondary to deep brain implantation. *Headache* 1998; 38: 507–15.

Waldenlind E, Ekbom K, Torhall J. MR-angiography during spontaneous attacks of cluster headache: a case report. *Headache* 1993; 33: 291–5.

White JC, Sweet WH. Pain: its mechanisms and neurosurgical control. Springfield (IL): Charles C. Thomas; 1955.

Young GB, Blume WT. Painful epileptic seizures. *Brain* 1983; 106: 537–54.

Received November 14, 2001. Revised January 5, 2002.

Accepted January 5, 2002