Trigeminal neuralgia—pathophysiology, diagnosis and current treatment

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Historical aspects

The first known description of trigeminal neuralgia (TGN), or a similar condition, was written in the second century AD by Aretaeus of Cappadocia, a contemporary of Galen. Also known for his descriptions of migraine, he makes reference to a pain in which ‘spasm and distortion of the countenance take place’.113 Jujani, an 11th century Arab physician, mentions unilateral facial pain causing spasms and anxiety in his writings. Interestingly, he suggests that the cause of the pain is ‘the proximity of the artery to the nerve’.4 The first full account of TGN was published in 1773 when John Fothergill presented a paper to the Medical Society of London. He described the typical features of the condition in detail, including paroxysms of unilateral facial pain, evoked by eating or speaking or touch, starting and ending abruptly, and associated with anxiety.113 Some time earlier, Nicolaus André had used the term ‘tic douloureux’ to describe what he thought was a new clinical entity. However, it has been suggested, that no more than two of the patients he described in fact had TGN.4

Sporadic observations later in the 18th and 19th century by Pujol, Chapman and Tiffany helped to complete the clinical picture and differentiate TGN from common facial pain conditions such as toothache. In the early 20th century, Oppenheim alluded to an association between multiple sclerosis (MS) and TGN and Patrick commented on its familial incidence.39

A wide range of treatments was in use by the beginning of the last century. Modern neurosurgical treatment can be traced back to 1925 when the concept of vascular compression was introduced.29 However, it took over half a century before microvascular decompression (MVD) gained wide-spread acceptance as a treatment method. Gardner and Miklos promoted the theory and modified the technique further in the 1950s and 1960s.41 It was not until the large case series published in 1970s by Jannetta58 that a major shift in neurosurgical practice began to appear. Neuroablative procedures kept evolving throughout the century, with attempts to balance the adverse effects of neural injury with sufficient pain control. Radiosurgery is the latest innovation in this process.

Pharmacotherapy had little success in this condition until Bergouignan’s discovery in 1942 that phenytoin was effective in preventing pain paroxysms.12 Soon, following the introduction of carbamazepine for treatment of epilepsy, controlled trials were published showing its superiority over placebo in TGN. Since then, anticonvulsants have remained the mainstay of pharmacological treatment, though controlled trials have been surprisingly rare.

Definition of TGN

Both the International Association for the Study of Pain (IASP) and International Headache Society (IHS) have suggested their own diagnostic criteria for TGN.91 143 These are remarkably similar and highlight the sudden, explosive nature of the pain (Table 1). In further descriptions of the condition, both classifications allude to vascular compression, MS and tumours as known aetiological causes. The IASP classification makes a distinction between TGN (including MS) and secondary neuralgias (caused by structural lesions and injuries, but not including MS), while IHS separates idiopathic TGN from the ‘symptomatic form’ depending on the presence of a structural lesion; it is not quite clear if vascular compression qualifies as such. Neither approach includes reference to variant forms of TGN, which satisfy the diagnostic criteria but display additional features as well.
Diagnosis

Several authors have used a slightly different approach by classifying TGN patients into subgroups depending on how ‘pure’ the pain is. We agree with this viewpoint, because our own experience reflects the general conclusion that the outcome is dependent on the nature of the pain. We have also frequently witnessed, in our tertiary referral clinic, both over- and under-diagnosing of TGN, which seems to reflect difficulties in interpreting the painful symptoms in the context of an unnecessarily restrictive ‘official’ definition.

Our own classification and diagnostic criteria are presented in Table 2. We use it as guidance, rather than a fixed set of rules. While arbitrary, it has worked well in our hands and greatly helped communication between various specialists. It is obvious that, in some cases, pain slowly evolves from one category to another. A typical form of TGN may, in prolonged cases, develop atypical signs, as observed by Burchiel. By contrast, many cases of TGN start with pain lacking the typical characteristics of TGN, but respond well to carbamazepine, and later developing all the hallmark signs of TGN (‘pre-TGN’).

Trigeminal neuropathy, whether painful or non-painful, is associated with a structural lesion or systemic disease. It may be seen following direct trauma to the nerve (e.g. supra- and infraorbital neuralgias following facial fractures); we also classify dysaesthesiae and anaesthesia dolorosa following neuroablative procedures as trigeminal neuropathy. On occasion, it can be seen caused by severe arterial compression, usually from an ectatic basilar artery. The pain description in this condition is different from that in TGN and more akin to that in painful peripheral neuropathy. Pain is usually constant and associated with allodynia and sensory loss. Central nervous system lesions, even if they predominantly involve the trigeminal pathways and very occasionally mimic TGN, are not classified as either trigeminal neuropathy or TGN, but fall under the heading of central pain.

TGN remains a clinical diagnosis dependent on a history of sudden shooting or stabbing pain, coming as solitary sensations or paroxysms and separated by pain-free intervals. Optimally, it is the patient who volunteers this description. However, many patients with facial pain have considerable difficulty in finding precise expressions to convey the characteristics of their symptoms. In such a case, the interviewer may suggest descriptive words with as little prompting as possible. Some patients identify the type of pain if an acoustic equivalent of the pain is provided, for example, by the interviewer sharply clapping his hands. Although the McGill Pain Questionnaire has been shown to be useful in differentiating a group of TGN patients from those with other facial pains, our observations suggest that, in individuals, taking a careful history is unsurpassed in providing the most reliable elements for the diagnosis.

Patients with atypical TGN also give the history of stabbing or shooting pains. Unlike in typical TGN, they relate a history of other kinds of pain as well. Many have constant or near constant discomfort on the same side of the face. We are not aware of studies focussing on atypical forms. Many patients we see are those with recurrent TGN with a history of previous neuroablative procedures. It remains a possibility that compression of the nerve, when protracted, can lead to intrinsic changes in the nerve and modify the clinical picture.

In addition, non-verbal behaviour may be very helpful in aiding the diagnosis. Patients with severe TGN either wince or interrupt their speech as a result of a tic. Many show major aversion to anyone or anything touching the face. This may, in fact, influence the clinical examination. By contrast, patients with other types of facial pain, including trigeminal neuropathy, usually seem not to be bothered by the their hand or the examiner’s hand touching their face.

Differential diagnosis

The list of differential diagnoses is long and includes a number of pathological conditions affecting the sinuses, teeth, temporomandibular joints, eyes, nose, and the neck. Most of these are easily ruled out after the interview and brief clinical examination. However, a few conditions remain that bear considerable similarity to TGN and are listed in Table 3.

Other cranial neuralgias (glossopharyngeal neuralgia, neuralgia of nervus intermedius, neuralgia of the superior laryngeal nerve, and occipital neuralgia) can all cause diagnostic difficulty. These neuralgias are rare and can produce pain that is identical to that of TGN. However, the location is different.

Aetiology of TGN

There are obvious problems in determining aetiological causes for a syndrome, which is formulated on the basis of

<table>
<thead>
<tr>
<th>IASP definition</th>
<th>IHS definition</th>
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<tr>
<td>Sudden, usually unilateral, severe brief stabbing recurrent pains in the distribution of one or more branches of the Vth cranial nerve</td>
<td>Painful unilateral affliction of the face, characterized by brief electric shock like pain limited to the distribution of one or more divisions of the trigeminal nerve.</td>
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</table>

Table 1 Definition of TGN provided by the International Association for the Study of Pain, IASP and International Headache Society, IHS.
subjective pain rather than hard signs or laboratory abnormalities. However, in the last three decades, evidence has been mounting that in a large proportion of cases, compression of the trigeminal nerve root at or near the dorsal root entry zone by a blood vessel is a major causative or contributing factor. There are several lines of evidence that support this view. First, novel imaging methods (MRI) and observations during posterior fossa surgery for TGN have consistently shown a blood vessel in contact with the nerve root. Second, elimination of the compression leads to long-term pain relief in most patients. Third, intra-operative recordings show immediate improvement in nerve conduction following decompression, fitting with the general experience that patients tend to wake up from the operation pain-free. Fourth, sensory functions recover as well following decompression (though this recovery is slower than that in nerve conduction).

Some authors have questioned the significance of the vascular compression by pointing out that it is not unusual to see blood vessels in the vicinity of or touching the nerve during a routine autopsy in patients with no history of TGN. However, as underlined by many others, the critical abnormality is vascular contact at the dorsal root entry zone, rather than more distally; such is seen in 3–12% of trigeminal nerves at autopsy. The way the autopsy is carried out may be relevant. Hamlyn and colleagues have suggested that their method of positioning the cadaver to mimic the positioning during the actual operation and perfusing the arteries and veins at physiological pressures to prevent them from collapsing leads to a more reliable assessment of any significant neurovascular compression. They found a blood vessel contact in 13% of the cadavers, but without concomitant grooving of any of the affected nerves. A contact at the level of the dorsal root entry zone by an artery was found in 3% and by a vein by 6% of their material.

Of other known aetiological factors, the association of MS with TGN is well established. MS is seen in 2–4% of patients with TGN. Conversely, TGN is diagnosed in 1–5% of patients with MS. In a small proportion of patients with MS, TGN is the first manifestation of the disease. These patients are younger than the TGN population as a whole and their neuralgia is more frequently bilateral. A latent demyelinating disease

<table>
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<tr>
<th><strong>Table 2</strong> Comparison of definitions of TGN. <em>Key items</em>*</th>
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<tbody>
<tr>
<td>TGN (IASP and IHS definition)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
</tr>
<tr>
<td><strong>Quality of pain</strong></td>
</tr>
<tr>
<td><strong>Duration of pain</strong></td>
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<tr>
<td><strong>Duration of paroxysms</strong></td>
</tr>
<tr>
<td><strong>Refractory period</strong></td>
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<tr>
<td><strong>Continuous pain</strong></td>
</tr>
<tr>
<td><strong>Alloynia</strong></td>
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<tr>
<td><strong>Associated features</strong></td>
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<tr>
<td><strong>Radiation</strong></td>
</tr>
<tr>
<td><strong>Provoking factors</strong></td>
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<tr>
<td><strong>Variability of pain</strong></td>
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<tr>
<td><strong>Sensory loss</strong></td>
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<tr>
<td><strong>Pain behaviour</strong></td>
</tr>
<tr>
<td><strong>Course of pain</strong></td>
</tr>
</tbody>
</table>

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Table 3  Differential diagnosis of TGN. *SUNCT, Short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing; **CPH, chronic paroxysmal hemicrania. Sources: Goadsby and Lipton,43 Merskey and Bogduk,91 and Zakrzewska141

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location of pain</th>
<th>Duration of pain or attack</th>
<th>Shooting pain or paroxysms</th>
<th>Autonomic symptoms</th>
<th>Pain relief with carbachamazepine</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster headache</td>
<td>Retrobulbar, check, chin</td>
<td>20 min to several hours</td>
<td>Only superimposed on deep dull pain</td>
<td>Prominent</td>
<td>Slight</td>
<td>Triptans help</td>
</tr>
<tr>
<td>SUNCT*</td>
<td>Forehead, retrobulbar</td>
<td>5 s to several minutes</td>
<td>Yes</td>
<td>Prominent</td>
<td>None</td>
<td>Almost exclusively in women; rare</td>
</tr>
<tr>
<td>CPH**</td>
<td>Forehead, retrobulbar</td>
<td>2–45 min</td>
<td>No</td>
<td>Prominent</td>
<td>None</td>
<td>Responsive to indomethacin</td>
</tr>
<tr>
<td>Cracked tooth syndrome</td>
<td>Upper jaw, lower jaw</td>
<td>Seconds</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>Provoked on biting and chewing</td>
</tr>
<tr>
<td>Jabs and jolts syndrome</td>
<td>Anywhere in the head</td>
<td>Seconds</td>
<td>Yes</td>
<td>None</td>
<td>Good</td>
<td>No precipitating factors</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>Forehead, eye, cheek (rarely)</td>
<td>Continuous</td>
<td>Superimposed background pain</td>
<td>Variable, mild</td>
<td>Variable, usually modes</td>
<td>History of shingles, Tactile alldynia, Sensory impairment</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Forehead, neck, temple</td>
<td>Continuous</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Jaw claudication</td>
</tr>
</tbody>
</table>

should be considered in young patients with TGN and appropriate diagnostic tests performed, as disease-modifying treatment for MS is emerging.57

Neuropathological and imaging studies suggest that the common denominator in patients with typical TGN and MS is the involvement of the trigeminal nerve entry zone in the pons.42 60 In contrast, plaques in other parts of the brain stem or elsewhere in the CNS do not necessarily lead to development of TGN. Interestingly, there are reports of vascular compression of the trigeminal nerve in patients with MS,16 17 89 and pain relief following decompression, though the results are less favourable than in other TGN subgroups.16 17

Tumours, usually posterior fossa meningiomas or neuromas, are found in 2% of patients who present with typical TGN.26 The localization of the tumour dictates the nature of facial symptoms. Tumours affecting the peripheral branches or the Gasserian ganglion usually give rise to sensory change and constant pain, in other words, trigeminal neuropathy.19 26 Slowly growing tumours which distend the trigeminal root rather than invade it, are usually found in TGN.56 In Cheng’s series, the average delay in diagnosis of the tumour was 6.3 yr. Half of the patients developed sensory or motor deficits later.

Pathophysiology

Although there is general agreement that none of the many existing theories fully explain all known characteristics of TGN pain,67 129 the bulk of current evidence points to the trigeminal nerve rather than the CNS as the site of generation of TGN pain.105 More specifically, the existing evidence suggests that a slowly evolving process, whether a compression exerted on the nerve by a blood vessel or tumour or alteration of neural functions by an MS plaque at the level of the dorsal root entry zone, leads to increased excitability in some of the trigeminal afferents and subsequently to typical TGN.

Part of the controversy that surrounds the pathophysiology of TGN is based on misquotations and inaccuracies. Against popular belief, sensory impairment in TGN—albeit small—has been documented by several groups, both using quantitative sensory testing and neurophysiological methods,18 75 100 As already mentioned, these changes normalize following successful MVD.76 92 The trigeminal ganglion in TGN is not normal but shows unique pathological changes, such as degenerative hypermyelination and formation of microneuromas, not explained by tissue artefacts, effects of aging or occult disease.11 62 63 The ganglion cells themselves appear mostly intact. While the exact mechanisms of how these changes have come about is not clear, it is of interest that such changes were reported in a patient with MS and TGN.11 At the site of vascular compression of the trigeminal root, electron microscopic studies show demyelination and remyelination.63 106

It has been suggested25 that lack of neurogenic inflammation in TGN is evidence against a major peripheral nervous system involvement. However, vasodilatation is known to occur in TGN and it normalizes when pain is controlled.101

A puzzling fact in TGN is that very different treatments yield seemingly similar results in controlling TGN pain. However, closer inspection of the long-term effects suggests that simple blocks or minimally destructive peripheral procedures lead to transient pain relief, much shorter than seen in more proximal lesions or decompression.10 44 95 126 138 Also, following neuroablative procedures, the degree of sensory loss correlates positively with the duration of pain relief.126 If one assumes that the dynamic pain of TGN reflects a state of hyperexcitability in the trigeminal afferents rather than a fixed anatomical aberration constantly driving the pain mediating fibres, then either permanent destruction of the relevant fibres or complete restoration of their normal functions (e.g. following decompression) will
only achieve sustained pain relief. The key feature of TGN pain is its very dynamic nature, which is difficult to explain in purely anatomical terms.105

It is hard to dismiss as insignificant the observations made by numerous neurosurgeons during decompressive surgery that arterial compression of the root at the dorsal root entry zone is the common finding in typical TGN.10 20 68 73 78 79 104 111 120 Similarly, in MS patients suffering from TGN, a common finding is the plaque extending into the dorsal root entry zone.42 The dorsal root entry zone represents the junction between the peripheral and central myelins of Schwann cells and astrocytes. The central branches of the unipolar ganglion cells enter the pons through this transition zone on their course toward the brainstem and spinal nuclei. Any process at this level can potentially alter the function of the whole neurone.

The fact that TGN pain is not continuous but paroxysmal speaks against a simple compression induced generation of ectopic impulses at the level of the injury. It is more likely that the paroxysms of pain in this condition represent spontaneous discharges in select neurones whose threshold for repetitive firing has been altered. To comply with the characteristics of TGN, such firing should not only occur spontaneously but be produced frequently by innocuous tactile stimuli. Recent observations have shown that dorsal root ganglion cells possess properties that, in certain circumstances, lead to this type of firing behaviour.6 Following spinal nerve injury, in which afferent neurones are axotomized close to their soma, most of the ectopic barrages originate in the dorsal root ganglion.83 Intracellular recordings have indicated that this is because of an increase in subthreshold oscillations in the resting membrane potentials of a subpopulation of A-neurones reaching threshold.83 Increased spike activity can in turn depolarize and cross-excite hyperexcitable neighbouring C-cells.5 If sufficient neurones are recruited into this spreading cluster of discharging cells, it will lead to a nociceptive signal perceived as pain.5 6 105 That such a signal would abruptly stop, as happens in TGN, is because of the inherent cellular self-quenching mechanisms.

As suggested by Rappaport and Devor,105 the above cross-excitation may be at the root of the unique pain seen in TGN and offers a logical explanation for the extraordinary initial responsiveness of pain in TGN to almost any procedure aimed at the nerve. We think it is unlikely that the generator of pain is located in the central nervous system but central sensitization may well develop following prolonged barrage of nerve impulses which can explain the development of some features of atypical TGN. Equally, continuous pain in the atypical form can result from the progressive damage to the central terminals of trigeminal afferents, which become the source of continuous ectopic discharges.20

**Investigations**

No specific tests exist for the diagnosis of TGN. There is no excuse for not carrying out a clinical examination, including assessment of cranial nerve function, given the frequency of MS and tumours found in this population. Definite facial sensory loss or other cranial nerve dysfunction, if it cannot be explained by a previously known injury to the nerve, should prompt cerebral imaging.

Even in typical TGN, imaging studies may well be of use. Following the first reports of successful use of MRI in detecting vascular compression of the nerve in TGN,8 127 Meaney and colleagues developed a specific technique to optimally image the relationship of the nerve and the blood vessels in its vicinity (magnetic resonance tomographic angiography, MRTA).89 Essentially, by choosing specific scanning parameters to visualize blood vessels as high signal intensity structures and using thin slices, they were able to perform reconstructions around the nerve in any orientation. While arteries were easily identifiable, veins could be properly visualized only after enhancement with i.v. gadolinium (Figs 1 and 2). They validated this method in 50 patients with 55 symptomatic nerves (five patients had bilateral TGN) who underwent posterior fossa exploration. In all, 52 explorations were carried out. Neurovascular contact was confirmed at operation in all 49 cases suggested by MRTA. A further case with negative MRTA had no vascular contact. There were two false negative MRTAs and no false positives. This corresponds to a sensitivity of 100% and specificity of 96%.89

In a similar study of 27 patients with unilateral TGN, neurovascular compression, or its absence as shown by MRTA, was confirmed in 24 cases.13 There were two false positives and one false negative (sensitivity of 92%, specificity of 50%). A further small study, in which visualization of nerve dislocation or actual compression only were accepted as positive findings, led to 100% specificity at the cost of low sensitivity (44%).85

Because to date there are no prospective studies comparing different facial pain groups and healthy controls, evaluated by radiologists blinded to the condition and side, the accuracy of MRTA in differentiating TGN form other painful trigeminal neuropathies remains uncertain. Therefore, MRTA cannot be used to diagnose TGN. Our current practice is to use MRTA to help in determining the likelihood that, at operation, a significant vessel contact will be found.

Several groups have developed electrophysiological techniques for assessment of trigeminal nerve function in the clinic.28 56 75 There is insufficient evidence of their usefulness in either confirming or ruling out TGN. However, abnormalities in tests for eye blink and jaw reflexes strongly point to trigeminal neuropathic pain or ‘atypical facial pain’.56
Treatment

Procedures

MVD
Since the original theory, outlined by Dandy in 1925, of vascular compression as a prominent feature of TGN, it took almost half a century until MVD was accepted as one of the major surgical methods for treating this condition. Advances in neuroanaesthesia, adoption of the operation microscope and developments in surgical techniques during this time helped to make the procedure safer and more effective.

In MVD, the target area lies at the nerve-pons junction. The posterior fossa is approached through a suboccipital craniotomy. After aspiration of the cerebrospinal fluid, the operator advances toward the nerve by gently retracting the superolateral margin of the cerebellum. The most common finding is a segment of the superior cerebellar artery compressing the nerve at the root entry zone (Fig. 3). Less frequently, the anterior inferior cerebellar artery or the superior petrosal veins are the cause of the compression. After the arachnoid is dissected and the vessel freed, the operator places a piece of shredded Teflon felt between the vessel and the nerve to separate them.

Monitoring of brainstem-evoked potentials during the operation (to prevent post-operative hearing loss) frequently shows temporary changes, because of traction on the eighth cranial nerve. These usually disappear if the retractor is temporarily relaxed. Most authors recommend partial section of the root if no vascular compression is found or the artery cannot be mobilized. Adams has recommended deliberate bruising of the nerve in addition to decompression, but we have not found any evidence that such a manoeuvre improves the outcome.

There is no age limit for the procedure as long as the patient is fit for general anaesthesia. In our recent retrospective study in patients over 70 yr of age, pain relief and complications were no different from those seen in a group of patients under the age of 50. There are anecdotal reports of MVD carried out in children less than 18 with similar results. Interestingly, venous compression appears much more common in this age group than in adults.

Several published series suggest a high level of initial success with MVD, most patients (87–98%) experiencing...
immediate pain relief. Those series that present the proportion of patients with unrelied or recurrent pain using Kaplan–Meier plots, show relatively similar results. At 1–2 yr the incidence of complete pain relief is 75–80%. After 8–10 yr, this proportion has been reduced to 58–64%, with a further 4–12% suffering from minor recurrence only.

Overall, results from definite arterial compression are better than when only an offending vein is found. In a recent retrospective survey, the authors observed a recurrence rate of 31% in patients with TGN caused by venous compression. In most cases, the recurrence took place within the first 12 months of the operation. Reports of worse outcome after MVD in those patients with a history of previous neuroablative surgery are not substantiated by other studies. Opinions differ as to what is the best policy in cases of recurrence following MVD and both re-exploration and neuroablative procedures have been recommended. Findings at re-operation are so varied that it is unlikely that any consensus will be arrived at. Perhaps with the advent of imaging, it will be possible to pinpoint the cause of recurrence and decide on the most appropriate course of action.

In experienced hands, MVD is well tolerated. Although in early series a mortality rate of 0.2–1% was described, surgical innovations have since improved the results. In two large recent series consisting of 44473 and 199586 patients, no deaths were reported. Cerebellar injury was reported in 0.45%, eighth nerve injury in 0.8% and CSF leak in 1.85% in a recent retrospective study. However, other centres report higher complication rates. It is likely that the results are much better in centres that operate frequently on these patients and have regularly reviewed their technique and improved perioperative monitoring systems.

Although the popularity of MVD has undoubtedly increased in the last two decades, there is ongoing debate regarding its advantages over neurodestructive procedures. In the absence of prospective, randomized comparative studies on this issue, the way various surgical treatments are used depends on clinical judgement which inevitable varies across centres.

Radiofrequency gangliolysis

Disillusionment with complications resulting from an uncontrollable spread of alcohol or phenol injected into Meckel’s cave for treatment of neuralgia led to the development of thermocoagulation of the Gasserian ganglion in the 1930s. The concept was first explored by Kirchner whose large series was published in 1942. The technique was modified to produce more precise and safer lesions by several authors. In 1974, Sweet presented his method which, by and large, is used today. Essentially, it involves a selective partial lesioning of the affected ganglion or retrogasserian root. Sweet and Wepsic suggested that what resulted from thermocoagulation was selective loss of pain mediating thinly myelinated or non-myelinated fibres. This hypothesis has been challenged by observations that, following this procedure, all sensory functions are found to be affected.

The procedure is carried out in the intermittently anaesthetized patient under fluoroscopic control. The radiofrequency needle is inserted through the foramen ovale into Meckel’s cave using bony landmarks. The relationship of the trigeminal rootlets to the foramen ovale is such that by stepwise advancement of the needle the third, second and first divisions will be in succession stimulated, the closer to the clival line the needle tip is (Fig. 4). As soon as the needle has entered Meckel’s cave, aspiration will usually yield CSF. Once the needle has travelled the pre-planned distance, the patient is allowed to awake, the stylet replaced by the electrode and stimulation of the nerve root carried out. The paraesthesiae elicited must conform to the location of the neuralgia, otherwise the needle must be repositioned. Once appropriate siting has taken place, the patient is anaesthetized again for thermal lesioning. This is performed in cycles of 45 to 90 s at temperatures of 60–90°C. After each lesioning the patient is awakened and manual sensory testing of the face carried out. Additional thermal lesions are performed until clear hypalgesia has ensued.

Use of fluoroscopy, and stepwise increases of needle temperatures make this procedure a relatively safe alternative. Most patients only need an overnight stay. Mortality is virtually nil and severe complications (cerebral haemorrhage, carotid-cavernous fistula, meningitis, and cranial nerve lesions) are very rare.

Unfortunately, this method can cause dysesthesiae in up to 25%, mostly mild. Dysesthesiae requiring medical treatment are seen in approximately 8%. Unfortunately, the quality of life in these patients is not improved even if the

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**Fig 3** Microscopic view of the trigeminal nerve (star) showing an arterial loop (triangle) compressing it. A vein (cross) is seen in close proximity to the nerve as well.
original pain has been controlled. There is some indication that this adverse effect is more common in patients with atypical TGN. Frank anaesthesia dolorosa is rare (mostly under 1%). Corneal anaesthesia is a potentially serious complication as it may lead to keratitis in 1–2% of cases. Other rare complications include meningitis, carotid-cavernous fistula, intracranial haemorrhage, and cranial nerve deficits.

The success of pain relief reflects patient selection and the degree of sensory loss the operator is keen to achieve. Zakrzewska identified 38 reports of RFL from the literature, with variable follow-up. The variability in patient selection and follow-up make comparisons very difficult.

We have found three published prospective studies on the long-term efficacy of RFL. Taha and colleagues reported results from a prospective follow-up of 100 patients (from the original group of 154 patients). Those with mild hypalgesia had a recurrence rate of 60% at 3 yr, after which no more recurrences occurred. Those with deep hypalgesia or actual anaesthesia had a recurrence rate of 20% at 15 yr. No lifetime analysis was provided. Zakrzewska and colleagues reported on 31 patients with pure TGN and 17 with atypical (or ‘mixed’) TGN in a prospective longitudinal study. In this series, ‘pure’ TGN patients seem to have the characteristics of the ‘typical neuralgia’ category whereas ‘mixed’ neuralgia cases were similar to our ‘atypical TGN’ category; sensory abnormalities were not mentioned but depression was common in this group. The lifetime analysis indicated a steady increase in the proportion of patients with recurrent pain in both groups. At 3 yr, 40% of both groups complained of recurrent TGN. However, patients belonging to the ‘mixed’ group reported other facial pain in 75% of cases (while the same was true of 12% of patients with typical TGN).

In a study of 215 patients, the vast majority experienced immediate pain relief (92%). Recurrence of TGN pain occurred in 27% at a mean follow-up of 32 months. The authors did not state the number of patients lost to follow-up. Side effects were similar in intensity and quality to those reported in other series.

Certain conclusions can be drawn from these prospective and retrospective series. Immediate pain relief in typical TGN is high, with diminution of effectiveness over time so that at 3 yr one-third of patients will have recurrent neuralgia. Long-term annoying paraesthesiae following the procedure is experienced by 5–10%, but frank anaesthesia dolorosa is rare. Life-threatening complications occur in less than 1%.

Glycerol gangliolysis

The method was introduced by Håkansson after a fortuitous discovery, during the development of a stereotactic technique for gamma radiation, that glycerol mixed with tantalum powder not only visualized the trigeminal cistern but also abolished pain in patients with trigeminal neuralgia. The first series consisted of 75 patients with a mean follow-up of 18 months. The method was quickly adopted by several centres so that by 1993 over 20 case series had been published describing results in some 2500 patients. The results were rather variable and, in some cases, early enthusiasm was followed by quick disappointment. Several authors have given up the method, either because of poor long-term results or adverse effects while advocates of the procedure point out that, with a proper technique, not only is the procedure well tolerated but yields good long-term results.

The procedure can be done under local anaesthesia in fully awake patients, although mild sedation is usually used. The needle is inserted into the trigeminal cistern through the foramen ovale using similar trajectories as in radiofrequency lesioning and balloon compression. Needle positioning must be precise to ensure the tip lies in the ganglion and not the subarachnoid space beneath the temporal lobe. Free CSF flow is the norm, except in previously treated cases. Fluoroscopic control is mandatory but the use of radio opaque contrast (cisternography) to visualize the cistern varies from centre-to-centre. (Håkansson strongly advises its use.) Once the needle is optimally placed, the patient is brought into a sitting position and a small test dose of sterile anhydrous glycerol injected. This is followed by small dose increments up to a total of 0.1–0.4 ml, depending on the divisions involved. Some authors argue that the patient’s head must be positioned in a specific way to allow the glycerol to reach the intended root. Patients are usually able to perceive the effect of the injection as a tingling or burning sensation in

Fig 4 Lateral radiograph of radiofrequency needle inserted into the gasserian ganglion.
the affected divisions. They remain in the sitting position for 2 h after the injections.

Although pain relief is usually immediate, it may take up to 7 days to occur in some patients. Most authors report initial pain relief in over 80% of their patients but long term results are highly variable. At 12 months, reported recurrence rates vary from 10 to 53%. At 5 yr, 34–83% of the patients will have experienced recurrence of neuralgia. The authors differ in their views on the usefulness of repeat lesioning in case of recurrence. Patients with atypical TGN or painful trigeminal neuropathy are likely to have less favourable results.

This method is generally well tolerated and mortality is negligible. There are anecdotal reports of meningitis, cranial nerve palsies, and local haematomas. Activation of herpes labialis occurs in one third and permanent masseter weakness is seen in a small proportion of patients.

Although sensory change is usually thought to be limited and not necessary for pain relief, Steiger showed that in a series of 122 patients treated with glycerol rhizolysis, post-operative sensory loss was directly correlated with a good long-term outcome. Reports of dysaesthesiae vary from 0 to 44%. This variability may, in part, be a result of many authors including in their series patients previously treated with neuroablative procedures. Keratitis related to corneal sensory loss is reported in most series although it is very rare.

Glycerol rhizolysis has probably caused more controversy than any other procedure with strong views expressed by both proponents and critics. It seems that in centres where this method is commonly used, and the technique meticulously employed, the results are similar to those with other ganglion-level procedures.

Balloon compression

In the 1950s, several groups reported that compression of the ganglion seemed to produce similar, if not better, results compared with the techniques used at the time for root decompression. In 1983, Mullan and Lichtor published their first series of 50 patients who had undergone compression of the trigeminal ganglion using a Fogarty-type balloon. This procedure is performed under general anaesthesia. Using fluoroscopic control, a guide needle is inserted into the foramen ovale, but not beyond it. Through the needle, the Fogarty catheter is advanced until its tip lies in Meckel’s cave and the balloon is slowly inflated with 0.5–1.0 ml of contrast dye until it occupies the cave, ensuring adequate compression (Fig. 5). Total compression times vary from 1–6 min. This produces only a mild sensory loss with immediate pain relief in practically all patients. Interestingly, masseter weakness is very common although, in most cases, there is complete recovery in a matter of weeks. The patient usually only requires an overnight stay.

This method has been used in both typical and atypical TGN, in patients with MS and in those who have had previous neurodestructive procedures (or MVD) for their TGN. Recurrence is reported in 6–14% in the first year. Very few studies employing long-term follow-up are available. In Abdennabi’s series, one-third needed readmission during a mean follow-up of 4.3 yr. Lichtor and Mullan obtained slightly better results in that recurrence was seen in 20% of patients at 5 yr follow-up, and 28% of a small number of patients followed even longer (up to 10 yr). Troublesome dysaesthesia following the procedure are reported in all series. Mullan and Lichter comment on 6% of their patients having significant discomfort from these dysaesthesiae and Fraioli and colleagues indicate that 7% required transient medical treatment for the same problem. In Abdennabi’s series, severe dysaesthesiae were seen in 1.5% and ‘moderate’ dysaesthesiae in a further 15%. Interestingly, 11% of patients were reported to be discontent or very discontent with the outcome. Many had atypical TGN with dysaesthesia possibly as a result of previous surgery and this dysaesthesia was not relieved by balloon compression.

Stereotactic radiosurgery

Well-localized lesions in the trigeminal nerve can be generated also by stereotactic radiosurgery. Some 50 yr ago, Lars Leksell developed a radiosurgical tool, the so-called ‘Gamma Knife’, to treat functional brain disorders as an alternative to open intracranial procedures. Among the first patients he treated were two with TGN. However, it took decades before the technique had been refined and imaging developed sufficiently to allow precision targeting for the procedure. Initial attempts at irradiation of the Gasserian ganglion yielded discouraging results. However, in recent years, the target has been the proximal trigeminal root near the pons, with a much improved outcome.

The Gamma Knife is a focused array of 201 intercepting beams of gamma radiation, produced by separate cobalt sources. A stereotactic frame is first secured to the patient’s head, followed by MRI to identify the trigeminal nerve. Radiosurgery is carried out with the patient supine with the head under the collimator helmet. Local anaesthesia is used for securing the frame and irradiation is frequently carried out under mild oral or i.v. sedation.

The dose used is 70–90 Gy. Pain relief is usually not immediate. The mean time to pain relief in two series was approximately one month. The histopathological effects of radiosurgery on the trigeminal root were investigated in an experiment performed on two male baboons. Six months after radiosurgery at 80 and 100 Gy, focal axonal degeneration and necrosis were observed. This appears to correlate with contrast enhancement seen on MRI months after radiosurgery. No changes in the ganglion were seen.

In 1996, the first systematic study on the use of stereotactic radiosurgery in TGN was published. Although a multicentre study involving 50 patients, it was designed to evaluate various techniques and radiation doses.
Nevertheless, at a median follow-up of 18 months, 58% were pain-free, 36% had significant pain relief, while 6% of procedures were considered to have failed. In two more recent single-centre studies, more favourable results were obtained. Young and colleagues treated 51 patients with TGN with a maximum dose of 70 Gy with excellent immediate effects in 74% and good (pain reduction of more than 50% with or without medication) in 14%. At a mean follow-up of ‘more than a year’ the incidence of excellent, good and failed relief were 70, 10, and 20%, respectively. In a study involving 106 patients with radiosurgery doses ranging from 70 to 90 Gy, the long-term (median 18 months, range 6–48 months) results were excellent (no pain) 60%, good (50–90% pain reduction) 17%, and poor (less than 50% pain reduction) 24%. In this latter group, only 22 patients had not had previous surgery. The majority had undergone either radiofrequency or glycerol gangliolysis while one-third had undergone MVD. In both studies, side effects were minimal. Facial paraesthesiae were reported in 10%.

This method seems a valuable addition to the existing treatments as it is very patient-friendly and safe. However, as yet, long-term results are lacking and it is not clear which of the other methods can be applied in case of recurrence. Currently, the limiting factor for this treatment is the small number of centres capable of providing this service.

Peripheral neurectomy
Neurectomies of the affected branches were attempted for the first time in the 18th century with variable success. Mainly employed by present day maxillofacial surgeons, the technique is too under-reported to allow evaluation of its usefulness against other treatments. Khanna and Galinde described a successful outcome at 1–5 yr follow-up in 75% of 118 patients who underwent several neurectomies while Mason achieved a success rate of 64% at 12 months and 26% at 4 yr. In a subgroup of 11 patients who had infra-orbital neurectomy followed by occlusion of the canal, seven were pain-free at 4 yr. However, he makes a point that, in this retrospective analysis, careful selection of patients was employed conforming to the strictest of TGN criteria. Recently, a small retrospective series was published on 40 patients with typical TGN who underwent this procedure. The majority had previously undergone radiofrequency lesioning. At a follow-up of 24 months, six (15%) had experienced a recurrence; these were treated successfully with repeat neurectomies. Surprisingly, none of the above authors discuss adverse effects at all.

By contrast, Danish investigators found that, during a mean follow-up of 7 yr, 78% of patients who had undergone neurectomy experienced a recurrence. One-half of the patients had their first recurrence within a month. In their series, neurectomy (as well as alcohol block) compared unfavourably with radiofrequency lesioning. Complications (mainly eye problems and dysesthesiae) were reported in just under 10%, similar to those who had undergone radiofrequency lesioning or alcohol blocks.

Neurectomies are performed through an incision made at the eyebrow (supra-orbital nerve) or intraorally (infra-orbital, alveolar and lingual nerves). All branches are divided and avulsed under magnification. The relevant foramen is blocked by bone wax, wooden sticks or silicone plugs. The remnant of the nerve may also be cauterized. Despite these efforts, remnants may be found on re exploration and dealing with them in the same way is said to lead to pain relief.

From the existing scarce literature, it cannot be concluded how this procedure sits on the map of TGN management. It does not appear to offer any benefit over other well established surgical procedures, but it may be useful in cases where other treatments have failed and the patient or doctor are reluctant to consider procedures aimed at the ganglion or root.

Cryotherapy
Cryotherapy is a surgical technique in which a peripheral branch of the three major divisions of the trigeminal nerve is exposed and frozen by direct application of a cryoprobe with a tip temperature from −50 to −70°C. The patient requires i.v. sedation or general anaesthesia. Although well tolerated by patients, the results are modest. Of 145 patients who underwent 1–11 sessions of cryotherapy (56% had more than one session), the effect lasted less than 6 months in one half and at 12 months, only 27% were pain-free. Perhaps because of the peripheral approach, the pain broke through in another nerve, requiring a repeat procedure. Almost two-thirds had to remain on their previous medica-
tion. Although improvement in individual nerves was better, from the pain point of view, cryosurgery falls short of results obtained either with procedures aimed at the ganglion or the root.

Some 4% of patients develop post-operative local infection requiring treatment with antibiotics. Frank dysesthesiae are not common but a sizable proportion of patients, (40%) describe a facial pain which—according to the authors—‘does not have the characteristics of TGN or anaesthesia dolorosa’. As in the case of neurectomy, we find little reason to advocate the use of this method except in circumstances where more sophisticated surgical or radiation treatments cannot be carried out.

Alcohol block
Peripheral and ganglionic alcohol blocks have been used since the beginning of the last century but have fallen into disrepute within the neurosurgical and neurological community, mainly because of capricious results and reports of adverse effects. Those still employing the technique underline its simplicity and the fact that results are similar to other peripheral ablative procedures. Unfortunately, there is little documentation on the sensory aftermaths of this procedure. In a retrospective analysis of 45 patients treated with one or several alcohol blocks, 84% of patients had a recurrence of pain during the mean follow-up of 8 yr. One-half had a recurrence within a month. As an aftermath, eye problems and dysesthesiae were reported by 5–8%. In a report of 413 alcohol blocks performed on 82 patients over a period of 22 yr, ‘serious’ complications were reported in three patients only (cutaneous necrosis, development of bony sequestrum, diplopia). Other complications include facial nerve palsy and loss of vision.

Alcohol injections must be administered directly into the nerve and they are painful and cause local oedema. In our view, the high risk of recurrence of pain combined with a moderate risk of dysesthetic and other complications exclude this procedure from routine use, except in frail or medically unfit patients, or those who refuse more extensive surgery.

Other peripherally targeted procedures
Other methods of producing controlled peripheral neural trauma include radiofrequency lesions and injections using glycerol, phenol, high concentration tetracaine or a mixture of lignocaine and streptomycin. In all, the average reported pain relief is measured in months and many of these methods are associated with a high number of initial failures. From the existing literature, it is difficult to draw conclusions as to their true efficacy, but it is doubtful whether they ever provide long-lasting benefit. Authors advocating the use of these measures frequently quote failure rates or complications from other, more invasive treatments that do not accurately reflect the current literature.

Pharmacotherapy
In general agreement, pharmacotherapy remains the mainstay of treatment of TGN despite the fact that only few randomized controlled trials have been conducted. Carbamazepine has been compared with placebo in three separate studies, involving a total of 151 patients with a good initial effect in approximately 70%. The NNT (number-needed-to-treat) for effective pain control (>50% pain relief compared with placebo) from these three studies is 2.6, while NNH (number-needed-to-harm; i.e., adverse effects in excess to those seen with placebo) is about 3.4. These studies, and its subsequent wide-spread use in TGN, made carbamazepine something of a gold standard against which other drugs have been compared in subsequent controlled trials. These drugs include tizanidine, baclofen,
pimozide, tocainade, and oxcarbazepine. While none have been shown to be superior to carbamazepine, the small number of patients evaluated in individual trials (usually less than 20) precludes firm judgement in this regard. Table 4 lists the drugs most commonly used in this condition.

Baclofen alone seems to have a moderate effect on TGN only, and its long-term efficacy remains in doubt. One weak study suggests that clonazepam is of value but, in our hands, it has been disappointing as most patients with good initial response quickly recognize that the effect is lost. Anecdotally, several patients have been treated by ourselves with the combination of carbamazepine or lamotrigine and gabapentin. Doses needed are usually in the low-to-moderate range (carbamazepine 400–800 mg day\(^{-1}\); lamotrigine 200–400 mg day\(^{-1}\); gabapentin 900–1200 mg day\(^{-1}\)), which are usually well tolerated by patients, and preferred to monotherapy with high doses of carbamazepine alone.

Using these drugs requires a good understanding of their pharmacokinetics, metabolism, and interactions. There are several good reviews available.

### Which treatment to choose first?

With considerable amount of information about TGN readily available, many patients and their relatives are keen to consider surgery as first-line treatment, in anticipation of a permanent cure. It is, therefore, imperative for the doctor to have an understanding of the relative efficacy of various treatments, including complications and recurrence rates. Our policy is to view requests of early surgical treatment with sympathy, even if the patient responds well to pharmacotherapy, but to ensure that he has a realistic view of what it entails.

Table 5 summarizes our current thinking with respect to preferred treatments in individual cases. We emphasize that it reflects only our experience and conclusions we have drawn from the often conflicting literature. As long as there is no evidence-based medicine to guide treatment choice, the doctor will have to combine theory with clinical experience in as balanced a way as possible.

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