

Trigeminal neuralgia and persistent idiopathic facial pain

A neuralgia do trigêmeo e a dor facial persistente idiopática

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ABSTRACT

Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are two of the most puzzling orofacial pain conditions and affected patients often are very difficult to treat. TN is characterized by paroxysms of brief but crucial pain, followed by asymptomatic periods without pain. In some patients a constant dull background pain may persist. This constant dull pain sometimes makes the distinction from PIFP difficult. PIFP is defined as continuous facial pain, typically localized in a circumscribed area of the face, which is not accompanied by any neurological or other lesion identified by clinical examination or clinical investigations. The pain usually does not stay within the usual anatomic boundaries of the trigeminal nerve distribution and is a diagnosis of exclusion. Epidemiologic evidence on TN and even more so on PIFP is quite scarce, but generally both conditions are considered to be rare diseases. The aetiology and underlying pathophysiology of TN and more so PIFP remain unknown. Treatment is based on only few randomized controlled clinical trials and insufficiently evaluated surgical procedures.

Keywords: Trigeminal neuralgia; Persistent idiopathic facial pain; Atypical facial pain; Pathophysiology; Treatment; Differential diagnosis

RESUMO

A neuralgia do trigêmeo (NT) e a dor facial persistente idiopática (DFPI) são duas das mais intrigantes condições dolorosas orofaciais, e os pacientes afetados são, frequentemente, muito difíceis de tratar. A NT é caracterizada por paroxismos de dor breve mas excruciante, seguidos por períodos assintomáticos sem dor. Em alguns pacientes, uma dor de fundo maçante e constante pode persistir. Esta torna

difícil, às vezes, distinguir a NT da DFPI. A DFPI é definida como uma dor facial contínua, localizada tipicamente em uma região circunscrita da face e que não é acompanhada por qualquer lesão – neurológica ou de outra natureza – identificada através do exame clínico ou de investigação complementar. A dor geralmente não permanece restrita aos limites anatômicos da distribuição do nervo trigêmeo e é um diagnóstico de exclusão. Evidências epidemiológicas sobre a NT, e ainda mais sobre a DFPI, são bastante escassas, mas usualmente ambas condições são consideradas doenças raras. A etiologia e a fisiopatologia da NT e, mais ainda, da DFPI, permanecem desconhecidas. O tratamento é baseado em apenas uns poucos ensaios clínicos randomizados e controlados e em procedimentos cirúrgicos insuficientemente avaliados.

Descritores: Neuralgia do trigêmeo; Dor facial persistente idiopática; Dor facial atípica; Fisiopatologia; Tratamento; Diagnóstico diferencial

INTRODUCTION

The prevalence of orofacial pain in the general population was estimated between 17%-26% with 7%-11% of those patients having been considered as presenting a chronic condition.⁽¹⁾ The disorders that are often summarized as orofacial pain are quite heterogeneous and include acute and chronic pain syndromes that often show a considerable overlap in

clinical presentation or present with atypical features. This makes the differential diagnosis very difficult sometimes. Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are two of the most common forms of orofacial pain assessed and treated by neurologists and pain specialists.⁽²⁾

DEFINITION AND CLINICAL PRESENTATION OF TRIGEMINAL NEURALGIA

Trigeminal neuralgia (TN) is defined by the International Headache Society (IHS) as "unilateral disorder characterized by brief electric shock-like pains, abrupt in onset and termination, and limited to the distribution of one or more divisions of the trigeminal nerve".⁽³⁾ The IHS recommends the classification of TN in classical (essential or idiopathic) TN and symptomatic TN ("pain indistinguishable from that of classical TN, but caused by a demonstrable structural lesion other than vascular compression").⁽³⁾ The absence of clinically evident neurological deficit is required for the diagnosis of classical TN. It generally starts in the second or third divisions of the trigeminal nerve, affecting the cheek or the chin.⁽³⁾ The ophthalmic division alone is involved in less than 5% of cases.⁽⁴⁾ A typical TN attack lasts between less than a second and a few seconds, but it may present in clusters of variable intensity with up to two minutes duration. In many cases it is followed by a brief refractory period during which a new stimulation is not able to evoke another attack. Between paroxysms the patient is usually pain free, but a dull background pain may persist in some cases.⁽³⁾ The mechanisms associated with the development of this persistent pain are not well understood but concomitant background pain is associated with poor medical and surgical outcome.⁽⁵⁻⁷⁾

DEFINITION AND CLINICAL PRESENTATION OF PERSISTENT IDIOPATHIC FACIAL PAIN

Persistent idiopathic facial pain (PIFP) was previously termed atypical facial pain and was first introduced by neurosurgeons in the 1920s as a distinct clinical entity.⁽⁸⁾ The IHS defined it, as "a persistent facial pain that does not have the characteristics of cranial neuralgias, presents daily and persists for all or most of the day. The pain is confined at onset to a limited area on one side of the face and is deep and poorly localized".⁽³⁾ Common sites of onset are the nasolabial fold or the side of the chin. It may spread to the upper or lower jaw or a wider area of

the face and neck, not following specific peripheral neuroanatomic distributions. It is most often felt unilaterally, but over time, in about one-third of patients the pain becomes bilateral. The pain is often initiated by minor surgery or injury to the face, teeth or gums, but persists without any demonstrable cause.⁽³⁾ Sensory loss or other physical signs are not present and clinical investigations are usually unremarkable. The diagnosis of PIFP is one of exclusion and should be made only after local orofacial disease, neurologic disorders, and related systemic diseases are ruled out.⁽⁹⁾ The IHS added a comment on their classification that a facial pain located in the area of the ear or temple may be associated with undiagnosed lung cancer causing referred pain as a result of vagal nerve involvement.⁽³⁾

EPIDEMIOLOGY OF TRIGEMINAL NEURALGIA

TN is the most common form of cranial neuralgias with an incidence of 4.3 per 100,000 persons per year, with a slightly higher incidence for women (5.9/100,000) compared to men (3.4/100,000).⁽¹⁰⁾ The gender ratio women to men is approximately 2:1.⁽¹¹⁾ The prevalence of this relatively rare disorder has been reported to be 15.5 cases per 100,000 in the United Kingdom.⁽¹²⁾ In Germany the prevalence of TN is prevalence of 0.3% of the general population.⁽¹³⁾ Sjaastad et al. (2007) found only two patients out of 1838 to fit the diagnostic criteria for TN (0.1%) in a large Norwegian epidemiological study (Vågå-Study).⁽¹⁴⁾ TN can first appear at any age, but disease onset is after the age of 40 years in over 90% of cases. The peak age is between the ages of 50 to 60 years.⁽¹²⁾ The right side of the face is more often involved than the left.⁽¹⁵⁾ About 2% of the patients with MS complain about symptoms identical to those of TN.⁽¹⁴⁾ TN seldomly affects more than one member of the family, but increased risk was reported in patients living in the same household, suggesting disease associated environmental factors.^(16,17)

EPIDEMIOLOGY OF PERSISTENT IDIOPATHIC FACIAL PAIN

PIFP prevalence remains largely unclear. In general, orofacial pain is considered to be a common problem affecting between 17%-26% of the adult population with increasing prevalence corresponding to increasing age.⁽¹⁸⁾ Approximately 7%-11% of patients have chronic facial pain in this regard.⁽¹⁹⁾ Atypical odontalgia, often

considered a subtype of PIFP and defined as a continuous pain in the teeth or in a tooth socket after extraction in the absence of any identifiable dental cause, occurs in 3%-6% of patients that undergo endodontic treatment.⁽²⁰⁾ A large population based sample reported the prevalence of PIFP in the general population in Germany at 0.03% [95% CI < 0.08%].⁽¹³⁾ The incidence was estimated at one patient out of 100,000 in PIFP but the authors proposed that there might be a huge underestimation of PIFP in their large patient population due to the lack of diagnostic reconfirmation tests.⁽²¹⁾ A gender ratio of women compared to men of 2:1 was reported and female hormones were suggested as a risk factor for the development of PIFP.⁽²²⁾

AETIOLOGY AND PATHOPHYSIOLOGY OF TRIGEMINAL NEURALGIA

Current opinion is that TN is caused by a proximal compression of the trigeminal nerve root close to the brainstem (root entry zone) by a tortuous or ectatic blood vessel (artery or vein) leading to mechanical twist of nerve fibers and secondary demyelination, probably mediated by microvascular ischemic damages.⁽²³⁾ These changes lower the excitability threshold of affected fibers and promote inappropriate ephaptic propagation towards adjacent fibers.⁽²⁴⁾ Thus, tactile signals coming from the fast myelinated (A-beta) fibers can directly activate the slow nociceptive (A-delta) fibers resulting in the high-frequency discharges characteristic for TN. After a few seconds these repetitive discharges spontaneously run out and are followed by a brief period of inactivity that resembles the refractory period observed clinically.⁽²⁾ Demyelination and remyelination processes within the root entry zone (i.e., 6 mm of central myelin from the brainstem; Obersteiner-Redlich line = transition of central to peripheral myelin of the trigeminal nerve) observed in electronic microscopy studies might provide one explanation for the periodicity of the syndrome.^(25,26) Spontaneous remission of at least 6 months were described in 50% of the cases and remissions of over one year in 25%.⁽²⁷⁾ Marinkovic et al. (2007) described trigeminal vascular pathology with immunoreactivity in TN patients suggesting a more local concentrated pathological origin of disease.⁽²³⁾ A recent diffusion tensor imaging (DTI) study showed a reduced fractional anisotropy (FA) of the trigeminal nerve in six patients with TN on the affected side confirming tissue damage associated with demyelination likely due to compression.⁽²⁸⁾

While Jannetta et al. (1967) described 88% of their investigated patients to have a nerve vessel conflict, 6% had MS and 6% showed a cerebellar-pontine angle tumour,⁽²⁹⁾ more recent investigations demonstrated that not all patients that were considered classical TN did have a nerve vessel conflict (usually the superior cerebellar artery) and that at least 25% of people without any clinical signs of TN did show a nerve artery contact on magnetic-resonance imaging (angio-3D-TOF).⁽³⁰⁾ A different study showed that out of 220 investigated trigeminal nerves 110 (49%; 51 women, 57 men) came into contact with some vasculature on routine MRI performed for different reasons.⁽³¹⁾ The quick pain relief following microvascular decompression surgery in 90% of patients is a strong indicator for the relevance of this mechanism, but lacks explanation as to why a large percentage of patients experience recurrence of their complaints.⁽³²⁾ It was suggested that hyperexcitability of the compressed nerve is necessary but alone insufficient to cause the disease, so that a nerve-vessel conflict may represent a risk factor for the development of TN.⁽³³⁾ Possible involvement of central factors come more and more into focus of current research, suggesting a central facilitation and resulting hyperexcitability of the trigeminal system sustained by peripheral as well as central mechanisms.⁽³⁴⁾ Sensitisation of second order wide dynamic range (WDR) neurons in lamina V of the dorsal horns and the trigeminal nerve nuclei due to hypersensitivity of tactile A-beta fibers were discussed as additional pathophysiological mechanism. Since these WDR neurons receive convergent information from tactile (A-beta) and nociceptive (A-delta and C) fibers, their sensitization could facilitate nociceptive input while promoting the perception of pain in response to tactile stimuli (i.e., allodynia, trigger factors). Central facilitation was recently demonstrated in TN patients with additional constant dull background pain besides their typical TN attacks using pain-related evoked potentials (PREP) and nociceptive blink reflex (nBR).⁽⁶⁾ This provides strong evidence for the involvement of supraspinal structures in TN. Borsook et al. (2007) reported increased fMRI activation of a single TN patient in the primary somatosensory cortex, insula, anterior cingulate, and thalamus to further support supraspinal involvement.⁽³⁵⁾ Whether supraspinal facilitation is part of the underlying cause of TN or merely a consequence of the disease will need further research. While concomitant constant pain is a predictor for poor surgical and medical outcome it is probably not due to progressing disease or illness duration as it is frequently observed in patients with

average disease duration.^(6,34) It might be regarded as disease variant.

AETIOLOGY AND PATHOPHYSIOLOGY OF PERSISTENT IDIOPATHIC FACIAL PAIN

The aetiology and pathophysiology of PIFP is not as well understood. Surgery or injury in the distribution of the trigeminal nerve was suggested as the initiating event as many patients attribute their pain to an antecedent event such as dental procedure/ extraction or other minor trauma to the face.⁽³⁶⁾ PIFP could represent a neuropathic pain condition. It was suggested, that the pain may be a consequence of deafferentation and long term neuroplastic changes initiated by the frequently occurring minor injuries of afferent trigeminal nerve fibers explaining the suggested peripheral as well as central component of this complex disease.⁽²⁾

For many years, a psychogenic origin of PIFP was assumed mainly based on the often observed psychiatric comorbidities presented by patients such as depression and anxiety disorders.⁽³⁷⁾ The prevalence of psychiatric disorders in fact was shown to be increased with up to 30% of PIFP patients suffering from anxiety disorders, 16% from affective disorders, 15% from somatoform disorders, and 6% with psychosis.⁽³⁸⁾ This pure psychological concept is disputed more and more recently with emerging evidence of measurable neurobiological correlates for the patients' complaints that are similar to other chronic pain conditions. A recent imaging study showed structural brain changes in regions well known to be associated with central pain processing.⁽³⁹⁾ A decrease in gray matter volume in the anterior cingulate cortex (ACC), the temporo-insular region, as well as the sensory-motor area projecting to the representational area of the face were demonstrated in patients with PIFP similar to previously described brain alterations in primary headache disorders (i.e., tension-type headache) and other chronic pain conditions (i.e., chronic back pain).⁽³⁹⁾ Whether these changes are due to the PIFP pathophysiology or merely represent changes due to chronic pain remain uncertain, but these results support the opinion of a neurobiological origin of PIFP. A functional imaging study with positron emission tomography (PET) on six patients with PIFP showed an increased blood flow in the ACC and a decreased blood flow in the prefrontal cortex compared to healthy controls after application of heat pain stimuli applied to the hand.⁽⁴⁰⁾ A similar PET study showed an increased D2

receptor density in the putamen stressing the relevance of dopaminergic neurotransmission in the modulation of pain perception in PIFP.⁽⁴¹⁾ Neurophysiological testing using blink reflex (BR) recordings and quantitative sensory testing (QST) showed neuropathic changes and central hyperexcitability similar to alterations described in TN and other neuropathic causes of chronic orofacial pain.⁽²⁾ These test results, however, were quite heterogeneous across the investigated patients and did not show reliable abnormalities in all investigated PIFP patients. Therefore, authors underlined a multifactorial and heterogeneous origin of disease in PIFP with a peripheral (i.e., nerve injury, small-fiber neuropathy) and central component (i.e., disturbed or dysregulated pain regulation of ascending or descending nociceptive and antinociceptive brain centers).⁽⁴²⁾ Besides the neuropathy part of suspected peripheral pathology in PIFP, a neuromuscular component of PIFP pathology was described only recently in a study that found an increased muscular activity of the masseter muscles and the anterior temporal muscles in PIFP using electromyography (EMG). This increased activity decreased after rehabilitation with a neuromuscular orthosis in parallel to the reduction of individual pain perception on a visual analogue scale (VAS) from 9.5 to 3.1.⁽⁴³⁾

Further research is needed to identify responsible mechanisms and subdivide the different pathophysiological aspects and contributing factors possibly leading to PIFP.

DIAGNOSTICS AND DIFFERENTIAL DIAGNOSIS

The correct clinical diagnosis is the most important factor for sufficient treatment in both orofacial pain conditions alike. History remains the essential tool for diagnosis. The following six questions were proposed to determine the correct diagnosis in orofacial pain:⁽⁴⁴⁾

- 1) Does the pain occur in attacks or is it constant?
- 2) How long are the attacks (seconds to minutes)?
- 3) Are the attacks electric shock like or dull, pressing or pulsating?
- 4) Is the pain unilateral?
- 5) Is the pain confined to the distribution of a particular branch or branches of the trigeminal nerve (ophthalmic = V1, maxillary = V2, mandibular = V3)?
- 6) Are trigeminal autonomic symptoms present (e.g., lacrimation, rhinorrhea, conjunctival injection, nasal congestion, ptosis)?

Table 1 - Differential diagnoses of trigeminal neuralgia and persistent idiopathic facial pain

Acute glaucoma, refraction anomalies, strabismus
Ear disorders
Sinusitis
Disorders of the jaw, teeth, and related structures
Disorders of the temporomandibular joint (TMD)
Disorders of cranial nerves such as:
- trigeminal compression
- optic neuritis, diabetic ocular neuritis
- herpes zoster, postherpetic neuralgia
- Tolosa-Hunt syndrome
- neck-tongue syndrome
Other cranial neuralgias:
- glossopharyngeal neuralgia
- intermediate nerve neuralgia
- superior laryngeal neuralgia
- nasociliary neuralgia
- supraorbital neuralgia
Trigeminal autonomic cephalalgias (TAC):
- cluster headache
- hemicrania continua
- SUNCT/SUNA = short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing/ short-lasting, unilateral neuralgiform headache attacks with autonomic symptoms)
Pain due to bone disorders of the skull
Cervicogenic headache
External compression headache and cold stimulus headache
Ophthalmic migraine
Anaesthesia dolorosa
Central post-stroke pain

Trigeminal autonomic cephalalgias (e.g., cluster headache, SUNCT, paroxysmal hemicrania) are important to differentiate, especially in patients with first division pain only.⁽⁴⁵⁾

Other important differential diagnoses are nasopharyngeal tumors and hidden dental problems such as infections of the maxillary cavities or jaws after previous tooth extraction as well as disorders of the temporomandibular joint (Table 1). For correct differentiation a thorough examination by an oral/maxillofacial surgeon or facial pain experienced dentist is required. The finding of septal deviation is irrelevant and does not rule out the diagnosis.⁽⁴⁶⁾ Cranial magnetic resonance imaging (MRI) should be performed in patients with atypical presentation of TN and PIFP even though data on clinical specificity or sensitivity are unavailable. Thorough diagnostic workup is especially important in PIFP as it is a diagnosis of exclusion. It should include a radiologic examination of the chest, since in rare

occasions PIFP may be the presenting symptom of a lung cancer.⁽⁴⁷⁾

In TN the main objective of special diagnostic procedures is the differentiation of classical TN (CTN) from symptomatic TN (STN). Clinical presentation with bilateral TN as well as trigeminal sensory deficits are indicative of STN, but due to low sensibility, their absence does not rule out STN.^(32,48) Magnetic resonance imaging detects symptomatic causes other than nerve vessel conflict in approximately 15% (95% CI, 11-20) of patients. Multiple sclerosis (MS) plaques and cerebello-pontine angle tumours are the most common findings. Blink reflex studies and other trigeminal reflex testing has a considerably high diagnostic value with sensitivity of 94% (95% CI, 91-97), and specificity of 87% (95% CI, 77-93). Evoked potentials are insufficient to separate STN from CTN.^(32,48)

The sensitivity and specificity of imaging techniques such as MRI to detect a microvascular conflict were reported with wide range (sensitivity 52% to 100%; specificity 29% to 93%).^(32,48) The usefulness of MRI in the assessment of TN remains subject to debate. Newer imaging techniques and MR-sequences try to fill this gap. The combination of 3D reconstructed high-resolution balanced fast-field echo (BFFE) images, 3D time-of-flight (TOF) magnetic resonance (MR) angiography, and Gd-enhanced 3D spoiled gradient recalled sequence were able to identify 15 out of 18 CTN patients. This clearly shows that more sophisticated techniques as well as higher resolution of ultra-high field MRI scanners at 7 tesla may be able to revolutionize the diagnostic possibilities for TN in the future.^(49,50) One patient diagnosed as PIFP with concomitant nerve vessel conflict did not improve after decompression surgery.⁽⁵¹⁾

MEDICAL TREATMENT

Treatment options for TN are numerous including both medical and surgical treatment options, but mostly restricted by low clinical evidence. The treatment options of PIFP generally consist of medical treatment with newer and conventional antidepressants (tricyclics and selective-serotonin reuptake inhibitors) as well as antiepileptic drugs. No class I or II evidence exists.⁽⁴⁴⁾ Psychological support in terms of behavioural therapy is strongly recommended by many authors in PIFP. In general psychological support should be considered in all chronic pain conditions. Active participation in support groups may help many patients dealing better with their disease and with suggested therapy.⁽⁵²⁾

TRIGEMINAL NEURALGIA MEDICAL TREATMENT

General recommendation is to start with medical therapy and consider surgical procedures in patients that are refractory to medical treatment.

First-line treatment options

First-line therapy should be carbamazepine (CBZ; 200-1200 mg/day) and oxcarbazepine (OXC; 600-1800 mg/day) according to current evidence based treatment guidelines.^(32,48) Although the evidence for CBZ is stronger,⁽⁵³⁻⁵⁶⁾ OXC has a better safety profile.⁽⁵⁷⁾ Approximately 6% to 10% of patients cannot tolerate CBZ.⁽⁵⁸⁾ Multiple pharmacologic interactions and a narrow therapeutic window of tolerability further limit the use of CBZ. As the incidence of TN increases with age,⁽⁵⁹⁾ age related physiologic changes that alter pharmacokinetics such as reduced hepatic and renal function, blood flow decline, less predictable drug protein-binding and interactions with multiple other medications required due to concomitant illness will come more and more into focus. Hyponatraemia is an issue with both medications and can become a serious problem in elderly patients.

Second line treatment options

Second line treatment is based on very little evidence and includes add-on therapy with lamotrigine (400 mg/day),⁽⁶⁰⁾ or a switch to lamotrigine, baclofen (40-80 mg/day)⁽⁶¹⁾ or pimizide (4-12 mg/day). Other antiepileptic drugs have been investigated in small open-label studies. Benefit was suggested from phenytoin, clonazepam, gabapentin, pregabalin, topiramate and valproate, as well as tocainide (12 mg/day).⁽⁶²⁾ Especially the newer antiepileptic drugs (AED) with less interaction to other medication and lesser side effects will be worth further investigation. The newer AED that were tested within the past two years were topiramate and pregabalin. Pregabalin was tested in an open-label study including 53 patients (14 with concomitant constant facial pain) with one year follow-up. Pregabalin (150-600 mg/day) proved to be effective in reducing TN pain in 74% of patients with minor efficacy reduction over the one-year observational period. Patients without concomitant facial pain showed better response rates (32 of 39, 82%) compared to patients with concomitant chronic facial pain (7 of 14, 50%, $p = 0.020$).⁽⁶⁾ Topiramate (100-400 mg/day) was effective in 75% of patients in a very small sample

of only eight patients.⁽⁶³⁾ Two small open label trials investigated the efficacy of levetiracetam (Keppra) in the treatment of TN and showed moderate efficacy. Both studies concluded that randomized controlled trials of levetiracetam will be needed to reconfirm these findings.^(64,65)

Alternative treatment options

Alternative treatment options are subcutaneous sumatriptan and botulinum neurotoxin type A (BoNT-A) injections. Sumatriptan and zolmitriptan showed efficacy in controlling allodynic pain following nerve injury in an animal model for trigeminal neuropathic pain.⁽⁶⁶⁾ A single-blind study of subcutaneous sumatriptan compared to placebo showed efficacy of sumatriptan on pain symptoms in patients with TN after 15 and 30 minutes compared to placebo. This effect lasted only 7 h on average and limits the clinical usefulness substantially.⁽⁶⁷⁾ Several descriptions postulated an analgesic effect of BoNT-A through local release of anti-nociceptive neuropeptides such as substance P, glutamate and calcitonin-gene related peptide (CGRP) inhibiting central and possibly peripheral sensitization.⁽⁶⁸⁾ Reports of isolated TN patients treated with BoNT-A and a small, uncontrolled clinical trial (N = 13) showed significant relief from symptoms after treatment with BoNT-A.⁽⁶⁹⁾

MEDICAL TREATMENT FOR PERSISTENT IDIOPATHIC FACIAL PAIN

Treatment of PIFP can be difficult and unsatisfactory due to the modest knowledge of the underlying pathophysiological mechanisms. Sufficient evidence from randomized controlled clinical trials is scarce. Tricyclic antidepressants (TCA) have a moderate efficacy at doses between 25-100 mg/day.⁽⁷⁰⁾ Positive results were also reported with selective serotonin- and serotonin-noradrenalin reuptake inhibitors (SSNRI) fluoxetine⁽⁷¹⁾ and venlafaxine⁽⁷²⁾ (Table 2). In the fluoxetine study 178 patients with chronic facial pain but without depression improved in pain severity.⁽⁷¹⁾ Venlafaxine was efficient in 30 patients with PIFP in a randomized, double-blind, crossover comparison study, but only twenty patients completed the trial due to adverse events and/ or non-compliance.⁽⁷²⁾ A single case report suggested efficacy of topiramate in PIFP treatment.⁽⁷³⁾ Calcitonin did not show sufficient pain relief in a randomized controlled trial on PIFP.⁽⁷⁴⁾ Sumatriptan showed only a transient effect on pain score reduction but this effect was very small so that sumatriptan was not

Table 2 - Treatment options in persistent idiopathic facial pain

Drug/Treatment	Dose
Amitriptyline	25-100 mg/day
Venlafaxine	50-75 mg/day
Fluoxetine	10-20 mg/day
Topiramate	25-100 mg/day
Transcutaneous nerve stimulation (TNS)	Conventional and acupuncture-like
Pulsed radiofrequency treatment (PRF)	Sphenopalatinum ganglion 45 V with max. temp. of 42° for 120 seconds once or several times
Spinal cord stimulation (SCS)	Upper thoracic dorsal column stimulation
Cognitive behavioural therapy	

considered an appropriate therapeutic option for the treatment of PIFP in two randomized placebo-controlled clinical trials.^(75,76) Hydrocodone was used successfully in one patient and further supports a central origin of PIFP.⁽⁴⁶⁾ Kanpolat et al. showed pain relief after percutaneous trigeminal tract and nucleus ablation, also suggesting that central, rather than peripheral mechanisms may be the dominant factor in this disorder.⁽⁷⁷⁾

Cognitive behavioural therapy is recommended for the treatment of PIFP, but objective assessment of efficacy remains unavailable.⁽⁴⁴⁾

Invasive treatment of persistent idiopathic facial pain

Transcutaneous nerve stimulation (TNS) demonstrated satisfactory analgesia in 45% (N = 20) of patients from conventional and acupuncture-like TNS in a two-year follow-up evaluation.⁽⁷⁸⁾ Pulsed radiofrequency (PRF) treatment of the ganglion sphenopalatinum in patients with different orofacial pain conditions including PIFP was evaluated retrospectively. Out of the treated patients 21% reported complete pain relief, and 65% experienced a good to moderate improvement in this observational trial.⁽⁷⁹⁾ One patient showed almost complete pain relief from his PIFP following upper thoracic spinal cord stimulation (SCS) for refractory angina.⁽⁸⁰⁾

SURGICAL TREATMENT

Before surgical intervention is being considered in the treatment of TN most experts suggest at least three adequate conventional treatments attempts with different drugs at sufficient dosage. One of the drugs should be carbamazepine. However, there are patients that

specifically request surgery despite sufficient pain relief by medication, because they are concerned of disease progression or relapse over time. Medical treatment was patients' least favourite choice when asked what treatment they would choose for themselves⁽⁸¹⁾ mostly because they were afraid of side effects. Surgery in the treatment of TN is generally considered safe and has good efficacy.⁽⁸²⁾ Zakrzewska and Lopez (2003) suggested a checklist that should be done before surgery in order to improve the evaluation quality of surgical treatment.⁽⁸³⁾

Surgical treatment of PIFP is currently not recommended. Trigeminal vascular decompression and deep-brain stimulation of the hypothalamus were not effective. Patients should be preserved from unnecessary dental or surgical procedures as long as a causal understanding of any procedure to alleviate pain is reached.

Surgical treatment of trigeminal neuralgia

A lot of literature on possible interventional treatment for medical refractory TN was presented in the past without sufficient scientific evidence for general treatment recommendation. Currently considered efficient are percutaneous procedures on the Gasserian ganglion, gamma knife surgery, and microvascular decompression. These methods are either destructive (ablative) with intentionally destroying the trigeminal nerve sensory function, or non-destructive decompressive where the normal nerve function is preserved. Gasserian ganglion percutaneous techniques include radiofrequency thermocoagulation (RFT), balloon compression (BC) and percutaneous glycerol rhizolysis (PGR). Pain relief is reported by 90% of patients following these procedures. However, the persistence of this pain relief in many patients does not persist with a recurrence rate of 15-32% within the first year, after three years recurrence rate is between 36%-46%, and half of the patients have a return of symptoms after five years post radiofrequency thermo-coagulation. Most common side effects are sensory loss (50%), dysesthesias (6%), anesthesia dolorosa (4%), corneal numbness with risk of keratitis (4%). Gasserian ganglion therapies require short acting anaesthetics, are primarily overnight minor procedures with extremely low mortality.^(32,48)

Gamma knife surgery severs the trigeminal nerve at the root in the posterior fossa with a focused beam of radiation. Sixty nine percent of patients were pain free without additional medication after gamma knife surgery with 52% remain pain free at three years follow-up. Pain

relief may be delayed by one month and longer (mean one month). Side effects were sensory complications in 6%, facial numbness 9%-37% which improves over time and paresthesias 6%-13% (no anaesthesia dolorosa).^(32,48) Quality of life improves by 88%.⁽⁸⁴⁾

The most sustained pain relief is achieved by microvascular decompression with 90% of patients reporting initial pain relief and over 80% remain pain free at one year follow-up. 75% after three years and 73% after five years. However, to reach the trigeminal nerve in the posterior fossa major surgery craniotomy is required with corresponding complications. The average mortality rate ranges from 0.2%-0.5%, and up to 4% of patients suffer from major problems such as CSF leakage, infarcts, or hematomas. Most common complication is aseptic meningitis (11%), sensory loss (7%), and hearing loss (10%) as long-term complication.^(32,48)

More recent investigations have focused mainly on treatment evaluation in long-term follow-up studies.^(85,86) and improvement of existing surgical techniques.⁽⁸⁷⁻⁸⁹⁾ Even though this has been the most active field of TN research over the past years the vast majority of studies remain on a descriptive level making evidence based comparison and recommendation difficult. The right timing for surgical intervention is yet to be determined.⁽⁸¹⁾ Some TN experts suggest early surgical referral in patients that fail to respond to first-line medical therapy, while others request to have tried at least two different medical regimens including combination therapy before considering surgery including carbamazepine at a sufficient dose. There is no supporting evidence for either of the two opinions. Referral for surgical intervention seems reasonable in TN patients refractory to medical therapy.

EXPERT COMMENTARY

For the correct diagnosis and accurate management of TN a stepwise diagnostic and treatment approach is mandatory. The diagnosis of TN and the distinction between symptomatic TN and classical TN is generally made clinically. Suspicious of STN are bilateral involvement or sensory deficits. In STN MRI should be considered. Blink reflex studies may also be helpful in the distinction of STN and CTN. Carbamazepine (600-1200 mg/day) or oxcarbazepine (600-1800 mg/day) should be the first line therapy. It may be supplemented with or switched to lamotrigine (200-400 mg/day), pregabalin (150-600 mg/day), gabapentin (1800-4200 mg/day) or topiramate (100-400 mg/day). In

case the the combination therapy is insufficient baclofen (40-80 mg/day) can be tried. The option of surgical intervention should be discussed early on with the patient and reluctance in referral to surgery may be disadvantageous to the patient after three different medications and at least one combination therapy turned out to provide insufficient pain relieve. The patient should be involved in the decision on what kind of intervention (Gasserian ganglion procedures, gamma knife surgery, microvascular decompression) deems appropriate regarding his own individual wishes and overall medical condition. As a general rule of thumb the consenting physician should remember that older patients with serious co-morbidities should receive less invasive treatment depending on their biological age and current medical status.

The diagnosis of persistent idiopathic facial pain is generally made by elimination of other causes and often requiring multidisciplinary examination and consultation. The underlying pathophysiological mechanisms remain unclear and probably are a combination of peripheral nervous and muscular as well as central and psychological mechanisms. It may represent one end of the spectrum of neuropathic pain when understood in broader terms to also include subclinical neuropathies, pure small-fiber neuropathies, or neurogenic dysfunction in the form of deficient central top-down inhibitory control. Pharmacological treatment with tricyclic antidepressants and selective serotonin-noradrenalin reuptake inhibitors may be tried. Amitriptyline (25-100 mg/day) is commonly considered first line therapy along with venlafaxine (50-75 mg/day) and fluoxetine (10-20 mg/day). When pharmacological therapy fails, PRF treatment of the ganglion sphenopalatinum may be considered. Cognitive behavioural therapy should accompany medical therapy if possible.

Five-year view

Continuous scientific research has worked towards a better understanding of orofacial pain over the past decades and provided an increased awareness of these diverse and very disabling painful conditions in neurologists, neurosurgeons, dentists, and primary care physicians. More recent clinical, electrophysiological, and imaging studies provided greater insight into the underlying pathophysiological mechanisms and will continue to do so in the coming years. The focus of future research should be mainly on the central component and the associated nociceptive and antinociceptive modulatory

networks that influence chronic orofacial pain conditions like TN or PIFP. Better imaging techniques will be necessary to untangle these networks. Controlled studies with long term follow-up will be needed that compare surgical and medical therapy directly with one another and determine the optimal timing for surgical intervention. This also includes studies that investigate second-line medical therapy after the first-line has failed in stepwise, standardized regimen. The development of newer, antinociceptive drugs for the treatment of orofacial pain needs thorough investigation toward treatment efficacy in TN as well as PIFP.

KEY ISSUES

– Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are rare, but excruciatingly painful disorders mainly affecting the second and third division of the trigeminal nerve.

– TN with concomitant, dull, less intense, but constant facial pain is a variant of classical TN and has poor response to medical and surgical treatment. This is sometimes hard to distinguish from PIFP.

– Magnetic resonance imaging (MRI) and trigeminal reflex testing are reliable to differentiate symptomatic TN from classical TN, but no reliable test exists to confirm PIFP.

– First-line therapy for TN is carbamazepine (CBZ; 600-1200 mg) or oxcarbazepine (OXC; 600-1800 mg). First-line therapy for PIFP is amitriptyline (25-100 mg) as well as fluoxetine (10-20 mg) and venlafaxine (50-75 mg).

– Lamotrigine (400 mg/day), Baclofen (40-80 mg/day), Pimozide (4-12 mg/day) are second line treatment options for TN.

– TN patients refractory to medical treatment should receive early surgical therapy (percutaneous procedures on the Gasserian ganglion, gamma knife, or microvascular decompression). PIFP patients not responding to medical treatment may be considered for pulsed radiofrequency treatment (PRF) of the sphenopalatine ganglion.

– Cognitive behavioural therapy is generally recommended as supportive treatment in PIFP patients and may be helpful in all other chronic orofacial pain patients as well.

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