

REVIEW ARTICLE

Trigeminal neuralgia Pathology and pathogenesis

Seth Love¹ and Hugh B. Coakham²

Departments of ¹Neuropathology and ²Neurosurgery,
Institute of Clinical Neurosciences, Frenchay Hospital,
Bristol BS16 1LE, UK

Correspondence to: Professor S. Love, Department of
Neuropathology, Institute of Clinical Neurosciences,
Frenchay Hospital, Bristol BS16 1LE, UK
E-mail: seth.love@bris.ac.uk

Summary

There is now persuasive evidence that trigeminal neuralgia is usually caused by demyelination of trigeminal sensory fibres within either the nerve root or, less commonly, the brainstem. In most cases, the trigeminal nerve root demyelination involves the proximal, CNS part of the root and results from compression by an overlying artery or vein. Other causes of trigeminal neuralgia in which demyelination is involved or implicated include multiple sclerosis and, probably, compressive space-occupying masses in the posterior fossa. Examination of trigeminal nerve roots from patients with compression of the nerve root by an overlying blood vessel has revealed focal demyelination in the region of compression, with close apposition of demyelinated axons and an absence of intervening glial processes. Similar foci of nerve root demyelination and juxtaposition of axons have been demonstrated in multiple sclerosis patients with trigeminal neuralgia. Experimental studies indicate that this anatomical arrangement favours the ectopic generation of spontaneous nerve impulses and their ephaptic conduction to adjacent fibres, and that spontaneous nerve activity is likely to be increased by the deformity associated with pulsatile vascular indentation.

Decompression of the nerve root produces rapid relief of symptoms in most patients with vessel-associated trigeminal neuralgia, probably because the resulting separation of demyelinated axons and their release from focal distortion reduce the spontaneous generation of impulses and prevent their ephaptic spread. The role of remyelination in initial symptomatic recovery after decompression is unclear. However, remyelination may help to ensure that relief of symptoms is sustained after decompression of the nerve root and may also be responsible for the spontaneous remission of the neuralgia in some patients. In addition to causing symptomatic relief, vascular decompression leads to rapid recovery of nerve conduction across the indented root, a phenomenon that, we suggest, is likely to reflect the reversal of compression-induced conduction block in larger myelinated fibres outside the region of demyelination. Trigeminal neuralgia can occur in association with a range of other syndromes involving vascular compression and hyperactivity of cranial nerves. Clinical observations and electrophysiological studies support the concept that demyelination and ephaptic spread of excitation underlie most, if not all, of these conditions.

Keywords: trigeminal neuralgia; neurovascular compression; demyelination; multiple sclerosis; ephaptic conduction; conduction block; cranial nerve hyperactivity syndromes

Introduction

Classical trigeminal neuralgia (*tic douloureux*) has an annual incidence of ~4.5 per 100 000 (Yoshimasu *et al.*, 1972; Katusic *et al.*, 1991). It is characterized by recurrent episodes of intense, lancinating pain localized to small areas of the face. The onset is usually in middle or old age, but young adults and children can also be affected (Mason *et al.*, 1991; Resnick *et al.*, 1998; Childs *et al.*, 2000). Attacks usually

last only seconds but may recur repeatedly within a short period of time. The attacks are often, but not always, precipitated by mild sensory stimulation of so-called trigger zones, which may be located anywhere within the territory of the affected trigeminal nerve. Typical antecedent stimuli include light touching, draughts of wind, eating, drinking, washing, shaving and applying make-up. The neuralgia tends

to occur in bouts over a period of weeks or months, with subsequent spontaneous remission that may last months or years. In time, however, attacks usually become more frequent and the pain more sustained (Fromm, 1989). Although not usually significant clinically, the cutaneous perception of temperature and light touch is slightly impaired within the affected trigeminal divisions (Bowsher, 1997; Bowsher *et al.*, 1997).

Aetiology

Most cases are caused by compression of the trigeminal nerve root, usually within a few millimetres of entry into the pons, i.e. the root entry zone. In a few cases, trigeminal neuralgia is due to a primary demyelinating disorder. Other, rare causes include infiltration of the nerve root, gasserian ganglion or nerve by a tumour or amyloid, and small infarcts or angiomas in the pons or medulla. Once all of these possibilities have been excluded, there remains a small proportion of patients in whom the aetiology is undetermined.

Compression of the trigeminal nerve root

Much the commonest cause of trigeminal neuralgia is focal compression of the trigeminal nerve root, close to its point of entry into the pons, by an aberrant loop of artery or vein. This was first recognized as a cause of trigeminal neuralgia by Jannetta (Jannetta, 1967) and is now thought to account for 80–90% of cases (Haines *et al.*, 1980; Jannetta, 1980; Richards *et al.*, 1983; Fukushima, 1990; Meaney *et al.*, 1995a; Bowsher, 1997; Hamlyn, 1997; McLaughlin *et al.*, 1999). The part of the nerve root that is usually compressed (the root entry zone) is actually within CNS tissue, which extends several millimetres along the root, so that the junction between CNS and PNS is well away from the surface of the pons. Rarely, trigeminal neuralgia results from vascular compression of the nerve root by a saccular aneurysm (Ildan *et al.*, 1996) or an arteriovenous malformation (Figueiredo *et al.*, 1989; Ito *et al.*, 1996).

A wide range of other compressive lesions can cause trigeminal neuralgia. These include vestibular schwannomas (Matthies and Samii, 1997), meningiomas (Haddad and Taha, 1990; Ogasawara *et al.*, 1995), epidermoid cysts (Jamjoom *et al.*, 1996; Mohanty *et al.*, 1997) and various other cysts and tumours (Kato *et al.*, 1995; Revuelta *et al.*, 1995; Jamjoom *et al.*, 1996; Matsuura and Kondo, 1996). In several reported cases, the neuralgia was contralateral to the side of the mass lesion (Haddad and Taha, 1990; Revuelta *et al.*, 1995; Matsuura and Kondo, 1996). Compression of the trigeminal nerve root may be mediated by the tumour itself, by an interposed blood vessel or by distortion of the contents of the posterior fossa with displacement of the nerve root against a blood vessel or the skull base. In a series of 26 patients whose trigeminal neuralgia was associated with an extra-axial tumour in the posterior fossa, vascular compression of the trigeminal nerve root entry zone was

found in all cases (Barker *et al.*, 1996). Fujimaki and colleagues described recurrent trigeminal neuralgia in two patients in whom prosthetic material (in one case Teflon, in another polyurethane sponge) used in the course of microvascular decompression of the trigeminal nerve root gradually hardened, eventually compressing the root and causing recurrence of the neuralgia (Fujimaki *et al.*, 1996). Rarely, trigeminal neuralgia results from bony compression of the nerve, e.g. due to an osteoma (Ruelle *et al.*, 1994) or deformity resulting from osteogenesis imperfecta (Reilly *et al.*, 1995). Schwannomas arising from the trigeminal nerve root may present with typical trigeminal neuralgia (McCormick *et al.*, 1988).

Primary demyelinating disorders

Trigeminal neuralgia is a well-recognized complication of multiple sclerosis (Jensen *et al.*, 1982; Moulin *et al.*, 1988; Soustiel *et al.*, 1996; Moulin, 1998). Typically, a plaque of demyelination encompasses the root entry zone of the trigeminal nerve in the pons (Lazar and Kirkpatrick, 1979; Hilton *et al.*, 1994; Meaney *et al.*, 1995b; Crooks and Miles, 1996; Gass *et al.*, 1997). Rarely, patients with peripheral nerve demyelination due to Charcot–Marie–Tooth disease develop trigeminal neuralgia (Coffey and Fromm, 1991). Vascular compression of the trigeminal nerve root may contribute to trigeminal neuralgia even in patients with demyelinating disorders; compression of the root entry zone by a blood vessel has been demonstrated in a sizeable minority of patients with multiple sclerosis and trigeminal neuralgia (Meaney *et al.*, 1995a, b; Crooks and Miles, 1996; Broggi *et al.*, 1999, 2000) and in an occasional patient with Charcot–Marie–Tooth disease (Meaney *et al.*, 1995a). In many such cases, decompression of the nerve root leads to relief of symptoms.

Infiltrative disorders of the trigeminal nerve root, gasserian ganglion and nerve

The principal infiltrative causes of trigeminal neuralgia are carcinomatous deposits within the nerve root, gasserian ganglion and nerve (Chong, 1996) and trigeminal amyloidomas (Bornemann *et al.*, 1993; Love *et al.*, 1997).

Non-demyelinating lesions of the pons or medulla

Small numbers of patients have been reported in whom trigeminal neuralgia was associated with a small infarct (Nakamura *et al.*, 1996; Golby *et al.*, 1998) or angioma (Saito *et al.*, 1989) in the brainstem.

Familial trigeminal neuralgia

In the vast majority of cases, trigeminal neuralgia is a sporadic disorder. Familial occurrence has been reported in

Charcot-Marie-Tooth disease (Coffey and Fromm, 1991). A family with trigeminal and/or glossopharyngeal neuralgia affecting several individuals in three generations was described by Knuckey and Gubbay (Knuckey and Gubbay, 1979), and Duff and colleagues described a family with seven affected family members in two successive generations (Duff *et al.*, 1999). A further inherited disorder in which there is a theoretical risk of trigeminal neuralgia is autosomal dominant hypertension and brachydactyly. Naraghi and colleagues, who had previously mapped this disorder to chromosome 12p, reported that the hypertension was consistently associated with neurovascular anomalies, consisting of loops of posterior inferior cerebellar or vertebral artery that compressed the ventrolateral aspect of the medulla (Naraghi *et al.*, 1997) (see below, Relationship to other syndromes involving vascular compression and hyperactivity of cranial nerves); one might expect these patients also to be at increased risk of trigeminal neuralgia because of compression of the trigeminal nerve root by the abnormally tortuous blood vessels.

Pathology

Early ultrastructural studies (Kerr and Miller, 1966; Beaver, 1967) concentrated on the morphology of the trigeminal ganglion and nerve and described a range of abnormalities of myelin sheaths, including proliferative degenerative changes and myelin disintegration. However, most of these changes were probably artefactual and similar findings were present in some of the control cases. These studies antedated the observations of Jannetta and others on the association of trigeminal neuralgia with vascular compression of the nerve root.

Compression of the trigeminal nerve root

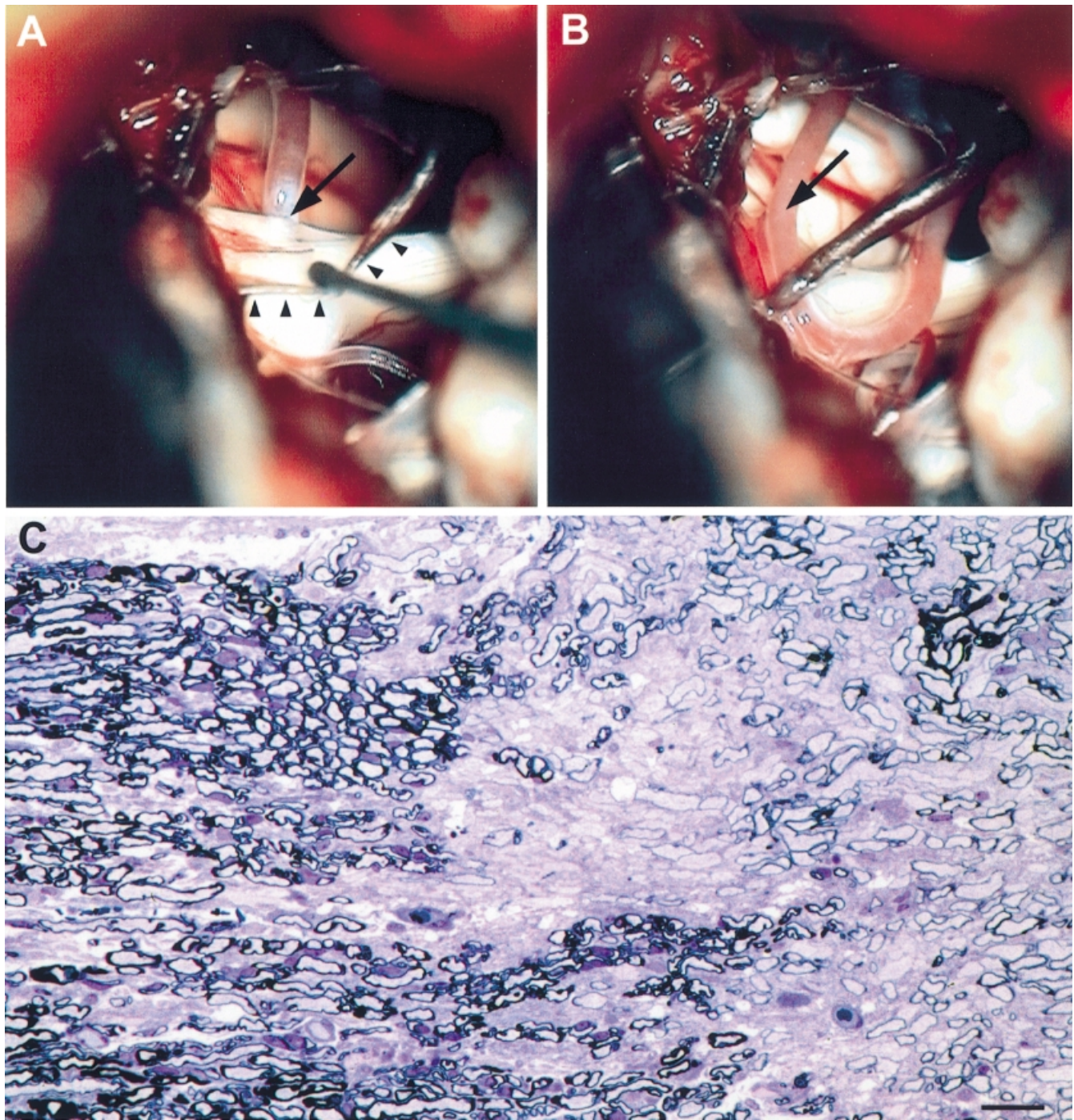
The first detailed description of ultrastructural abnormalities in the nerve root in the region of vascular compression was by Hilton and colleagues (Hilton *et al.*, 1994). The authors observed focal loss of myelin and close apposition of demyelinated axons. There were few residual oligodendrocytes and no inflammatory cells. Immunoelectron microscopy for glial fibrillary acid protein revealed that astrocyte processes were largely confined to the periphery of the lesion. Of a further six trigeminal rhizotomy specimens from patients with trigeminal neuralgia in the absence of detectable vascular compression of the nerve root, only one, from a patient with multiple sclerosis, showed demyelination, but in that case astrocyte processes separated many of the demyelinated axons and the lesion contained perivascular clusters of perivascular lymphocytes and scattered lipid-laden macrophages.

The findings in relation to vascular compression of the nerve root were confirmed in a subsequent electron microscope study of trigeminal rhizotomy specimens from two further patients with medically intractable trigeminal neuralgia, in whom, because of the local vascular anatomy,

the compressing artery or vein could not safely be repositioned (Love *et al.*, 1998). In both specimens, examination revealed a circumscribed zone of chronic demyelination immediately beneath the region of indentation. As in cases we have seen subsequently, the demyelination was restricted to proximal (CNS) tissue but occurred close to the junction of this part of the root with distal (PNS) tissue. Adjacent to the zone of demyelination were small numbers of thinly myelinated axons, reflecting either demyelination and remyelination, or partial demyelination of the affected fibres. In some cases a single thin myelin sheath encircled several adjacent axons that were still in close apposition, a finding that was interpreted as suggesting that aberrant remyelination had occurred. Similar findings were described by Rappaport and colleagues (Rappaport *et al.*, 1997). However, although Rappaport and colleagues illustrated disrupted myelin in the proximal, CNS part of the trigeminal root, they also described (but did not illustrate) the presence of large numbers of collagen fibrils in the extracellular matrix, suggesting that the abnormalities in their cases also involved the distal part of the nerve root.

Since our initial reports, we have demonstrated demyelination in several further trigeminal rhizotomy specimens from patients with vascular compression of the nerve root (Fig. 1). In rhizotomy specimens large enough to allow assessment of the size of the zone of demyelination, this zone has been limited to the immediate vicinity of the point of vascular indentation, extending no more than ~2 mm in any direction. Foci of apposition of demyelinated axons and a paucity of glial and inflammatory cells have been relatively consistent ultrastructural features in these biopsies, although in one specimen we did find a focal infiltrate of lipid-laden macrophages, suggesting that there had been recent demyelinating activity. It should also be noted that we have found the trigeminal rhizotomy specimen from a small number of patients with visible vascular compression of the nerve root on neuroimaging or at craniotomy to be ultrastructurally normal, without demyelination. However, as the region of demyelination has rarely been visible macroscopically in the cases of vascular compression and a typical rhizotomy specimen measures no more than a few millimetres in diameter, it seems likely that the lack of abnormality in a small proportion of specimens reflects sampling error rather than heterogeneity in the pathology and pathogenesis of the disorder.

In several of the reports of trigeminal neuralgia associated with tumours (see above), the nerve root was described as stretched or attenuated, but none of the resected specimens was subjected to detailed histological assessment with reference to the possibility of demyelination. However, it is of note that demyelination has been demonstrated in several experimental models of acute or chronic compression of central white matter (Gledhill *et al.*, 1973; McDonald, 1975; Harrison and McDonald, 1977; Fish and Blakemore, 1983; Clifford-Jones *et al.*, 1985). Both Fish and Blakemore (Fish and Blakemore, 1983) and Clifford-Jones and colleagues (Clifford-Jones *et al.*, 1985) commented on the occurrence



of partial demyelination after chronic compression of white matter. The most persuasive evidence of this was the finding of variations in the thickness of the myelin sheath along individual internodes. In trigeminal rhizotomy specimens from patients with trigeminal neuralgia, the distribution and extent of changes are more variable than in the experimental animals and the thinly myelinated fibres, in particular, tend to be distributed quite unpredictably. In consequence, we have had only limited opportunity for detailed assessment of

these fibres in longitudinal section. To date, we have not been able to demonstrate convincing variations in the thickness of myelin sheaths along individual internodes in our specimens, but this may simply reflect the limitations of our examinations. None of the reports on experimental compression of white matter refers to demyelinated axons in direct apposition or to the encirclement of occasional groups of apposed axons by a single, thin myelin sheath. This may reflect several differences between these experimental models and trigeminal

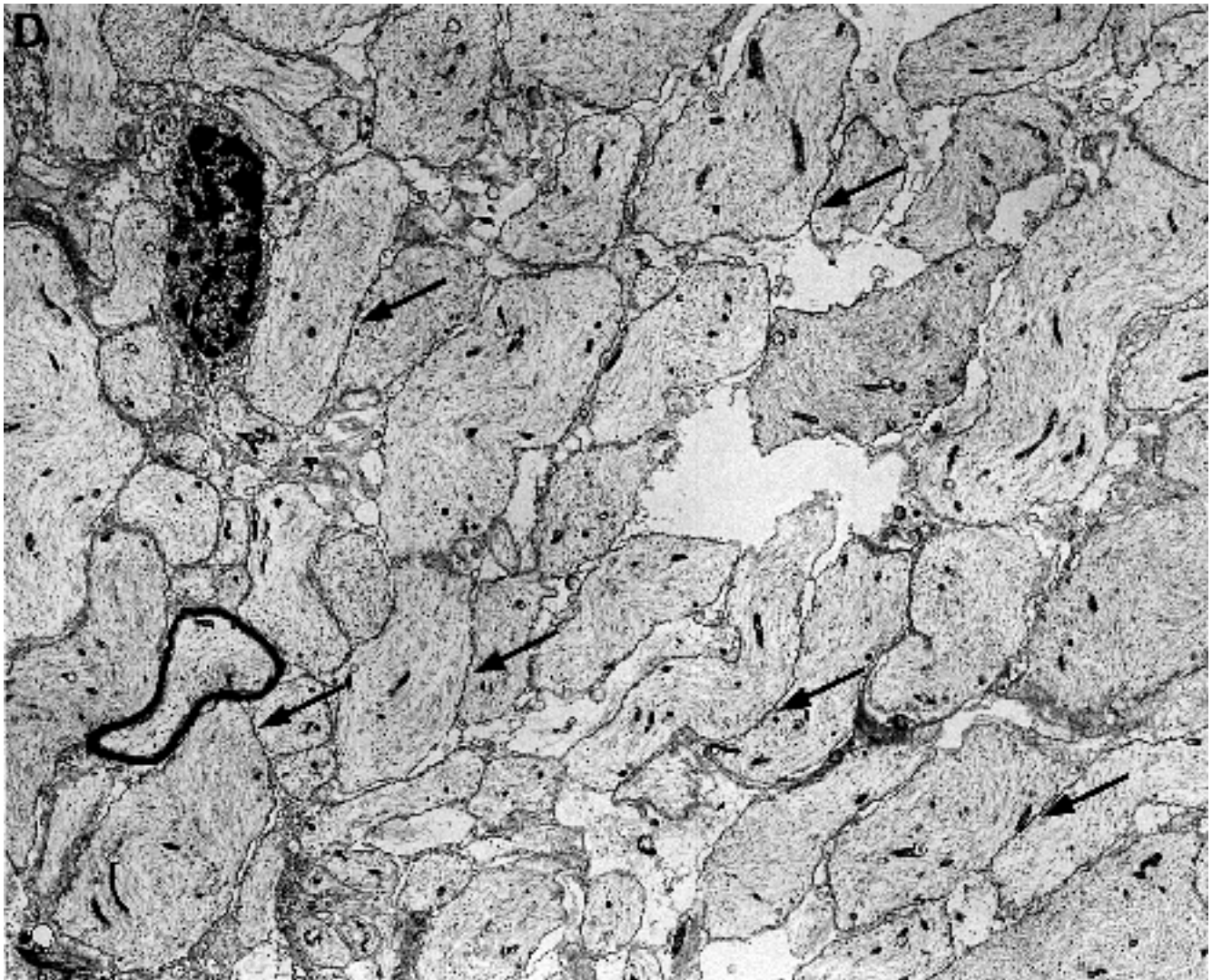


Fig. 1 Trigeminal neuralgia due to compression of the nerve root by an aberrant loop of artery. **(A)** The surgical approach to the trigeminal root is posterolateral. Retraction of a vein (arrowheads) discloses a region of indentation (arrow) by an anteriorly placed artery. **(B)** The offending loop of artery (arrow) has now been mobilized and repositioned behind the nerve root. **(C)** Examination of toluidine blue-stained semithin sections through a region of trigeminal nerve root compression reveals a zone of demyelination within the proximal, CNS part of the nerve root, close to the junction with the PNS. Several thinly myelinated fibres are present within the zone of demyelination. Scale bar = 25 μm . **(D)** Electron microscopy shows large numbers of demyelinated nerve fibres in the region of compression, many of the fibres being in direct apposition; some of them are indicated by arrows. Scale bar in **C** = 4 μm .

neuralgia, including the greater chronicity of the compression in the human disorder and the fact that the compression is likely to be pulsatile in nature, particularly if an artery is involved rather than a vein.

Primary demyelinating disorders

We have been able to examine trigeminal rhizotomy specimens from several patients with multiple sclerosis and intractable trigeminal neuralgia in the absence of a compressive lesion (Love *et al.*, 2001). As noted in two other case reports (Lazar and Kirkpatrick, 1979; Hilton *et al.*, 1994), demyelination has been found to extend along the proximal part of the trigeminal nerve root, in some cases

right up to the junction with the PNS. The appearances have tended to differ slightly from those in vascular compression in that astrocyte processes have usually been more numerous and widely distributed within the regions of demyelination in the multiple sclerosis patients. Furthermore, the rhizotomy specimens from these patients have more often shown disease activity, as evidenced by the presence of lipid-laden macrophages. However, as in the compressed nerve roots, groups of juxtaposed axons have been a consistent finding in all of the specimens from multiple sclerosis patients (Fig. 2) (Love *et al.*, 2001). The specimens have also all contained variable numbers of thinly myelinated fibres, both within and immediately adjacent to the regions of demyelination.

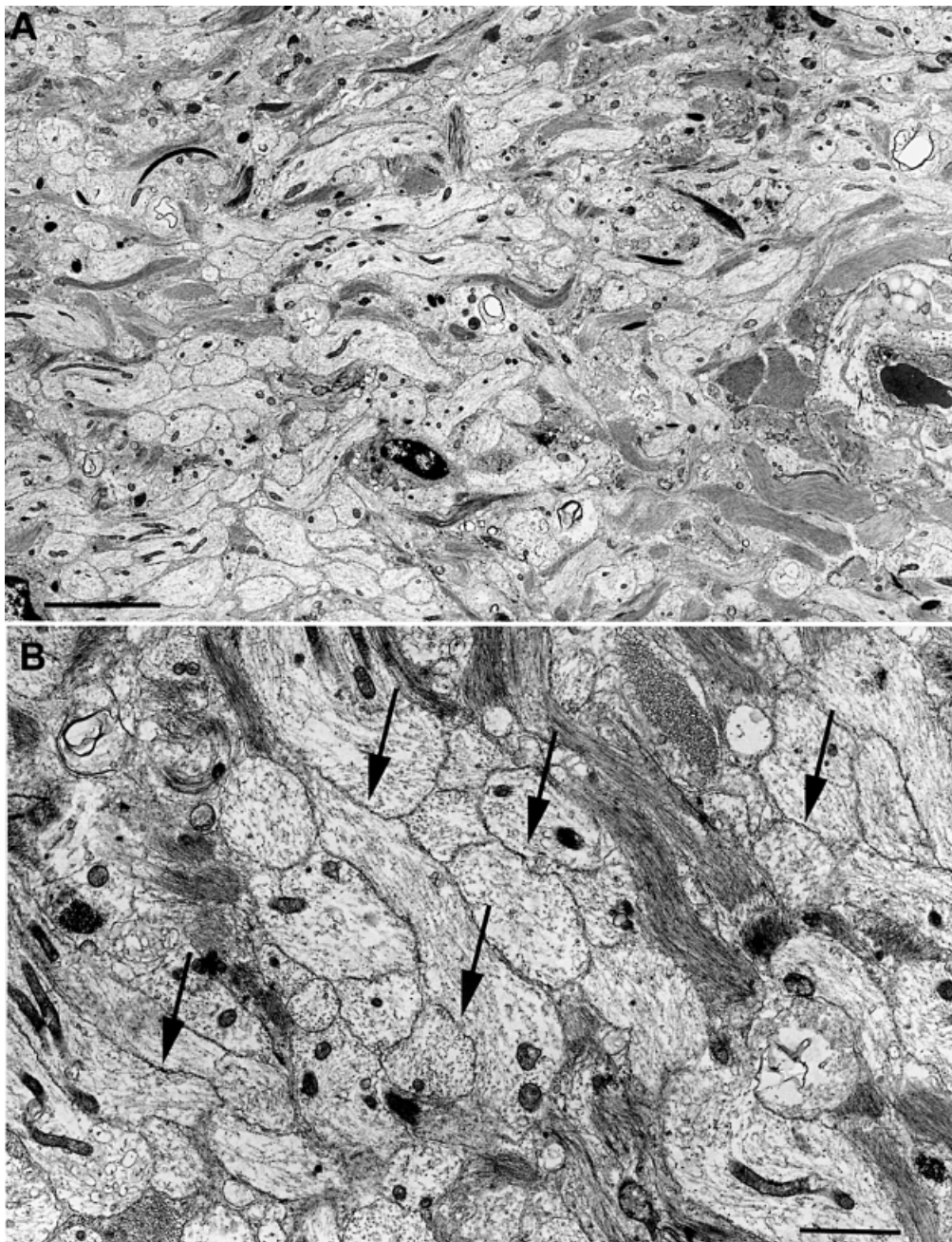


Fig. 2 Trigeminal neuralgia due to multiple sclerosis. (A) Electron micrograph illustrating a focus of chronic nerve root demyelination in a patient with multiple sclerosis. Scale bar = 10 μ m. (B) Higher magnification shows areas of apposition (arrows indicate some of them) between several of the axons. Scale bar = 2 μ m. Reproduced with permission from Love *et al.*, 2001.

Infiltrative disorders

The pathological findings in these conditions depend on the nature of the infiltrative process, which is usually carcinoma. Like infiltration by carcinoma, infiltration by amyloid may be very extensive, involving the trigeminal nerve, gasserian ganglion and both the distal and proximal parts of the nerve root (Love *et al.*, 1997).

Changes secondary to lesioning of the nerve root or gasserian ganglion

Although microvascular decompression is now widely regarded as the treatment of choice in medically intractable trigeminal neuralgia, ablative procedures are still used to treat patients in whom (i) no compressing blood vessel is demonstrable; (ii) symptoms persist despite adequate

microvascular decompression; (iii) a compressing blood vessel is present but not technically amenable to safe repositioning; (iv) there are medical contraindications to surgery under general anaesthesia; and (v) appropriate surgical expertise is not available. Numerous types of ablative procedure have been used in the past (Sweet, 1985, 1986; Rosenkopf, 1989; Tekkök and Brown, 1996). The ablative techniques most commonly used nowadays are partial rhizotomy, and lesioning at the level of the gasserian ganglion by percutaneous radio-frequency thermocoagulation, injection of glycerol or balloon compression (Sweet, 1986, 1988; Rosenkopf, 1989; Fujimaki *et al.*, 1990; Moraci *et al.*, 1992; Walchenbach *et al.*, 1994; Tekkök and Brown, 1996). The precise pathological findings in such cases depend on the site of lesioning but include Wallerian-type degeneration in the part of the nerve root that is proximal to the lesion and in the affected intrapontine trigeminal fibres. If the nerve root is examined soon after the ablative lesion has been made, fibres will show acute degenerative changes associated with accumulation of myelin debris and infiltration by macrophages. Older lesions result in patchy depletion of nerve fibres, astrocytic gliosis and, if the lesion is sufficiently distal (e.g. after radio-frequency lesioning), fibrosis of affected fascicles in the distal, PNS part of the nerve root. If the ganglion itself is damaged, there is also degeneration of peripheral trigeminal nerve fibres.

Pathogenesis of trigeminal neuralgia

The pathophysiology of trigeminal neuralgia has been much debated, the pain being ascribed variously to hyperactivity or abnormal discharges arising from the gasserian ganglion, the 'injured' nerve root and the trigeminal nucleus within the brainstem (Møller, 1991; Burchiel, 1993; Pagni, 1993; Rappaport and Devor, 1994; Moulin, 1998). Any credible explanation of the pathophysiology has to account for both the abnormal generation of sensory impulses and their spread from fibres subserving light touch to pathways involved in the perception of pain in non-congruous regions of the face. The explanation has also to be reconciled with the observation that the pathological substrate of this condition in the great majority of cases appears to be demyelination, especially in the trigeminal root entry zone.

We suggest that both the abnormal generation of sensory impulses and their subsequent spread to pathways subserving the perception of pain can be accounted for by the pathological findings. There is good experimental evidence that ectopic impulses can arise from demyelinated axons (Rasminsky, 1978; Smith and McDonald, 1980, 1982). Smith and McDonald demonstrated that many experimentally demyelinated nerve fibres in the dorsal spinal white matter of the cat were spontaneously active, discharging either in small bursts or steadily at 15–45 impulses per second for many hours (Smith and McDonald, 1980, 1982). Small deformations of the spinal cord in the region of demyelination not only increased the level of activity in fibres already discharging, but also

transiently induced activity in fibres that had previously been electrically silent. In the context of vascular compression of the trigeminal nerve root, these observations raise the possibility that pulsatile compression of demyelinated axons by an overlying blood vessel may be responsible for initiating the aberrant impulses in some patients.

Insofar as the subsequent spread of impulses is concerned, we have previously argued (Hilton *et al.*, 1994; Love *et al.*, 1998, 2001) that the close apposition of demyelinated axons in regions of vascular compression should facilitate the ephaptic transmission of nerve impulses, as has been demonstrated between immediately adjacent non-myelinated axons in experimental studies (Ramon and Moore, 1978; Rasminsky, 1978). Ephaptic cross-talk between fibres mediating light touch and those involved in the generation of pain may account for the precipitation of attacks of neuralgia by light tactile stimulation of facial trigger zones. The frequency of involvement of the trigeminal nerve root entry zone in multiple sclerosis patients with trigeminal neuralgia as well as in patients with vascular compression probably reflects the fact that fibres subserving light touch and those involved in the generation of pain are in closest proximity in this region, so that ephaptic cross-talk between the two pathways is most likely to occur when the demyelination is in this region (Love *et al.*, 2001).

Other evidence for the roles of focal demyelination and ephaptic transmission in the production of trigeminal neuralgia come from observations in patients with multiple sclerosis. Soustiel and colleagues documented a correlation between abnormal brainstem trigeminal evoked potentials and presentation with trigeminal neuralgia or dysaesthesiae in patients with multiple sclerosis (Soustiel *et al.*, 1996), and Hartmann and colleagues described a patient with a plaque involving the right lateral lemniscus and right trigeminal tract in whom right-sided trigeminal neuralgia was precipitated by auditory stimuli to the right ear, strongly suggesting ephaptic spread of impulse activity within the pontine lesion (Hartmann *et al.*, 1999).

An objection that has been raised to a central role for demyelination in the development of trigeminal neuralgia relates to the rapid clinical and electrophysiological recovery that usually occurs after surgical decompression of the affected nerve root. Many patients experience complete relief of symptoms immediately after operation, and electrophysiological monitoring of conduction through the compressed nerve root has shown very substantial recovery of conduction almost immediately after microvascular decompression in many patients (Leandri *et al.*, 1998). The explanation, we suggest, is that the clinical improvement and recovery of conduction reflect two distinct processes.

(i) The rapid relief of clinical symptoms probably reflects the cessation of the ectopic generation of impulses and of their ephaptic spread to adjacent fibres. Experimental studies indicate that reversal of the focal indentation and distortion of demyelinated axons is likely to reduce spontaneous impulse activity within the region of demyelination (Smith and

McDonald, 1980, 1982). Release from compression should also lead to the separation of demyelinated axons that were previously compacted together, and this would be expected to prevent ephaptic cross-talk. Reperfusion through previously compressed endoneurial capillaries and venules and endoneurial oedema resulting from the trauma of surgical manipulation may further contribute to separation of the demyelinated fibres.

(ii) The recovery of conduction probably reflects rapid reversal of conduction block in relatively large-calibre, fast-conducting fibres that are not demyelinated. Reversible conduction block is a well-documented manifestation of nerve fibre compression. Although most extensively investigated in the PNS, several studies have demonstrated compression-induced conduction block within the CNS (Bennett, 1983; Sakatani *et al.*, 1989; Shi and Blight, 1996). This is most likely to occur during the conduction of high-frequency trains of impulses (Sakatani *et al.*, 1989). In compression of low-to-moderate severity, large-calibre myelinated fibres seem to be more susceptible than smaller fibres to conduction block (Battista and Alban, 1983; Fern and Harrison, 1991). Reversal of conduction block in these larger fibres would account for the rapid fall in conduction latencies across the trigeminal nerve root as soon as it is decompressed. Compression-induced conduction block in a proportion of the larger myelinated fibres may also explain the mild reduction in the perception of light touch over a more extensive area of trigeminal innervation than could be attributed to the impairment of conduction across the relatively small zone of nerve root demyelination.

The fact that clinical improvement appears to be dissociated from recovery of conduction in some patients after microvascular decompression supports the concept that these are two distinct processes that are simply related by their common aetiology: nerve root compression.

The pathogenesis of some phenomena related to trigeminal neuralgia remains unclear. These include the very occasional triggering of attacks by stimuli outside of the field of innervation of the trigeminal nerve, and even by bright lights or loud noises (Bowsher, 1997), which must involve central pathways. Another well-documented finding in some patients is the occurrence of a refractory period of seconds to minutes after an attack of trigeminal neuralgia, during which further attacks cannot be provoked (Kugelberg and Lindblom, 1959). Experimental studies have shown the length of time for which nerve fibres are refractory to further excitation to be increased after demyelination in both the PNS (Smith and Hall, 1980) and the CNS (Smith *et al.*, 1981), but the duration of the refractory period in these experimental studies is much shorter than that in patients with trigeminal neuralgia. However, factors other than the demyelination *per se* could conceivably delay the restoration of membrane potentials and excitability after an episode of trigeminal neuralgia. These include impaired mitochondrial generation of ATP in an environment of focal endoneurial ischaemia due to the nerve root compression, with resulting delay in the restoration of

ionic gradients after a burst of discharges, and the paucity of extracellular fluid and increased longitudinal resistance to ionic current between closely juxtaposed demyelinated axons.

The role, if any, of remyelination in initial symptomatic recovery after microvascular decompression is unclear. Clearly, remyelination cannot account for the immediate relief from neuralgia. In the longer term, however, it is possible that remyelination helps to ensure that relief of symptoms is sustained. Remyelination may also be responsible for spontaneous remission of trigeminal neuralgia in some patients. Failure of microvascular decompression to relieve symptoms is most common in patients with very long-standing disease, in whom severe local depletion of oligodendrocytes and astrocytes may prevent effective remyelination after decompressive surgery. A further possibility is that the aberrant remyelination that is occasionally seen in the compressed nerve root (Love *et al.*, 1998) may, by preventing the separation of groups of apposed axons after decompression, contribute to the failure of this procedure in a few patients.

Relationship to other syndromes involving vascular compression and hyperactivity of cranial nerves

Several syndromes involving hyperactivity and the abnormal spread of activity within the distribution of innervation of cranial nerves VII–XII are now known to be associated with vascular compression of the relevant cranial nerve roots in most patients. The credit for recognizing this goes to Jannetta, whose description of the common basis of these disorders is difficult to better (Jannetta, 1980):

‘As we age, our arteries elongate and our brains “sag”. As a consequence of these processes, redundant arterial loops and bridging or intrinsic hindbrain veins may cause cross-compression of cranial nerve root entry zones in the cerebellopontine angle. This pulsatile compression can be seen to produce hyperactive dysfunction of the cranial nerve. Symptoms of trigeminal or glossopharyngeal neuralgia (somatic sensory), hemifacial spasm (somatic motor), tinnitus and vertigo (special sensory) and some cases of ‘essential’ hypertension are caused by these vessels compressing cranial nerves V, IX–X, VII, VIII, left X and the medulla oblongata. Using microsurgical techniques, the symptoms may be relieved by vascular decompression.’

As indicated by Jannetta, these syndromes share many pathogenetic features. Some of the information that has been acquired in the study of these disorders provides further insight into the pathophysiology of trigeminal neuralgia. There is now overwhelming evidence that vascular compression of the facial and glossopharyngeal nerves is responsible for most cases of hemifacial spasm and glossopharyngeal neuralgia, respectively (Jannetta, 1977; Laha and Jannetta, 1977; Bruyn, 1983; Calbucci *et al.*, 1986; Michelucci *et al.*, 1986; Wakiya *et al.*, 1989; Fukushima,

1990; Sindou *et al.*, 1991; Tash *et al.*, 1991; Barker *et al.*, 1995; Du *et al.*, 1995; Hosoya *et al.*, 1995; Resnick *et al.*, 1995; Kondo, 1998; McLaughlin *et al.*, 1999). As is the case for trigeminal neuralgia, these other syndromes of cranial nerve hyperactivity are occasionally induced by compression resulting from tumours or bony deformity of the posterior fossa (Occhiogrosso *et al.*, 1980; Greene *et al.*, 1995; Ogasawara *et al.*, 1995; Matsuura and Kondo, 1996; Occhiogrosso *et al.*, 1996; Kamiguchi *et al.*, 1997; Glocker *et al.*, 1998), by multiple sclerosis (Minagar and Sheremata, 2000) and other pontine lesions (McCarron and Bone, 1999). Of relevance to our consideration of the pathogenesis of trigeminal neuralgia are electrophysiological studies showing ephaptic spread of impulses between different branches of the facial nerve to be a consistent finding in patients with hemifacial spasm (Moller and Jannetta, 1984, 1986; Nielsen and Jannetta, 1984; Tankere *et al.*, 1998; Eekhof *et al.*, 2000). Moller and colleagues found the latency of the earliest ephaptically induced response from the orbicularis oculi muscle after stimulation of the marginal mandibular branch of the facial nerve to be longer than the sum of the latencies to and from the root entry zone and suggested that ephaptic spread of impulses at the level of the root entry zone was therefore unlikely (Moller and Jannetta, 1984). However, this interpretation takes no account of delays in conduction resulting from the presence of thinly myelinated and demyelinated fibres in the region of compression. It is also of note that, in most patients, both ephaptic excitation and spontaneous afterdischarges cease rapidly after decompression (Nielsen and Jannetta, 1984; Moller and Jannetta, 1985), strongly supporting the concept that these phenomena are directly related to abnormalities at the site of compression.

More recently recognized syndromes of compression-induced cranial nerve hyperactivity include superior oblique myokymia due to vascular compression of the root entry zone of the trochlear nerve (Samii *et al.*, 1998); 'vestibular paroxysmia' (Brandt and Dieterich, 1994), hyperacusis and tinnitus, due to vascular compression of the vestibulocochlear nerve in the cerebellopontine angle (Jannetta, 1977; Lesinski *et al.*, 1979; Jannetta *et al.*, 1986; Moller *et al.*, 1993; Brandt and Dieterich, 1994; Ryu *et al.*, 1998a; Okamura *et al.*, 2000); geniculate neuralgia, due to vascular compression of the nervus intermedius (Lovely and Jannetta, 1997); spontaneous gagging and dysphagia due to vascular compression of the vagus adjacent to the medulla (Resnick and Jannetta, 1999); and spasmodic torticollis associated with vascular compression of the cranial accessory nerve close to the medulla (Pagni *et al.*, 1985; Saito *et al.*, 1993; Jho and Jannetta, 1995). In a significant proportion of patients with vascular compression of cranial nerve roots, multiple syndromes of cranial nerve hyperactivity are present in combination (Morales *et al.*, 1977; Jamjoom *et al.*, 1990; Kobata *et al.*, 1998; Ryu *et al.*, 1998b; Van *et al.*, 1999).

A disorder that is aetiologically related to syndromes of cranial nerve compression and hyperactivity is essential hypertension associated with arterial compression of the

ventrolateral aspect of the rostral medulla in the region of entry of the left glossopharyngeal and vagus nerve roots, and it usually responds well to vascular decompression (Fein and Frishman, 1980; Jannetta *et al.*, 1985a). This association has been confirmed in several studies (Kleineberg *et al.*, 1991, 1992; Naraghi *et al.*, 1994; Akimura *et al.*, 1995; Morimoto *et al.*, 1997a; Saglitz *et al.*, 1997; Geiger *et al.*, 1998). Other syndromes of cranial nerve compression and hyperactivity may be present in these patients (Jannetta *et al.*, 1985a; Platania *et al.*, 1997; Kobata *et al.*, 1998; Defazio *et al.*, 2000). Hypertension has also been induced experimentally by pulsatile compression of the rostral ventrolateral medulla in primates (Jannetta *et al.*, 1985b) and rats (Morimoto *et al.*, 1997b).

The precise pathogenesis of hypertension associated with vascular compression of the medulla is still unclear but involves increases in sympathetic nerve activity and heart rate and elevated plasma levels of noradrenaline and possibly adrenaline, but not renin, aldosterone or vasopressin (Makino *et al.*, 1999; Morimoto *et al.*, 1997b, 1999). Naraghi and colleagues conducted an autopsy study of 24 patients with essential hypertension, 10 with renal hypertension and 21 normotensive controls, and examined the anatomical relationships of blood vessels on the surface of the medulla whilst they were perfused artificially (Naraghi *et al.*, 1992). Although the authors observed vascular compression of the ventrolateral medulla in all cases of essential hypertension and in none of the other autopsies, there was no histological evidence that the compression had produced any structural lesions in the underlying medulla. The pathological and electrophysiological substrates of this condition, involving compression of the brainstem itself, may therefore be different from those of the syndromes of cranial nerve compression and hyperactivity. However, it remains possible that the pulsatile indentation of the medulla causes demyelination, as very small foci of demyelination, such as those in compressed trigeminal nerve roots, would not have been discernible on paraffin histology.

References

- Akimura T, Furutani Y, Jimi Y, Saito K, Kashiwagi S, Kato S, et al. Essential hypertension and neurovascular compression at the ventrolateral medulla oblongata: MR evaluation. *Am J Neuroradiol* 1995; 16: 401–5.
- Barker FG 2nd, Jannetta PJ, Bissonette DJ, Shields PT, Larkins MV, Jho HD. Microvascular decompression for hemifacial spasm. *J Neurosurg* 1995; 82: 201–10.
- Barker FG 2nd, Jannetta PJ, Babu RP, Pomonis S, Bissonette DJ, Jho HD. Long-term outcome after operation for trigeminal neuralgia in patients with posterior fossa tumors. *J Neurosurg* 1996; 84: 818–25.
- Battista AF, Alban E. Effect of graded ligature compression on nerve conduction. *Exp Neurol* 1983; 80: 186–94.
- Beaver DL. Electron microscopy of the Gasserian ganglion in trigeminal neuralgia. *J Neurosurg* 1967; 26: 138–50.

- Bennett MH. Effects of compression and ischemia on spinal cord evoked potentials. *Exp Neurol* 1983; 80: 508–19.
- Bornemann A, Bohl J, Hey O, Storkel S, Gamm H, Muller-Forell W, et al. Amyloidoma of the gasserian ganglion as a cause of symptomatic neuralgia of the trigeminal nerve: report of three cases. [Review]. *J Neurol* 1993; 241: 10–14.
- Bowsher D. Trigeminal neuralgia: an anatomically oriented review. [Review]. *Clin Anat* 1997; 10: 409–15.
- Bowsher D, Miles J, Haggett C, Eldridge P. Trigeminal neuralgia: a quantitative sensory perception threshold study in patients who had not undergone invasive procedures. *J Neurosurg* 1997; 86: 190–2.
- Brandt T, Dieterich M. VIIIth nerve vascular compression syndrome: vestibular paroxysmia. *Baillieres Clin Neurol* 1994; 3: 565–75.
- Broggi G, Ferroli P, Franzini A, Pluderi M, La Mantia L, Milanese C. Role of microvascular decompression in trigeminal neuralgia and multiple sclerosis [letter]. *Lancet* 1999; 354: 1878–9.
- Broggi G, Ferroli P, Franzini A, Servello D, Dones I. Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; 68: 59–64.
- Bruyn GW. Glossopharyngeal neuralgia. [Review]. *Cephalalgia* 1983; 3: 143–57.
- Burchiel KJ. Trigeminal neuropathic pain. [Review]. *Acta Neurochir Suppl (Wien)* 1993; 58: 145–9.
- Calbucci F, Tognetti F, Bollini C, Cuscini A, Michelucci R, Tassinari CA. Intracranial microvascular decompression for 'cryptogenic' hemifacial spasm, trigeminal and glossopharyngeal neuralgia, paroxysmal vertigo and tinnitus: I. Surgical technique and results. *Ital J Neurol Sci* 1986; 7: 359–66.
- Childs AM, Meaney JF, Ferrie CD, Holland PC. Neurovascular compression of the trigeminal and glossopharyngeal nerve: three case reports. *Arch Dis Child* 2000; 82: 311–15.
- Chong VF. Trigeminal neuralgia in nasopharyngeal carcinoma. *J Laryngol Otol* 1996; 110: 394–6.
- Clifford-Jones RE, McDonald WI, Landon DN. Chronic optic nerve compression. An experimental study. *Brain* 1985; 108: 241–62.
- Coffey RJ, Fromm GH. Familial trigeminal neuralgia and Charcot-Marie-Tooth neuropathy. Report of two families and review. [Review]. *Surg Neurol* 1991; 35: 49–53.
- Crooks DA, Miles JB. Trigeminal neuralgia due to vascular compression in multiple sclerosis—post-mortem findings. *Br J Neurosurg* 1996; 10: 85–8.
- Defazio G, Berardelli A, Abbruzzese G, Coviello V, De Salvia R, Federico F, et al. Primary hemifacial spasm and arterial hypertension: a multicenter case-control study. *Neurology* 2000; 54: 1198–200.
- Du C, Korogi Y, Nagahiro S, Sakamoto Y, Takada A, Ushio Y, et al. Hemifacial spasm: three-dimensional MR images in the evaluation of neurovascular compression. *Radiology* 1995; 197: 227–31.
- Duff JM, Spinner RJ, Lindor NM, Dodick DW, Atkinson JL. Familial trigeminal neuralgia and contralateral hemifacial spasm. *Neurology* 1999; 53: 216–18.
- Eekhof JL, Aramideh M, Speelman JD, Devriese PP, Ongerboer De Visser BW. Blink reflexes and lateral spreading in patients with synkinesia after Bell's palsy and in hemifacial spasm. *Eur Neurol* 2000; 43: 141–6.
- Fein JM, Frishman W. Neurogenic hypertension related to vascular compression of the lateral medulla. *Neurosurgery* 1980; 6: 615–22.
- Fern R, Harrison PJ. The effects of compression upon conduction in myelinated axons of the isolated frog sciatic nerve. *J Physiol (Lond)* 1991; 432: 111–22.
- Figueiredo PC, Brock M, De Oliveira AM Jr, Prill A. Arteriovenous malformation in the cerebellopontine angle presenting as trigeminal neuralgia. [Review]. *Arq Neuropsiquiatr* 1989; 47: 61–71.
- Fish CJ, Blakemore WF. A model of chronic spinal cord compression in the cat. *Neuropathol Appl Neurobiol* 1983; 9: 109–19.
- Fromm GH. Trigeminal neuralgia and related disorders. [Review]. *Neurol Clin* 1989; 7: 305–19.
- Fujimaki T, Fukushima T, Miyazaki S. Percutaneous retrogasserian glycerol injection in the management of trigeminal neuralgia: long-term follow-up results. *J Neurosurg* 1990; 73: 212–16.
- Fujimaki T, Hoya K, Sasaki T, Kirino T. Recurrent trigeminal neuralgia caused by an inserted prosthesis: report of two cases. *Acta Neurochir (Wien)* 1996; 138: 1307–10.
- Fukushima T. Microvascular decompression for hemifacial spasm and trigeminal neuralgia: results in 4000 cases. *J Neurol Neurosurg Psychiatry* 1990; 53: 173.
- Gass A, Kitchen N, MacManus DG, Moseley IF, Hennerici MG, Miller DH. Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with magnetic resonance imaging. *Neurology* 1997; 49: 1142–4.
- Geiger H, Naraghi R, Schobel HP, Frank H, Sterzel RB, Fahlbusch R. Decrease of blood pressure by ventrolateral medullary decompression in essential hypertension. *Lancet* 1998; 352: 446–9.
- Gledhill RF, Harrison BM, McDonald WI. Demyelination and remyelination after acute spinal cord compression. *Exp Neurol* 1973; 38: 472–87.
- Glocker FX, Krauss JK, Deuschl G, Seeger W, Lucking CH. Hemifacial spasm due to posterior fossa tumors: the impact of tumor location on electrophysiological findings. *Clin Neurol Neurosurg* 1998; 100: 104–11.
- Golby AJ, Norbash A, Silverberg GD. Trigeminal neuralgia resulting from infarction of the root entry zone of the trigeminal nerve: case report. *Neurosurgery* 1998; 43: 620–2.
- Greene KA, Karahalios DG, Spetzler RF. Glossopharyngeal neuralgia associated with vascular compression and choroid plexus papilloma. *Br J Neurosurg* 1995; 9: 809–14.
- Haddad FS, Taha JM. An unusual cause for trigeminal neuralgia: contralateral meningioma of the posterior fossa. [Review]. *Neurosurgery* 1990; 26: 1033–8.

- Haines SJ, Jannetta PJ, Zorub DS. Microvascular relations of the trigeminal nerve. An anatomical study with clinical correlation. *J Neurosurg* 1980; 52: 381–6.
- Hamlyn PJ. Neurovascular relationships in the posterior cranial fossa, with special reference to trigeminal neuralgia. 2. Neurovascular compression of the trigeminal nerve in cadaveric controls and patients with trigeminal neuralgia: quantification and influence of method. *Clin Anat* 1997; 10: 380–8.
- Harrison BM, McDonald WI. Remyelination after transient experimental compression of the spinal cord. *Ann Neurol* 1977; 1: 542–51.
- Hartmann M, Rottach KG, Wohlgemuth WA, Pfadenhauer K. Trigeminal neuralgia triggered by auditory stimuli in multiple sclerosis. *Arch Neurol* 1999; 56: 731–3.
- Hilton DA, Love S, Gradidge T, Coakham HB. Pathological findings associated with trigeminal neuralgia caused by vascular compression. *Neurosurgery* 1994; 35: 299–303.
- Hosoya T, Watanabe N, Yamaguchi K, Saito S, Nakai O. Three-dimensional MRI of neurovascular compression in patients with hemifacial spasm. *Neuroradiology* 1995; 37: 350–2.
- Ildan F, Gocer AI, Bagdatoglu H, Uzuneyupoglu Z, Tuna M, Cetinalp E. Isolated trigeminal neuralgia secondary to distal anterior inferior cerebellar artery aneurysm. *Neurosurg Rev* 1996; 19: 43–6.
- Ito M, Sonokawa T, Mishina H, Iizuka Y, Sato K. Dural arteriovenous malformation manifesting as tic douloureux. *Surg Neurol* 1996; 45: 370–5.
- Jamjoom A, Rawlinson N, Coakham HB. Multiple neurological lesions due to vertebrobasilar dolichoectasia. *Br J Neurosurg* 1990; 4: 147–54.
- Jamjoom AB, Jamjoom ZA, al-Fehaily M, el-Watidy S, al-Moallem M, Nain-Ur-Rahman. Trigeminal neuralgia related to cerebellopontine angle tumors. *Neurosurg Rev* 1996; 19: 237–41.
- Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. *J Neurosurg* 1967; 26 Suppl: 159–62.
- Jannetta PJ. Observations on the etiology of trigeminal neuralgia, hemifacial spasm, acoustic nerve dysfunction and glossopharyngeal neuralgia. Definitive microsurgical treatment and results in 117 patients. *Neurochirurgia (Stuttgart)* 1977; 20: 145–54.
- Jannetta PJ. Neurovascular compression in cranial nerve and systemic disease. *Ann Surg* 1980; 192: 518–25.
- Jannetta PJ, Segal R, Wolfson SK Jr. Neurogenic hypertension: etiology and surgical treatment. I. Observations in 53 patients. *Ann Surg* 1985a; 201: 391–8.
- Jannetta PJ, Segal R, Wolfson SK Jr, Dujovny M, Semba A, Cook EE. Neurogenic hypertension: etiology and surgical treatment. II. Observations in an experimental nonhuman primate model. *Ann Surg* 1985b; 202: 253–61.
- Jannetta PJ, Moller MB, Moller AR, Sekhar LN. Neurosurgical treatment of vertigo by microvascular decompression of the eighth cranial nerve. *Clin Neurosurg* 1986; 33: 645–65.
- Jensen TS, Rasmussen P, Reske-Nielsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. *Acta Neurol Scand* 1982; 65: 182–9.
- Jho HD, Jannetta PJ. Microvascular decompression for spasmodic torticollis. *Acta Neurochir (Wien)* 1995; 134: 21–6.
- Kamiguchi H, Ohira T, Ochiai M, Kawase T. Computed tomographic analysis of hemifacial spasm: narrowing of the posterior fossa as a possible facilitating factor for neurovascular compression. *J Neurol Neurosurg Psychiatry* 1997; 62: 532–4.
- Kato T, Sawamura Y, Abe H. Trigeminal neuralgia caused by a cerebellopontine-angle lipoma: case report. *Surg Neurol* 1995; 44: 33–5.
- Katusic S, Williams DB, Beard CM, Bergstralh EJ, Kurland LT. Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945–1984. *Neuroepidemiology* 1991; 10: 276–81.
- Kerr FW, Miller RH. The pathology of trigeminal neuralgia. Electron microscopic studies. *Arch Neurol* 1966; 15: 308–19.
- Kleineberg B, Becker H, Gaab MR. Neurovascular compression and essential hypertension. An angiographic study. *Neuroradiology* 1991; 33: 2–8.
- Kleineberg B, Becker H, Gaab MR, Naraghi R. Essential hypertension associated with neurovascular compression: angiographic findings. *Neurosurgery* 1992; 30: 834–41.
- Knuckey NW, Gubbay SS. Familial trigeminal and glossopharyngeal neuralgia. *Clin Exp Neurol* 1979; 16: 315–19.
- Kobata H, Kondo A, Iwasaki K, Nishioka T. Combined hyperactive dysfunction syndrome of the cranial nerves: trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia: 11-year experience and review. [Review]. *Neurosurgery* 1998; 43: 1351–61.
- Kondo A. Follow-up results of using microvascular decompression for treatment of glossopharyngeal neuralgia. *J Neurosurg* 1998; 88: 221–5.
- Kugelberg E, Lindblom U. The mechanism of the pain in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1959; 22: 36–43.
- Laha RK, Jannetta PJ. Glossopharyngeal neuralgia. *J Neurosurg* 1977; 47: 316–20.
- Lazar ML, Kirkpatrick JB. Trigeminal neuralgia and multiple sclerosis: demonstration of the plaque in an operative case. *Neurosurgery* 1979; 5: 711–17.
- Leandri M, Eldridge P, Miles J. Recovery of nerve conduction following microvascular decompression for trigeminal neuralgia. *Neurology* 1998; 51: 1641–6.
- Lesinski SG, Chambers AA, Komray R, Keiser M, Khodadad G. Why not the eighth nerve? Neurovascular compression—probable cause for pulsatile tinnitus. *Otolaryngol Head Neck Surg* 1979; 87: 89–94.
- Love S, Bateman DE, Hirschowitz L. Bilateral lambda light chain amyloidomas of the trigeminal ganglia, nerves and roots. *Neuropathol Appl Neurobiol* 1997; 23: 512–15.

- Love S, Hilton DA, Coakham HB. Central demyelination of the Vth nerve root in trigeminal neuralgia associated with vascular compression. *Brain Pathol* 1998; 8: 1–11.
- Love S, Gradidge T, Coakham HB. Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. *Neuropathol Appl Neurobiol* 2001; 27: 1–8.
- Lovely TJ, Jannetta PJ. Surgical management of geniculate neuralgia. *Am J Otol* 1997; 18: 512–17.
- Makino Y, Kawano Y, Okuda N, Horio T, Iwashima Y, Yamada N, et al. Autonomic function in hypertensive patients with neurovascular compression of the ventrolateral medulla oblongata. *J Hypertens* 1999; 17: 1257–63.
- Mason WE, Kollros P, Jannetta PJ. Trigeminal neuralgia and its treatment in a 13-month-old child: a review and case report. *J Craniomandib Disord* 1991; 5: 213–16.
- Matsuura N, Kondo A. Trigeminal neuralgia and hemifacial spasm as false localizing signs in patients with a contralateral mass of the posterior cranial fossa. Report of three cases. *J Neurosurg* 1996; 84: 1067–71.
- Matthies C, Samii M. Management of 1000 vestibular schwannomas (acoustic neuromas): clinical presentation. *Neurosurgery* 1997; 40: 1–9.
- McCarron MO, Bone I. Glossopharyngeal neuralgia referred from a pontine lesion. *Cephalalgia* 1999; 19: 115–17.
- McCormick PC, Bello JA, Post KD. Trigeminal schwannoma. Surgical series of 14 cases with review of the literature. [Review]. *J Neurosurg* 1988; 69: 850–60.
- McDonald WI. Mechanisms of functional loss and recovery in spinal cord damage. *Ciba Found Symp* 1975; No. 34: 23–33.
- McLaughlin MR, Jannetta PJ, Clyde BL, Subach BR, Comey CH, Resnick DK. Microvascular decompression of cranial nerves: lessons learned after 4400 operations. *J Neurosurg* 1999; 90: 1–8.
- Meaney JF, Eldridge PR, Dunn LT, Nixon TE, Whitehouse GH, Miles JB. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. Comparison with surgical findings in 52 consecutive operative cases. *J Neurosurg* 1995a; 83: 799–805.
- Meaney JF, Watt JW, Eldridge PR, Whitehouse GH, Wells JC, Miles JB. Association between trigeminal neuralgia and multiple sclerosis: role of magnetic resonance imaging. *J Neurol Neurosurg Psychiatry* 1995b; 59: 253–9.
- Michelucci R, Tassinari CA, Samoggia G, Tognetti F, Calbucci F. Intracranial microvascular decompression for 'cryptogenic' hemifacial spasm, trigeminal and glossopharyngeal neuralgia, paroxysmal vertigo and tinnitus: II. Clinical study and long-term follow up. *Ital J Neurol Sci* 1986; 7: 367–74.
- Minagar A, Sheremata WA. Glossopharyngeal neuralgia and MS. *Neurology* 2000; 54: 1368–70.
- Mohanty A, Venkatram SK, Rao BR, Chandramouli BA, Jayakumar PN, Das BS. Experience with cerebellopontine angle epidermoids. *Neurosurgery* 1997; 40: 24–9.
- Moller AR. The cranial nerve vascular compression syndrome: II. A review of pathophysiology. [Review]. *Acta Neurochir (Wien)* 1991; 113: 24–30.
- Moller AR, Jannetta PJ. On the origin of synkinesis in hemifacial spasm: results of intracranial recordings. *J Neurosurg* 1984; 61: 569–76.
- Moller AR, Jannetta PJ. Microvascular decompression in hemifacial spasm: intraoperative electrophysiological observations. *Neurosurgery* 1985; 16: 612–18.
- Moller AR, Jannetta PJ. Physiological abnormalities in hemifacial spasm studied during microvascular decompression operations. *Exp Neurol* 1986; 93: 584–600.
- Moller MB, Moller AR, Jannetta PJ, Jho HD, Sekhar LN. Microvascular decompression of the eighth nerve in patients with disabling positional vertigo: selection criteria and operative results in 207 patients. *Acta Neurochir (Wien)* 1993; 125: 75–82.
- Moraci A, Buonaiuto C, Punzo A, Parlato C, Amalfi R. Trigeminal neuralgia treated by percutaneous thermocoagulation. Comparative analysis of percutaneous thermocoagulation and other surgical procedures. [Review]. *Neurochirurgia (Stuttg)* 1992; 35: 48–53.
- Morales F, Albert P, Alberca R, de Valle B, Narros A. Glossopharyngeal and vagal neuralgia secondary to vascular compression of the nerves. *Surg Neurol* 1977; 8: 431–3.
- Morimoto S, Sasaki S, Miki S, Kawa T, Itoh H, Nakata T, et al. Neurovascular compression of the rostral ventrolateral medulla related to essential hypertension. *Hypertension* 1997a; 30: 77–82.
- Morimoto S, Sasaki S, Miki S, Kawa T, Itoh H, Nakata T, et al. Pulsatile compression of the rostral ventrolateral medulla in hypertension. *Hypertension* 1997b; 29: 514–18.
- Morimoto S, Sasaki S, Itoh H, Nakata T, Takeda K, Nakagawa M, et al. Sympathetic activation and contribution of genetic factors in hypertension with neurovascular compression of the rostral ventrolateral medulla. *J Hypertens* 1999; 17: 1577–82.
- Moulin DE. Pain in central and peripheral demyelinating disorders. [Review]. *Neurol Clin* 1998; 16: 889–98.
- Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology* 1988; 38: 1830–4.
- Nakamura K, Yamamoto T, Yamashita M. Small medullary infarction presenting as painful trigeminal sensory neuropathy. *J Neurol Neurosurg Psychiatry* 1996; 61: 138.
- Naraghi R, Gaab MR, Walter GF, Kleiber B. Arterial hypertension and neurovascular compression at the ventrolateral medulla. A comparative microanatomical and pathological study. *J Neurosurg* 1992; 77: 103–12.
- Naraghi R, Geiger H, Crnac J, Huk W, Fahlbusch R, Engels G, et al. Posterior fossa neurovascular anomalies in essential hypertension. *Lancet* 1994; 344: 1466–70.
- Naraghi R, Schuster H, Toka HR, Bähring S, Toka O, Oztekin O, et al. Neurovascular compression at the ventrolateral medulla in autosomal dominant hypertension and brachydactyly. *Stroke* 1997; 28: 1749–54.
- Nielsen VK, Jannetta PJ. Pathophysiology of hemifacial spasm: III. Effects of facial nerve decompression. *Neurology* 1984; 34: 891–7.

- Occhiogrosso M, De Tommasi A, Vailati G. Glossopharyngeal neuralgia due to exuberant choroid plexus. *Surg Neurol* 1980; 13: 459–61.
- Occhiogrosso M, De Tommasi A, Vailati G. Choroid plexus compression of glossopharyngeal nerve in patients with glossopharyngeal neuralgia. *J Neurosurg Sci* 1996; 40: 37–41.
- Ogasawara H, Oki S, Kohno H, Hibino S, Ito Y. Tentorial meningioma and painful tic convulsif. Case report. [Review]. *J Neurosurg* 1995; 82: 895–7.
- Okamura T, Kurokawa Y, Ikeda N, Abiko S, Ideguchi M, Watanabe K, et al. Microvascular decompression for cochlear symptoms. *J Neurosurg* 2000; 93: 421–6.
- Pagni CA. The origin of tic douloureux: a unified view. *J Neurosurg Sci* 1993; 37: 185–94.
- Pagni CA, Naddeo M, Faccani G. Spasmodic torticollis due to neurovascular compression of the 11th nerve. Case report. *J Neurosurg* 1985; 63: 789–91.
- Platania N, Nicoletti GF, Barbagallo G, Albanese V. Concurrent trigeminal and glossopharyngeal neuralgia, hemifacial spasm and hypertension by neurovascular compression. Case report. *J Neurosurg Sci* 1997; 41: 303–7.
- Ramon F, Moore JW. Ephaptic transmission in squid giant axons. *Am J Physiol* 1978; 234: C162–9.
- Rappaport ZH, Devor M. Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. [Review]. *Pain* 1994; 56: 127–38.
- Rappaport ZH, Govrin-Lippmann R, Devor M. An electron-microscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. *Stereotact Funct Neurosurg* 1997; 68: 182–6.
- Rasminsky M. Ectopic generation of impulses and cross-talk in spinal nerve roots of 'dystrophic' mice. *Ann Neurol* 1978; 3: 351–7.
- Reilly MM, Valentine AR, Ginsberg L. Trigeminal neuralgia associated with osteogenesis imperfecta. *J Neurol Neurosurg Psychiatry* 1995; 58: 665.
- Resnick DK, Jannetta PJ. Hyperactive rhizopathy of the vagus nerve and microvascular decompression. Case report. *J Neurosurg* 1999; 90: 580–2.
- Resnick DK, Jannetta PJ, Bissonnette D, Jho HD, Lanzino G. Microvascular decompression for glossopharyngeal neuralgia. *Neurosurgery* 1995; 36: 64–8.
- Resnick DK, Levy EI, Jannetta PJ. Microvascular decompression for pediatric onset trigeminal neuralgia. *Neurosurgery* 1998; 43: 804–7.
- Revuelta R, Juambelz P, Balderrama J, Teixeira F. Contralateral trigeminal neuralgia: a new clinical manifestation of neurocysticercosis: case report. *Neurosurgery* 1995; 37: 138–9.
- Richards P, Shawdon H, Illingworth R. Operative findings on microsurgical exploration of the cerebello-pontine angle in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry* 1983; 46: 1098–101.
- Rosenkopf KL. Current concepts concerning the etiology and treatment of trigeminal neuralgia. [Review]. *Cranio* 1989; 7: 312–18.
- Ruelle A, Datti R, Andrioli G. Cerebellopontine angle osteoma causing trigeminal neuralgia: case report. [Review]. *Neurosurgery* 1994; 35: 1135–7.
- Ryu H, Yamamoto S, Sugiyama K, Nozue M. Neurovascular compression syndrome of the eighth cranial nerve. What are the most reliable diagnostic signs? *Acta Neurochir (Wien)* 1998a; 140: 1279–86.
- Ryu H, Yamamoto S, Sugiyama K, Uemura K, Nozue M. Neurovascular decompression of the eighth cranial nerve in patients with hemifacial spasm and incidental tinnitus: an alternative way to study tinnitus. *J Neurosurg* 1998b; 88: 232–6.
- Saglitz SA, Gaab MR, Assaf JA, Naraghi R, Kleineberg B. Neurovascular compression at the left ventrolateral medulla as an etiological factor for arterial hypertension. *Exp Clin Endocrinol Diabetes* 1997; 105 Suppl 2: 9–11.
- Saito N, Yamakawa K, Sasaki T, Saito I, Takakura K. Intramedullary cavernous angioma with trigeminal neuralgia: a case report and review of the literature. [Review]. *Neurosurgery* 1989; 25: 97–101.
- Saito S, Moller AR, Jannetta PJ, Jho HD. Abnormal response from the sternocleidomastoid muscle in patients with spasmodic torticollis: observations during microvascular decompression operations. *Acta Neurochir (Wien)* 1993; 124: 92–8.
- Sakatani K, Ohta T, Yamagata Y, Shimo-Oku M. Effects of spinal cord compression on repetitive impulse conduction of the ascending fibers of the dorsal column. *Neurosurg Rev* 1989; 12 Suppl 1: 575–81.
- Samii M, Rosahl SK, Carvalho GA, Krzizok T. Microvascular decompression for superior oblique myokymia: first experience. *J Neurosurg* 1998; 89: 1020–4.
- Shi R, Blight AR. Compression injury of mammalian spinal cord in vitro and the dynamics of action potential conduction failure. *J Neurophysiol* 1996; 76: 1572–80.
- Sindou M, Henry JF, Blanchard P. Idiopathic neuralgia of the glossopharyngeal nerve. Study of a series of 14 cases and review of the literature. [Review]. [French]. *Neurochirurgie* 1991; 37: 18–25.
- Smith KJ, Hall SM. Nerve conduction during peripheral demyelination and remyelination. *J Neurol Sci* 1980; 48: 201–19.
- Smith KJ, McDonald WI. Spontaneous and mechanically evoked activity due to central demyelinating lesion. *Nature* 1980; 286: 154–5.
- Smith KJ, McDonald WI. Spontaneous and evoked electrical discharges from a central demyelinating lesion. *J Neurol Sci* 1982; 55: 39–47.
- Smith KJ, Blakemore WF, McDonald WI. The restoration of conduction by central remyelination. *Brain* 1981; 104: 383–404.
- Soustiel JF, Hafner H, Chistyakov AV, Yarnitzky D, Sharf B, Guilburd JN, et al. Brain-stem trigeminal and auditory evoked potentials in multiple sclerosis: physiological insights. *Electroencephalogr Clin Neurophysiol* 1996; 100: 152–7.

- Sweet WH. The history of the development of treatment for trigeminal neuralgia. *Clin Neurosurg* 1985; 32: 294–318.
- Sweet WH. The treatment of trigeminal neuralgia (tic douloureux). [Review]. *New Engl J Med* 1986; 315: 174–7.
- Sweet WH. Percutaneous methods for the treatment of trigeminal neuralgia and other faciocephalic pain; comparison with microvascular decompression. [Review]. *Semin Neurol* 1988; 8: 272–9.
- Tankere F, Maisonnobe T, Lamas G, Soudant J, Bouche P, Fournier E, et al. Electrophysiological determination of the site involved in generating abnormal muscle responses in hemifacial spasm. *Muscle Nerve* 1998; 21: 1013–18.
- Tash R, DeMerritt J, Sze G, Leslie D. Hemifacial spasm: MR imaging features. *Am J Neuroradiol AJNR* 1991; 12: 839–42.
- Tekkök IH, Brown JA. The neurosurgical management of trigeminal neuralgia. *Neurosurg Q* 1996; 6: 89–107.
- Van HT, Deguine O, Esteve-Fraysse MJ, Bonafe A, Fraysse B. Relationship between cochleovestibular disorders in hemifacial spasm and neurovascular compression. *Laryngoscope* 1999; 109: 741–7.
- Wakiya K, Fukushima T, Miyazaki S. Results of microvascular decompression in 16 cases of glossopharyngeal neuralgia. [Japanese]. *Neurol Med Chir (Tokyo)* 1989; 29: 1113–18.
- Walchenbach R, Voormolen JH, Hermans J. Microvascular decompression for trigeminal neuralgia: a critical reappraisal. [Review]. *Clin Neurol Neurosurg* 1994; 96: 290–5.
- Yoshimasu F, Kurland LT, Elveback LR. Tic douloureux in Rochester, Minnesota, 1945–1969. *Neurology* 1972; 22: 952–6.

*Received February 28, 1002. Revised May 14, 2001
Accepted June 11, 2001*