

TRIGEMINAL NEURALGIA: PATHOPHYSIOLOGY AND TREATMENT

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ABSTRACT

Trigeminal neuralgia is a very peculiar disease. The pain, also known as “tic douloureux”, is paroxysmic and very severe. It can be triggered by a light cutaneous stimulus on a very localized spot on the face (the so-called “trigger zone”). The patient can sometimes benefit from long remissions without any treatment. With the exception of multiple sclerosis and of uncommon cases of posterior fossa tumours or other lesions impinging on the trigeminal nerve, ganglion or root, trigeminal neuralgia is considered as “idiopathic”. Some benign abnormality had for long been suspected. The current opinion is now in favour of a “neurovascular conflict”: an artery, most often a loop of the superior or anteroinferior cerebellar artery, has an offending contact with the trigeminal nerve root, which results in localized demyelination and ectopic triggering of neuronal discharges. This hypothesis is in agreement with the relief provided by antiepileptic drugs and is supported by recent neuroimaging data. Therapeutic options are reviewed: very efficient drugs are available but fail to provide a significant relief and/or have important side effects in many cases. Surgical alternatives are available, for which guidelines are proposed.

KEYWORDS: Trigeminal neuralgia; pathophysiology; treatment; neurosurgery; radiosurgery.**INTRODUCTION**

Among neuropathic pains trigeminal neuralgia (TN) has a peculiar profile. It is not accompanied by sensory deficit, at least as we can judge by careful clinical examination. Spontaneous remissions are not unusual. TN can be cured by a small nerve or root lesion, whereas such lesions are ineffective, or even worsen the symptoms in many other neuropathic pains. With the exception of a few identified organic causes, its etiology for long remained uncertain, so it was called “idiopathic” neuralgia. Even now, with the sound hypothesis of neurovascular conflict (NVC), the pathophysiology of this disease still has obscure corners.

Clinical definition and diagnostic criteria

TN is characterized by brief paroxysms of pain, limited to the facial distribution of the trigeminal nerve and precipitated by stimuli to sensory endings in the trigeminal receptive area (Kugelberg and Lindblom, 1959). The presence of these “trigger-zones” leads the patient to avoid any stimulation of the face or mouth. The diagnostic criteria of the International Headache Society (IHS) (1988) are as follows.

- Paroxysmal attacks of facial pain which last a few seconds to less than two minutes.
- Pain has at least 4 of the following characteristics: (1) distribution along one or more divisions of the trigeminal nerve, (2) sudden, intense, sharp, superficial, stabbing or burning in quality, (3) pain intensity is severe, (4) precipitation from trigger

areas, or by certain activities such as eating, talking, washing the teeth or cleaning the face, (5) between paroxysms the patient is entirely asymptomatic.

- Attacks are stereotyped in the individual patient.
- No neurological deficit and exclusion of other causes.

Differential diagnosis

Pain resembling TN can be the consequence of a variety of tumours and other lesions involving, or impinging on, the trigeminal nerve, ganglion or sensory root: tumours of the cerebellopontine recess, of the middle fossa, of the cranium or extracranial tissues (often metastatic), and from the envelopes of the Gasser ganglion.

These neuralgias can usually be differentiated: a paroxysm of pain last longer, pain tends to be constant, neurologic deficit is often detected (cutaneous hypoesthesia, loss of corneal reflex, masticatory muscle weakness).

Epidemiology

Few data are available. Incidence rate of TN is about 3 to 5 cases/year/100.000 persons (Katusik *et al.*, 1990; Rothman and Monson, 1973). Prevalence has been estimated at 107.5 men and 200.2 women/1 million populations (Penman, 1968). Risk factors have been investigated: multiple sclerosis is well known but additional risk factors are not confirmed (Kitt *et al.*, 2000).

Is TN a neuropathic pain?

Considering painful conditions resulting from lesions of the trigeminal nerve, several diseases appear to be the cause of persistent pain. Among these conditions, we find postherpetic neuralgia, post-traumatic and post-surgical neuropathic pain, and anesthesia dolorosa. TN itself is known either as “idiopathic” TN or “symptomatic” TN (see differential diagnosis). These observations have led to a “continuous spectrum” hypothesis: from typical TN to atypical TN (TN-like pain but with sensory deficit) and finally to trigeminal neuropathic pain in cases of established nerve injury (Burchiel, 2000). As far as typical TN is concerned, *clinical evidence* in favour of a neuropathic pain is lacking. Routine clinical examination is normal and this is one of the IHS diagnostic criteria. Moreover, no disturbance could be found in a careful quantitative sensory examination of TN patients (Hampf *et al.*, 1990). *Pathological evidence* has however been found, such as focal demyelination at the root entry zone (Beaver, 1967; Kerr, 1967), as well as *neurophysiological evidence* (Burchiel, 1993).

Pathophysiology: central cause versus peripheral cause

In favour of a peripheral cause, we can point the following arguments:

- Space-occupying lesions, even distant from the nerve but distorting it, can provoke typical TN ;
- Microvascular compression (distortion) of the trigeminal root as a cause of “idiopathic” TN is now well documented;
- Pathologic findings in patients with TN : vacuolated ganglion cells, segmental demyelination, juxtaposition of denuded axons;
- It is well recognized that damaged nerves can be the source of pain, which is attributed to several possible mechanisms: hyperexcitability of demyelinated nerve fibers, ectopic impulse generation and cross-talk between sensory channels, deafferentation and impaired segmental inhibition (Burchiel, 1980; Sessle, 1991; Rappaport, 1994).

In favour of a central cause, we have to consider the following observations

- Typical TN can be due to multiple sclerosis ;
- Physiological observations on patients suffering from TN point to central mechanisms : spatial and temporal summation of the effects of stimulus, tendency of the attack to be self-maintained, refractory period after an attack, efficacy of antiepileptic drugs (Kugelberg and Lindblom, 1959);
- Experimental “models” of TN: application of certain substances into the trigeminal nucleus caudalis produces hypersensitivity of the face that resembles the TN trigger zone (King *et al.*, 1956; Black, 1974; Sakai *et al.*, 1979). A valid experimental model of TN is however still lacking.

According to present opinion, both could be true; TN may have a peripheral cause and a central pathogenesis (Fromm *et al.*, 1984). The most frequent cause appears to be chronic “irritation” of the nerve root. This leads to a sequence of neuronal (central) events producing paroxysms of pain.

Interestingly, two rare conditions producing similar pains, glossopharyngeal neuralgia and nervus intermedius neuralgia, and the abnormal motor discharges of hemifacial spasm, are believed to be associated with vascular compression of the nerve root. Tinnitus or “hyperactive dysfunction” of the eighth cranial nerve is also suspected to be caused by a neurovascular conflict.

Is neurovascular compression the main cause of “idiopathic” trigeminal neuralgia?

The early hypothesis of Dandy (1934) has been confirmed by modern neurosurgery.

As stressed by Moller (1991), there is a wide disparity in the proportion of patients with TN (or hemifacial spasm) in whom a blood vessel is identified as causing nerve compression. This disparity “seems to be related more to a particular surgeon than to the type of disease in question”!

We now have the help of preoperative magnetic resonance imaging (MRI). High resolution MRI is indeed able to demonstrate a neurovascular conflict (NVC) in nearly all cases of “idiopathic” TN. Although MRI also reveals neurovascular contact in about 6 to 32% of nerves in asymptomatic controls (Majoie *et al.*, 1997), the criteria of a significant conflict are now recognized: an *artery* (not a vein), *crossing* (not parallel to) the nerve and provoking *displacement/grooving* of it (Casselmann, 2000).

A comparison of MRI data with surgical findings (Meany *et al.*, 1995) on 50 consecutive patients with TN (among which 5 cases of bilateral neuralgia) shows full agreement regarding the presence or absence of NVC in 50/52 surgical explorations. Venous compression was found in 4 cases. MRI diagnosis of vascular compression of the nerve had been made in 42/45 unilateral cases and in 4/5 bilateral cases.

Treatment options

As in other fields of medicine, a *mechanismbased* treatment should be favoured. The neurosurgeon provides pain relief by alleviating an “offending contact” with the nerve. The neurologist stops epileptiform discharges in trigeminal nuclei by giving antiepileptic drugs.

History of TN is however characterized by many *symptom-based* treatments: peripheral nerve section or neurolytic blocs (alcohol), a variety of physical agents have been used to provoke a (hopefully) minimal

damage to the trigeminal ganglion or root, and surgical rhizotomy has also been proposed (summarized in Gybels and Sweet, 1989).

Medical treatment: carbamazepine (CBZ) remains the drug of first choice. Treatment begins with 100 to 200 mg two or three times daily. Doses should be increased very progressively and titrated to the severity of the patient's pain. Serum level is a useful way of monitoring treatment (6 to 12.5 µg/ml). In some cases a maintenance dosage of 200 mg or 400 mg per day is sufficient to keep the patient pain-free. With appropriate adjustments of dosage, pain can be controlled initially in about 75% of patients. *Side effects* of CBZ are not negligible: hypersensitivity reactions, drowsiness, decreased mental acuity, ataxia (in older patients), dose-related leucopenia.

If paroxysms of pain still occur with therapeutic blood levels, another drug should be added: baclofen or phenytoin. Other drugs, including sodium valproate, gabapentin, lamotrigine, and clonazepam, have been tried but formal conclusive studies are still lacking. Lamotrigine has recently been validated for refractory trigeminal neuralgia, especially in TN due to multiple sclerosis, with doses between 100 and 400 mg daily (Leandri *et al.*, 2000).

Surgical treatment: If a patient does not obtain relief from pain with medical treatment, some form of surgery will be proposed. It is estimated that up to 50% of the patients will sooner or later be in that situation (Taylor, 1981). Historically, many operations have been proposed, more or less invasive. Among invasive procedures, we find operations aimed at lesioning nerve fibers or ganglion cells (peripheral nerve section, ganglionectomy, rhizotomy), and a non-destructive operation aimed at relieving the nerve root from an offending contact ("decompression"). In order to reduce the risk, percutaneous approaches have been developed, using chemical or physical agents to impair transmission of impulses in the trigeminal pathway while avoiding major loss of function. Among these percutaneous procedures we find differential thermal rhizotomy, glycerol rhizotomy and compression of Gasser ganglion by a balloon (so-called "microcompression"). More recently, gamma rays have been used to make a sharply focalised lesion of the trigeminal nerve root by means of a stereotactic technique.

The open neurosurgical approach is however still in the race. Destructive procedures have been abandoned. Partial sensory rhizotomy, dorsal root entry zone (DREZ) lesions, and trigeminal tractotomy have few indications and will not be discussed here. Microvascular decompression (MVD) has become the main surgical treatment for TN.

PERCUTANEOUS PROCEDURES

- Differential thermal rhizolysis (Sweet and Wepsic, 1974)

- Retrogasserian glycerol rhizolysis (Hakanson, 1981)
- Trigeminal ganglion compression (Mullan and Lichtor, 1983 ; Meglio & Cioni, 1987)

All of these procedures are performed as outpatient surgery with minimal anesthetic risk, are particularly well suited for elderly or ill patients, and have relative advantages and disadvantages.

Main features of **radiofrequency thermal rhizolysis** are as follows (after Gybels and Sweet, 1989):

- 96 – 100% of patients have early pain relief
- Selectivity (based on electrophysiological control in a cooperative patient) ; this means that the degree of sensory loss provoked by the RF lesion can be progressively increased in a controlled manner and that the lesion can be focalized to the painful area.
- follow-up range : 1 – 21 years (n = 6,543 from 10 centers):

Recurrence rate

- ❖ not requiring reoperation : 4 – 9%
- ❖ requiring reoperation : 7 – 31% (21% on 1000 patients at 5.5 – 8 years, 31% on 1119 patients at 21 years)
- ❖ Complications: sensory loss in proportion to lesion temperature: dysesthesia in 5 to 24 % of cases, anesthesia in 0.2 to 8 %, keratitis in 0.4 to 3 %.
- Prospective studies have been published these last years (Taha *et al.*, 1995; Zakrzewska *et al.*, 1999). The mean time to recurrence in the group of 31 TN patients of Zakrzewska was 40 months.

In our own experience on the last 200 cases (1990 – 1999) using a 22-gauge electrode and lesion temperature under 65°C in most of the cases, recurrence rate is about 20% at five years and complications are rare : anesthesia, limited to one trigeminal division, is observed in less than 2% and keratitis in 0%.

Main features of **glycerol injection** (after Burchiel and Moore, 1998):

- pain relief is achieved within 48 hours in 72 to 96% of patients
- technical failure rate as high as 15%
- no selectivity
- recurrence rate at 1 year: 27%; mean time to recurrence : 16 – 36 months
- Complications: same as those of other percutaneous procedures.

Main features of **microcompression of the trigeminal ganglion** (after Burchiel and Moore, 1998):

- easy to perform (cooperation of the patient is not needed) but the 14-gauge needle may be difficult to cannulate through the foramen ovale
- 90% to 100% of patients have immediate pain relief
- no selectivity (but ophtalmic fibers are usually spared)

- recurrence is widely variable, from 30% at 10 years (Mullan and Lichtor, 1990) to 55% - 77% at 3 years (Meglio *et al.*, 1989)
- Complications: same as those of other percutaneous procedures.

RADIOSURGERY (“GAMMA-KNIFE”)

Stereotactic radiosurgery under local anesthesia has been used to treat patients with recurrent TN after medical or surgical management (Kondziolka *et al.*, 1996), and as first surgery with good results and few complications (Kondziolka *et al.*, 1998; Régis *et al.*, 2000). Many other publications appeared in the literature since 1996.

Several questions need further evaluation: what is the best target (dorsal root entry zone? retrogasserian portion the root?), what is the best dose (reported doses go from 40-45 Gy to 75-90 Gy) and how does GK compare to other techniques?

Régis *et al.* (2000) report better results and less side-effects with a target closer to the retrogasserian portion of the root and a higher range of doses (75-90 Gy), and this is the technique we are now currently using in our hospital.

OPEN SURGERY

As stated before, Dandy (1934) and Gardner and Miklos (1959) developed the hypothesis, based on their peroperative observations, that TN could be due to a mechanical compression or irritation of the nerve root. This compression could result from an artery, sometimes also from a vein, and sometimes from another lesion like an arteriovenous malformation or a tumour. On this basis, Jannetta (1967), using a binocular dissecting microscope, developed the technique of microvascular decompression (MVD), which became a widely applied procedure for TN.

MAIN FEATURES OF MVD

Reports from neurosurgical teams in different countries can be found in the literature.

Long term outcome of MVD has been published, among others by Barker *et al.* (1996), in the group of Jannetta, on an impressive number of patients (1185) during a 20-year study period. The mean follow-up time was 6.2 years. The rate of immediate pain relief is 70%. Most recurrences took place within the first 2 years after surgery. 30% of patients had recurrence during the study period (11% needed a second operation). Ten years after surgery, 70% were still free of pain without medication. Major complications were 2 deaths (0.2%), 1 brainstem infarct (0.1%) and 16 ipsilateral hearing loss (1.3%).

Results from other groups are more or less similar and detailed comparisons would be too long and not very pertinent considering the differences in the follow-up duration, rates of identified NVC *in vivo*, nature of offending vessel, “decompression” technique applied, and definition of recurrence (needing medication or not,

needing reintervention or not). The rate of reported immediate pain relief is often about 80% but can be higher. Recurrence rate is rather consistent; Burchiel *et al.* (1988) e.g. report a rate of about 6% at 60 months and of 42% (including minor and major recurrences) at 100 months.

Mortality varies among different series between 0.2 and 1%, hearing loss between 1.3 and 2%. Significant trigeminal sensory loss is close to 0%.

Management of drug-resistant trigeminal neuralgia

The best option in drug-resistant TN remains to be found. As described before, several techniques are currently used in clinical practice. There are no randomized controlled trials to guide comparisons between the surgical options available. If we want to favour a “mechanism-based treatment”, MVD would be the first choice, especially since we can rely on high resolution MRI. It should however be kept in mind that this treatment implies a small craniotomy and a deep general anesthesia.

The clinical situation can dissuade the neurosurgeon from doing a MVD, mainly in two circumstances.

1. high resolution MRI either does not show a significant NVC or discloses another etiology,
2. the risk of a surgical procedure under general anesthesia is too high considering age and/or medical condition of the patient.

In these situations (we put the age limit at 60-65 years), a percutaneous procedure should be proposed. In our experience, two techniques have demonstrated their validity and low risk: radiofrequency thermal rhizotomy (RF) and more recently radiosurgery (GK).

The advantages of RF are its selectivity and high rate of immediate pain relief. With a careful control of the lesion temperature, its unwanted effects like sensory disturbances are minimal. It is safer in V3 and V2 TN because of the risk of corneal anesthesia when the ophthalmic fibers are lesioned. It is considered as the most appropriate treatment in TN due to multiple sclerosis.

- GK has a very low rate of complications. It is a painless procedure, not directly “invasive” and not requiring patient cooperation during the procedure. Its relative merits will be appreciated after controlled and comparative studies with sufficient follow-up. It should be kept in mind that it is a very sophisticated and expensive technique not available in many hospitals, and not at all in many countries.

CONCLUSION

The pathophysiology of trigeminal neuralgia is now better understood. Neurovascular conflict is recognized as the main cause of “idiopathic” trigeminal neuralgia. Other uncommon causes are recognized as well. Medical

treatment remains the first step and we can rely on very efficient drugs. However, these drugs are not devoid of side-effects and often lose their efficacy with time. Some form of surgery will then be proposed, and an amazing number of procedures have been developed. It seems that any kind of light physical damage to the trigeminal nerve fibers is able to stop the triggering of paroxysms of pain. This should incite us to choose the less invasive techniques, sparing sensory and motor trigeminal functions.

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