ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)
IJDSIR : Dental Publication Service
Available Online at: www.ijdsir.com
Volume – 5, Issue – 2, April - 2022, Page No. : 190 - 200

Facial Neuralgias – Neurologist Puzzle

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Citation of this Article: Deepak Narang, "Facial Neuralgias – Neurologist Puzzle", IJDSIR- April - 2022, Vol. – 5, Issue - 2, P. No. 190 – 200.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Facial neuralgia, alone or combined with other symptoms, is a frequent complaint. Moreover, it is a symptom situated at, more than any other pain condition, a cross point where several disciplines meet, for example, dentists; manual therapists; ophthalmologists; psychologists; and ear-nose-throat, pain, and internal medicine physicians besides neurologists and neurosurgeons.

Facial neuralgias are produced by a change in neurological structure or function. This type of neuropathic pain affects the mental health as well as quality of life of patients. There are different types of neuralgias affecting the oral and maxillofacial region. These unusual pains are linked to some possible mechanisms. Various diagnostic tests are done to diagnose the proper cause of facial neuralgia and according to it the medical and surgical treatment is done to provide relief to patient.

The treatment of facial neuralgia can be very challenging despite the numerous options patients and physicians can choose from. This multitude of treatment options poses the question as to which treatment fits which patient best. The preferred medical treatment for facial neuralgia consists of anticonvulsant drugs, muscle relaxants and neuroleptic agents.

Large-scale placebo-controlled clinical trials are scarce. For patients refractory to medical therapy, Gasser Ian ganglion percutaneous techniques, gamma knife surgery and micro vascular decompression are the most promising invasive treatment options.

Current pharmacological and non-pharmacological approaches can provide long-lasting pain relief to a limited percentage of patients and lack safe and effective treatment options. Therefore, scientists are focusing on the introduction of novel treatment approaches, such as stem cell therapy

The aim of this review was to provide an overview of the most prevalent etiologies of facial neuralgia and to provide a generic framework for the neurologist on how to manage patients presenting with facial pain.

Keywords: Neuropathic, Nociceptive, Ectopic, Hemifacial

Introduction

Facial Neuralgia refers to any type of pain in the area bounded by the eyes and the lower mandibles, including the oral cavity. Pain is a complex human psycho physiological experience[1].

Neuralgic pain is produced by a change in neurological structure or function rather than by the excitation of pain receptors that causes nociceptive pain. Neuralgic pain follows the path of a nerve that may give rise to the sensation of tooth pain which often is a diagnostic dilemma for dentist.

This unusual pain is thought to be linked to four possible mechanisms: ion gate malfunctions; the nerve becomes mechanically sensitive and creates an ectopic signal; cross signals between large and small fibres and malfunction due to damage in the central processor. Neuropathic pain often has a negative impact on the mental health and quality of life in these groups of patients.

Exact prevalence data are acking, although facial pain with or without accompanying symptoms appears to be a very frequent complaint (with population prevalence around 1.9%). Women are more frequently affected (women: men ratio 2:1), and other described risk factors are psychological factors, low socioeconomic status, smoking, and the presence of other chronic pain conditions[2]

Virtually all structures in the head and neck region can provoke facial pain. Therefore, more than in other pain syndromes, multiple medical and paramedical disciplines are confronted with facial pain, for example, dentists, manual therapists, ophthalmologists, psychologists, and ear-nose-throat (ENT), pain, and internal medicine physicians in addition to neurologists and neurosurgeons.

This article aims to offer a stepwise framework, directed at neurologists in particular, when confronted with facial pain. Its goal is to provide quick-wins and thereby avoid a delay in diagnosis and exclude severe pathologies as soon as possible.

This goal can only be reached by a multidisciplinary approach. First-line treatments with ample clinical evidence are briefly described. More specific and detailed treatment modalities lie beyond the scope of this review.

Facial neuralgia encountered by the neurologist

Trigeminal neuralgia

The trigeminal nerve, one on each side of the face, is the largest nerve of the face. It transmits various kinds of signals, for example pain, pressure, and heat. Compression of the nerve root by a small blood vessel that causes spasms due to the pulsing of the blood vessel [3] which squeezes the nerve even more is considered to be the basic cause of Trigeminal neuralgia.

Trigeminal neuralgia (TN) is one of the best-known causes of facial pain, though perhaps over diagnosed. It consists of recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve.

Both TN and cluster headache are considered to be the cause of the most severe pain of neurological origin, hence the term “suicide disease.” The lifetime prevalence of TN varies between 0.07% (primary care record study) and 0.3% (population study)[4,5,6].

Damage to the myelin sheath can cause trigeminal pain typically seen with Multiple Sclerosis. Accidents, unsuccessful dental work, or various infections can damage the trigeminal nerve[7,8]

The disorder generally causes short episodes of excruciating pain, usually for less than two minutes and usually only one side of the face.[9]

Simple stimuli such as eating, talking, making facial expressions, washing the face, or any light touch or sensation can trigger an attack (even the sensation of a cool breeze).[10]

Some patients will have a muscle spasm which led to the original term for TN of "tic douloureux" ("tic", meaning 'spasm', and "douloureux", meaning 'painful', in French)[11]

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia (GPN) is also called vagoglossopharyngeal neuralgia. Calcification or ossification of the stylohyoid ligament is infrequent, often incidental finding on radiographs, however when the source of pain is from the styloid process or calcified stylohyoid ligaments it is referred to as Eagle's syndrome.[12,13]

The symptoms may be confused with other causes of head and neck pain. Glossopharyngeal neuralgia is characterized by shock like pains in the territory of the glossopharyngeal nerve. It is generally located near the tonsil although the pain may extend deep into the ear. It is usually triggered by swallowing, chewing, speaking, laughing or coughing[14].

Glossopharyngeal neuralgia sometimes results from nerve compression by an aberrant, pulsating artery similar to that in trigeminal neuralgia and hemi-facial spasm. Glossopharyngeal neuralgia usually begins after age forty and occurs more often in men. Symptoms include severe pain in the areas connected to the ninth cranial nerves.

This includes the throat, tonsillar region, posterior third of the tongue, nasopharynx (back of nose and throat), larynx, and ear. The pain is episodic and severe. The differential diagnosis of neuralgias should be included with an elongated styloid process as sources of head and neck pain[15].

Post herpetic neuralgia

Herpes Zoster (Shingles) is caused by reactivation of latent varicella zoster virus infection. Approximately 15-20% of cases of herpes zoster involves Trigeminal nerve mainly affect the ophthalmic division resulting in pain and lesion in region of the eyes and forehead.

In majority cases the pain of shingles resolves within a month after lesion heals. Pain that persist longer than a month is classified as Post Herpetic Neuralgia[16].

The pain and numbness of post herpetic neuralgia result from combination of both central and peripheral mechanisms.

The varicella zoster virus injures the peripheral nerve by demyelination, Wallerian degeneration and sclerosis but changes in the CNS include atrophy of dorsal horn cells in the spinal cord have also been associated with Post Herpetic Neuralgia[17]

Nervous intermedius (geniculate) neuralgia

It is uncommon paroxysmal neuralgia of cranial nerve VII, characterized by pain in the ear and less frequently the anterior tongue or soft palate. It involves the intermediate nerve of Wrisberg important component of VII nerve[18].

Pain may be provoked by the stimulation of trigger zone within the ipsilateral distribution of the nerve. The pain is not sharp or intense as in Trigeminal Neuralgia and there is often some degree of facial paralysis indicating involvement of motor root.

Geniculate Neuralgia commonly results from the Herpes Zoster of geniculate ganglion and nervous intermedius of cranial nerve VII a condition referred to as Ramsay Hunt Syndrome. Viral vesicles may be observed in the ear canal or on tympanic membrane[19]

Occipital neuralgia

It is a rare neuralgia in the distribution of the sensory branches of the cervical plexus (most commonly unilateral in the neck and occipital region). The most common causes are trauma, neoplasm, infection and aneurysms involving the affected nerves. Palpation below the superior nuchal line may reveal an exquisitely tender spot[20,21]

Primary headache disorders presenting as facial pain

Considering the differential diagnosis of a brief episodic unilateral pain in the trigeminal area, it is important to take into account some of the trigeminal autonomic cephalalgias (TACs). TACs are classified mainly based on the duration of symptoms.

The typically associated profound cranial autonomic symptoms, the occurrence of pain in a saw tooth pattern or as multiple stabs, as well as the lack of a refractory period, can help distinguish these syndromes from TN[22,23].

Rare syndromes

Eagle syndrome is a rare disorder due to inflammation of the stylohyoid ligament. Pain can be situated in the head or neck region, but pharyngeal and facial pain is also possible. Turning of the head typically provokes the pain[24].

Furthermore, clinical examination can confirm the diagnosis if pain is provoked by oral palpation of the tonsillar fossa or if a hard process is palpated. On the other hand, pain is improved by injection of a local anesthetic agent into the stylohyoid ligament, or by styloidectomy. Imaging reveals calcification or elongation of the stylohyoid ligament.

Another rare disorder characterized by symptoms after head turning is the neck-tongue syndrome. Turning of the neck provokes unilateral neck and/or occipital pain, as well as an abnormal sensation and/or posture of the ipsilateral tongue[25]

Pathogenesis of facial neuralgia.

In ICHD-3, 2 types of central neuropathic pain are explicitly mentioned as a cause of facial pain, namely, central neuropathic pain attributed to MS and central post stroke pain[26,27].

In both entities, a lesion of the ascending pathways of the trigeminal nuclei is mostly the cause, next to damage to the cervical spinothalamic pathways or cortical processing areas. Another cause of facial pain is cervical carotid or vertebral artery dissection[28].

The facial pain is usually ipsilateral to the side of the dissected vessel and mostly of sudden onset. An interesting entity is paratrigeminal oculosympathetic (Raeder's) syndrome, where the combination of facial pain in the ophthalmic region as well as ipsilateral miosis and ptosis warrants a search for disease of the carotid artery or surrounding paratrigeminal structures[29].

While not explicitly mentioned as a cause of facial pain in ICHD-3, in select patients cerebral ischemic events, hemorrhages, and vascular malformations, as well as pituitary apoplexy, can present with facial pain [30].

A practical approach to facial pain

When assessing facial pain, the first and most important step is a thorough history, usually leading to a substantial narrowing of the possible differential diagnoses. Next, the neurological examination might reveal directional signs.

Patient characteristic	Age Race Gender Medical history
Pain	Timing (periodicity and duration) Location and radiation Severity and quality Relieving and aggravating factors, for example, sleep Impact on daily life
Associated symptoms and conditions	Headache and/or migrainous features Neurological symptoms ENT symptoms Eye symptoms TMD symptoms Systemic symptoms Chronic pain conditions
Neurological and clinical examination	Complete neurological examination including fundoscopy Mouth, throat, nose, ear, and eye examination, including exploration of the trochlear area TMJ palpation Temporal arteries inspection and palpation Cervical manipulation

Table 1: Initial assessment of patients with facial pain

Table 1 illustrates important elements of this workup. Then, depending on the remaining possible diagnoses, technical investigations can be ordered to confirm a diagnosis or exclude others. Table 2 displays a framework for the assessment of facial pain, in which the associated symptoms and pain characteristics are of primary interest.

History of trauma?	CT skull
Age >50 years?	GCA?
Focal neurological symptoms or signs?	Central, carotid, orbital or trigeminal pathology? Brain MR
Strict facial pain?	Dental or TMJ cause? Appropiate referral
Associated ENT or eye symptoms?	Appropiate referral
Associated head or cervical pain? Autonomic symptoms?	Migraine? TAC? Cervicogenic headache?

Unilateral, paroxysmal and stereotypical attacks?	(Trigeminal) neuralgia? Brain MRI
Persistent facial pain?	PIFP? Psychological support

Table 2 Multistep generic approach to facial pain taking into account certain findings from history or clinical examination (boxes) aimed mainly at excluding life- or organ-threatening disorders and more oriented investigations/referrals and treatment strategies.

The intention of the presented scheme is not to cover all potential etiologies of orofacial pain but rather, by progressing through the scheme, to narrow the differential diagnosis and orient diagnostic examinations. An alternative approach to differentiate separate orofacial pain entities based on timing and lateralization can be found in another excellent review article [31].

Diagnosis

Neuro imaging, especially MRI, is essential for the aetiological subclassification of clinically identified trigeminal neuralgia into either primary trigeminal neuralgia or secondary trigeminal neuralgia typically caused by multiple sclerosis or a space-occupying lesion in the prepontine cistern. A combination of three high-resolution sequences: three-dimensional (3D) T2-weighted, 3D time-of-flight, and MR angiography along with 3D T1-weighted gadolinium has proved to be reliable in detecting vascular contact and in predicting the degree of root compression.[32,33]

Diffusion tensor imaging provides valuable information about the neural structure that cannot be captured by conventional imaging techniques. Several studies using diffusion tensor imaging provided in vivo evidence for how the nerve structure is altered as a result of the neurovascular compression in patients with trigeminal neuralgia[34,35]

Capturing diffusion tensor imaging metrics data from different anatomical compartments of the trigeminal nerve is highly informative. For instance, diffusivity abnormalities in brainstem trigeminal fibres were helpful in a-priori prediction of surgical non-responders in a Canadian neurosurgical study of 31 patients with primary trigeminal neuralgia and 16 healthy controls, in which 12 (86%) of 14 non-responders to neurosurgery could be identified on the basis of abnormal diffusivity in trigeminal pontine fibres.[36]

Additional advanced neuro imaging studies using brain grey matter analysis in addition to diffusion tensor imaging focus on the thickness of grey matter and specific CNS sub regions.

Management of trigeminal neuralgia

Single trigeminal neuralgia attacks are generally too short to be treated by medical intervention. Acute trigeminal neuralgia exacerbations are characterised by a very high attack frequency and can often lead to dehydration and anorexia because intake of fluids and food can trigger the pain.

In such severe cases, in-hospital treatment might be warranted for rehydration and titration of antiepileptic drugs. Acute pain relief can provide a window for adjustment of oral preventive medication and can be of help until neurosurgical intervention is arranged.

Infusion of fosphenytoin and lidocaine, intravenously, is effective according to clinical experience, but there is a low level of scientific evidence to support the use of these drugs.

Both fosphenytoin and lidocaine are potent drugs when used intravenously, and the treatment should only be

administered by skilled medical doctors and nurses in the setting of a high dependency unit[37].

Pharmacological management

The antiepileptics carbamazepine and oxcarbazepine are the first-choice drugs for long-term treatment of trigeminal neuralgia.[37] Both drugs are effective for the treatment of trigeminal neuralgia pain, but treatment is often hampered by side-effects. There is conflicting evidence regarding which of the two drugs is best tolerated, but clinical experience suggests that there is considerable variability of individual responses to both[38,39].

Hence, if one drug is not sufficiently effective the other one should be tried. However, if the first drug causes an allergic reaction, caution should be taken because of possible cross-reactivity. The drugs should be titrated slowly to the highest dose needed to control the pain with continuous monitoring of side-effects.[40]

If carbamazepine and oxcarbazepine are ineffective or poorly tolerated, lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen, or phenytoin could be used, either as add on or as monotherapy.[37]

The recommendation for use of botulinum toxin type A was the most important addition to the medical treatment field in the European Academy of Neurology guideline.[37]

However, large-scale randomised controlled trials of patients treated with botulinum toxin type a are needed. Other second-line options, such as local aesthetics, greater occipital nerve blocks, and topiramate, are used by some experts but the evidence is again scarce64–67 and randomised controlled trials are urgently needed [41].

Surgical management

There is no scientific evidence to support the view that surgery should be done early in the course of the disease.[42]

However, two trade-off studies indicate that some patients would have opted for surgery sooner had they had the chance, and when shown data of expected outcomes, adverse events, and surgical complications, most patients with trigeminal neuralgia valued neurosurgery more highly than medical treatment.[43]

Microvascular decompression is a non-destructive procedure, in which the trigeminal nerve is decompressed of conflicting blood vessels during open fossa posterior surgery (appendix p 1). Percutaneous procedures are destructive (ablative treatments) and involve penetration of the foramen ovale with a cannula and then controlled lesion of the trigeminal ganglion or root by various means, such as thermal (radiofrequency thermocoagulation), mechanical (compression by a balloon), or chemical (injection of glycerol). Stereotactic radiosurgery, such as the gamma knife, is the only non-invasive but destructive technique, which aims a focused beam of radiation at the trigeminal root entry zone.

In clinical practice, repetitive ablative procedures are common. Microvascular decompression is the first-choice surgery in patients with classical trigeminal neuralgia.[37]

A pooled analysis including 5149 patients showed that the efficacy of microvascular decompression is generally high, as 62–89% of patients are pain-free at follow-up (after 3–11 years).13 With respect to complications, severe complications, such as death (0·3%), oedema, haemorrhage, or stroke (0·6%), anaesthesia dolorosa (0·02%), and meningitis (0·4%), were rare. Less severe complications, such as cranial nerve palsy (4%), hearing loss (1·8%), and facial hypoesthesia (3%), were more common than the severe complications.13 When an MRI does not show any vascular contact, ablative treatments should be the preferred choice.

Pooled analyses reported that with a follow-up of 4–11 years, 55–80% of patients (n=755) with trigeminal neuralgia were pain-free after balloon compression, 30–66% (n=1168) after gamma knife surgery, 26–82% (n=4533) after radiofrequency thermocoagulation, and 19–58% (n=289) after glycerol injection.[37] The most common complications for the four ablative procedures were facial hypoesthesia (19%), corneal hypoesthesia (5%), and trigeminal motor weakness (5%). Meningitis (0·7%) and anaesthesia dolorosa (0·5%) were rare but severe complications.[37] Ideally, information on the neurosurgical options, expected outcome, and complication rates should be given early in the course of the condition, with the patient accompanied by a partner or family member.

In one Danish neurosurgical study of 59 patients with primary trigeminal neuralgia, microvascular decompression was statistically more effective in men than in women, but this possible gender difference is yet to be replicated in other studies. Concomitant continuous pain was in some studies related to a poorer outcome, whereas in other studies it did not turn out to be a negative prognostic factor.[44]

Future directions

Better knowledge of the a etiology and pathophysiology of trigeminal neuralgia could lead to new therapeutic targets with a higher degree of tolerability and individualization of treatment. It is highly probable that there are multifactorial causes for trigeminal neuralgia, which need to be especially explored in patients with the idiopathic condition.

Stem cell therapy

Over the last decade, stem cell transplantation has exhibited remarkable potential for the repair of nervous system damage in NP syndromes rather than simply providing temporary palliation. Stem cell therapy has thus emerged as an alternative therapeutic approach for NP.

In particular, human mesenchymal stem cells (hMSCs) have been characterized as neuroprotective in spared nerve injury (SNI) [45].

Mechanistically, stem cells represent a totipotent cellular source, replacing injured or lost neural cells. Further, they provide trophic factors to the injured nerve.

Following nerve injury, peripheral sensitization leads to the infiltration of immune cells, such as neutrophils, macrophages, and mast cells, at the injury site causing overexcitation and continuous discharge of nerve fibers [46].

Following inflammation, a large number of cytokines, chemokines, and lipid mediators are released, sensitizing and stimulating nociceptors, which in turn results in local homeostatic changes [80]. Reports from preclinical animal models suggested that anti-inflammatory cytokines exerted analgesic effects [46].

The immunomodulatory and angiogenic properties of stem cells have also been reported [47]. In a CCI sciatic nerve injury model, both IL-1β and IL-6 expression were greatly attenuated following transplantation of adipose-derived stem cells, whereas, anti-inflammatory factor IL-10 was significantly upregulated. These outcomes could be due to the interaction between stem cells and macrophages, leading to polarization of the latter into anti-inflammatory phenotypes[48,49].

Conclusion

When confronted with facial pain, a multidisciplinary approach is mandatory. The use of a uniform terminology according to a validated classification and a structured workup when assessing a patient with facial pain is recommended.

Abbreviations

CT, computed tomography

GCA, giant cell arteritis

MRI, magnetic resonance imaging

TMJ, temporomandibular joint

ENT, ear-nose-throat

TAC, trigeminal autonomic cephalalgia

PIFP, persistent idiopathic facial pain

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