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Neuropathic Orofacial Pain: Pathology, Management and Differential Diagnosis

[1]Dietrich Eva-Maria, [2]Papamitsou Theodora and [2]Dermentzopoulou-Theodoridou Maria
[1]Faculty of Dentistry, Aristotle University of Thessaloniki, Greece
[2]Laboratory of Histology-Embryology and Anthropology, Faculty of Medicine,
Aristotle University of Thessaloniki, Greece

Abstract: The aim of this review is to present signs and symptoms of two main types of neuropathic orofacial pain to support differential diagnosis. Types of studies reviewed: clinical investigations, reviews and case reports were reviewed via Pubmed. The terms trigeminal neuralgia, atypical odontalgia, gamma knife surgery and microvascular decompression were used as criteria. Studes not adressing cases of recurrent, atypical or idiopathic trigeminal neuralgia or atypical odontalgia were excluded due to the fact that these articles wouldt'n contribute to the main scope of the review which is to focus on the differential diagnosis of primary neuropathic orofacial pain. TN is treated according to the medical history of the patients, classifying them with refractory to pharmaceutical approaches pain as candidates for GKS. If an immediate pain relief is wanted GR is also an option if the possible side-effects and failure of the procedure are taken into account. In case of AO dental treatment is unnecessary and pharmaceutical treatment has a satisfactory result.

Key words: Trigeminal neuralgia, atypical odontalgia, gamma knife surgey, glycerol rhizotomy, macrovascular decompression, carbamazepine

INTRODUCTION

The Trigeminal Nerve (TN) branches off from the ventral part of the pons divided into a large sensory root and a smaller motor root. The main three divisions arise from the Gasserian ganglion.

Many pathological conditions are related to a trigeminal nerve injury or to a dysfunction of the nerve. In such cases the anatomical part of the nerve affected should be considered. The above mentioned dysfunction of the trigeminal nerve related to a specific part of its distribution makes the differential diagnosis of pathological conditions extremely difficult. This review tries to present signs and symptoms characterizing types of neuropathic orofacial pain in order to support the differential diagnosis.

MATERIALS AND METHODS

Literature search was carried out using Pubmed. Search terms included:
<<trigeminal neuralgia>>, <<atypical odontalgia>>, <<gamma knife surgery>> and <<microvascular decompression>>

Exclusion criteria used in the selection of studies were studies not relevant to the study, interviews, books and conferences abstracts, comments, replies to author and to editor, non English papers, unsupported opinion of expert, summaries for patients and editor's choice.

RESULTS AND DISCUSSION

Pathology: Neuropathic pain is defined (Lewis *et al*., 2007) as pain initiated by a primary lesion or dysfunction of the nervous system. Thus the presence of a trauma isn't necessary for the appearance of a neuropathy of the trigeminal nerve.

Many researchers suggest demyelination as one of the major causes of orofacial neuropathies. Demyelinating disorders affect the normal nerve or ganglia (Woolfall and Coulthard, 2001; Love and Coakham, 2001). This process is classified lesions involving the trigeminal nuclei (Woolfall and Coulthard, 2001).

Another major cause of neuropathies is vascular compression of the nerve. It mainly implies vascular malformations of the brainstem. There mainly is a compressive activity of an artery but vein malformations were also reported (Lewis *et al*., 2007; Love and Coakham, 2001). In case of an artery malformation, a vertebral or basilar artery were mainly involved. Neoplasms involving the cerebellopontine angle, pituitary gland and the base

Corresponding Author: Dietrich Eva-Maria, Faculty of Dentistry, Aristotle University of Thessaloniki, 57006 Thessaloniki P.B. 5, Vassilika, Greece

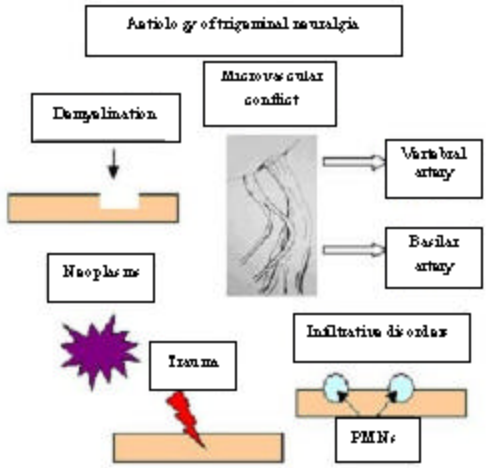

Fig. 1: Aetiology of trigeminal neuralgia

of the skull may also lead to neuropathies of the trigeminal nerve (Woolfall and Coulthard, 2001; Love and Coakham, 2001). Infiltrative disorders such as carcinomatous deposits within the nerve root and trigeminal amyloidomas, inflammations and traumas where also reported (Fig. 1). It is of high importance for the management of neuropathies to differentiate traumatic induced neuropathies from a dysfunction at the Dorsal Root Entry Zone (DREZ) of no traumatic origin.

Pathological conditions

Trigeminal Neuralgia (TN): Differentiating TN from dental pain is a challenge in order to minimize the misdiagnosis and unnecessary dental treatment. TN mostly affects the female population (3-2) in their fifties or sixties but it may also affect males older that 80 (Melis *et al*., 2003).

It is not often reported in younger age groups such as children. It is often of no traumatic origin. About 85% of the patients suffering from TN show the cardinal signs of classical TN. On the other hand idiopathic TN is not characterized by easily to mention and diagnose signs and symptoms.

The 2nd and 3rd trigeminal nerve divisions are mainly affected. In case of an ophthalmic nerve involvement (2-3%) a higher positiv response to gamma-knife surgery is reported (Brisman, 2000).

As mentioned, pathology is mostly based on neurovascular compression. It explains 80-90% of the cases. Imaging techniques can lead in 78% to a diagnosis showing a 4 mm compression of the nerve mainly in the brainstem (Lewis *et al*., 2007; Woolfall and Coulthard, 2001; Love and Coakham, 2001; Melis *et al*., 2003). Demyelinating and infiltrative disorders and familiar occurrence may also be present (Love and Coakham, 2001).

Pain characteristics: The pain is predominantly unilateral, paroxysmal and excruciating. Lasts for less that 2 min with respites of one month gradually decreasing in duration. The sharp, sudden, electrical pain occurs after stimulation of so called trigger zones. Typical stimuli are shaving, washing, eating, drinking, the wind. Pain sensation after activation of the trigger zones can be explained by the re-organization of receptic fields of wide-dynamic-range neurons, leading to depolarization of pain receptors. This receptic fields imply mechanoreceptors activated by shaving, eating and other stimuli. As analyzed above, the spontaneous pain sensation in addition to the absence of a traumatic incidence may help differentiating TN from dental pain.

Dental pain and atypical odontalgia: In order to unserstand the points of interest for differential diagnosis between tooth pain and facial pain a thoughrough presentation of the pain characteristics of each pathological condition is necessary.

Dental pain can be classified in pain induced by dentinal dysfunction dominated by the presence of plaque and demineralized hard substance of the tooth, pulpal pain arising due to pulpitis, periodontal and cemental pain.

If dentine is demineralized because of a dissolving action of dental plaque, pain arises by means of a hypersensitivity of dentine. As far as the metabolical products of plaque reach the pulp and inflammation sets on pain sensation tends to worsen. In the late stage of pulpitis the pain is dull and the tooth is sensitive to vertical pressure. There are many stages of a periapical disease but their discription falls out of the scope of this review.

Atypical Odontalgia (AO): Atypical odontalgia is often described as phantom tooth pain or persistent orodental pain. In contrast to the above mentioned diseases it does not apply to a pathological condition (Melis *et al*., 2003; Melis and Secci, 2007). It affects 3-6% of patients who underwent root canal therapy (Melis and Secci, 2007), mostly females in their 40s.

The pain is comparable to tooth pain and may be mentioned at a side of an extraction one month after. It is reported intraorally, surrounded by an area of less hyperalgesia. It is persistent or almost continuous has moderate pain intensity and long pain duration is present for more than four months, there is no sign of local or referred pain (Melis *et al*., 2003; Melis and Secci, 2007; List *et al*., 2007). There is a short period of time after awakening where there is no pain felt. On the other hand pain is characterized by periods of sharp pain sensation.

Pathology of Atypical Odontalgia (AO): AO is associated with peripheral nerve injury due to surgical procedures or a facial injury. Patients who had previously felt pain at the side where now AO symptoms appear are more prone to develop AO.

The fact that there is an aggravation of pain sensation and a spread to the hole mandible or maxilla may be explained by a re-organization of neuronal afferents in the area of their distribution, suggesting that neuropathic alteration of the trigeminal nerve may be an explanation (Clark, 2006). This leads to the conclusion that every surgical dental procedure such as tooth extraction or apicoectomy may have a distructive action on neuronal tissue causing pain.

Many reviews mention the role of psychology in the development of AO but there is yet no evidence for its relation to pain. AO patients had higher scores of depression and somatization in clinical trials and lower scores in quality of life (List *et al*., 2007), suggesting that psychological factors may contribute to the development of AO. In the same study AO patients showed tension-type headache and widespread pain in a higher rate than the control groups.

In conjunction to the above mentioned, depression, anxiety, hypochondrial psychosis and personality disorders where more common among AO patients. It's the never ending neuronal circle psyche-pain-psychiatric problems-chronic pain. Other explanations for AO are:

- The activation of normally non-nociceptive Ab-fibers from stimuli leading to pain sensation (allodynia). This action is characterized by the release of substance P
- The role of the sympathetic system is also confirmed because of the sympatholytic procedures reducing pain
- A dysfunction of the CNS may also be present in case of peripheral nerve injury causing AO
- In all the above mentioned conditions, down regulation of inhibitory agents plays a vital role in the expression of pain

In summary, former pain experience may trigger pain sensation without the presence of stimuli, building the base of AO.

Differential diagnosis: In order to diagnose the pathological conditions discribed, the following diagnostic procedures are helpful (Clark, 2006):

- Prove the vitality of the pulp with cold testing
- Perform a periapical radiograph and propably a panoramic radiograph for other maxillofacial diseases (other types of radiography can be used if the simple diagnostic procedures fail to show the identity of the condition)
- Examine the head and neck for abnormalities
- Test the cranial nerves with anesthetic testing

AO vs. cranial nerve injury: In order to differentiate AO from a cranial nerve injury the type and the frequency of pain plays a vital role. Pain through cranial nerve injury is tic like and not continuous such as in AO. AO vs. TN:

- TN pain is triggered by touch stimuli in the area of the distribution of a trigeminal nerve branch. In case of AO pain is elicited spontaneously (Table 1)
- Pain in TN and AO isn't normally due to an injury of the nerve but in case of AO there is a former re-organization of nerve affarents due to a dental surgical procedure such as tooth extraction
- TN is normally present in females in their 50s and 60s in contrast to AO which occurs in females in their 40s
- The type of pain felt may also differentiate TN from AO because pain in AO is dull and continuous not followed by pain-free intervals like in TN
- TN affects specific areas of the face or mouth in contrast to AO where the pain spreads from one tooth or tooth side with extraction to the hole mandible or maxilla
- In TN the pain is unilateral as in AO but may be bilateral which is uncommon

AO vs. pulpal pain: The differential diagnosis depends on the fact that there is no response of the tooth to dental treatment in case of AO. The pain remains continuous and the application of stimuli does not influence the pain sensation (Table 1). On the other hand in case of pulpitis there is an aggravation of pain sensation until the necrosis of the pulp commences and no stimulus can cause pulpal reaction.

Pain in pulpitis due to stimulation depends on the stimulus type and stage of inflammation. In acute pulpitis (in its late stage) pain is intense and colt stimuli leads to pain remission.

AO, TN or pulpal pain: As mentioned before AO or TN pain may also be misdiagnosed as pulpal pain, leading to unnecessary extractions or dental treatment. In this case the approach consisting of differential diagnosis based on pain type, duration, cause, distribution and trigger factors can help the diagnosis.

Table 1: Differential diagnosis of neuropathic orofacial pain

	Differential diagnosis		
Factors	TN	AO	Pulpal pain
Location	Usually unilateral can be bilateral	Unilateral	When the pain is due to hyperaemia the localization of the pain is impossible. The location can only be assessed when the inflammation procedes and affects the periapical region
Trigger points	Yes	No	No
Presence of a trauma	No	Yes Surgical procedure like tooth extraction	No Usually the cause is caries but it can also be elicited due to an occlusion trauma or injury
Age	50s, 60s	40s	In every age group
Gender	Females	Females	Males/Females
Pain characteristics	Paroxysmal, excruciating with pain-free intervals	Dull and continuous	They depend on the stage of Inflammation of the pulp
Duration	<2 min	Continuous	In the initial phase the pain is being elicited by stimuli and holds on until the stimulus stops. In the later phases the pain starts spontaneously and may remain for many minutes or hours
Spreading	No	Yes It spreads from one tooth to the other even to the hole maxilla or mandible	There can be pain projection to another area

Management: Treatment includes a pharmacological management suppressing nerve activity, surgical and percutaneous procedures and radiosurgery. The following analysis presents the current treatment approaches used in order to minimize the symptoms of TN and atypical odontalgia.

Pharmacological management of TN includes: carbamazepine (Sindou *et al*., 2002), phenytoin (Sindou *et al*., 2002), baclofen (also for AO, Melis and Secci, 2007), oxcarbazepine, gabapentin, pregabalin, tocainide, proparacaine and lamotrigine. Specifically the drugs used are:

- Anticonvulsant drugs, mentioned above
- Antidepressants: clinical trials have proven evidence of the benefit of mixed serotonin/noradrenaline or specific noradrenaline reuptake inhibitors in contrast to selective serotonin reuptake inhibitors. They are used for neuropathic pain other than TN. In cases of AO, tricyclic antidepressants are prescribed in association with phenothiazines because the later potentiate the analgesic action of tricyclic antidepressants (Melis *et al*., 2003). There is a permanent relief from pain, according to a survey of Mardach in 69% of the cases (Melis and Secci, 2007)
- Antiarrhythmics: tocainide was tested showing adverse effects ranging from nausea to ataxia (Lewis *et al*., 2007)

Local application: Local application of drugs is now very often suggested as a solution for pain relief because of a positiv result in clinical trials. For these reason topical amitriptyline or/and ketamine are used.

Proparacaine wasn't effective in TN when administered into the eye on the side of TN. Injections of local aneasthetics and corticosteroids and topical application of capsaicin and Eutectic Mixture of lidocaine and prilocaine bases (EMCA) may also be helpful in cases of AO (Melis and Secci, 2007).

Placebo response: Placebo response as a parameter of healing was tested using acupuncture and invisible Infrared (IR) diode laser. In the acupuncture group the placebo response wasn't significant compared to pain relief after traditional acupuncture. In contrast to the low power laser stimulation where placebo response was suggested to be superior to laser stimulation (Lewis *et al*., 2007).

MVD: Treatment of TN with MVD seems to be the best choice since Dandy expressed this theory in 1934. Even if a vascular compression of the nerve isn't detectable via MRI (Baechli and Gratzl, 2007) MVD is effective. It involves accessing the nerve via a retromastoid craniectomy and placing a Teflon pledget between the snerve and the vessel (Cheuk *et al*., 2004).

The neurovascular conflict is located in 52.3% of the patients-according to a clinical trial of Sindou *et al*., 2002 in the root entry zone in 54.3% in the midthird and in 9.8% at the exit of the nerve from Meckel's cave.

In the same trial in 88% of the patients the neurovascular conflict was accosiated with the Superior Cerebellar Artery (Fig. 2a), followed in 25.1% from the Anterior Inferior Cerebellar Artery (Fig. 2b). The contribution of a vessel to the suppression of the trigeminal nerve is assessed via MRTA (magnetic

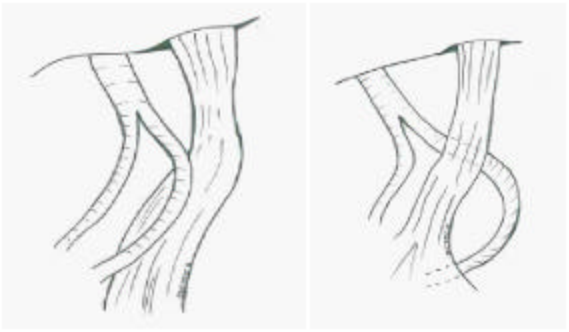

Fig. 2: Compressive activity of (a) superior cerebellar artery (b) an anterior inferior cerebellar artery

resonance tomographic angiography), imaging the area from Meckel's cave to DREZ (Hai *et al*., 2006). Current surveys have proven evidence of the fact that the compressive activity of a vessel may be present at any point of the distribution of the nerve (Hai *et al*., 2006).

As mentioned in previous paragraphs a Neurovascular Conflictv (NVC) mainly affects the second and third divisions of the trigeminal nerve. A supero-medial location of a NVC is associated with a higher territory of TN in contrast to an inferior location (Sindou *et al*., 2002) (Fig. 2a).

Pain relief: The rates of pain relief after MVD are very high but differ if compared to them of atypical TN patients.

Especially, 80% of pain relief was reported after MVD in the group of Typical Trigeminal Neuralgia (TTN) in contrast to 49% in the atypical TN group (ATN) (Tyler-Kabara *et al*., 2002).

Long term results: Long term pain relief was present in 73% of the TTN group and only in 35% of the ATN group in the clinical trial of Tyler-Kabara (Tyler-Kabara *et al*., 2002). In comparable studies, 90% of the participants felt pain relief in cases of a less severe and not longstanding disease (Lewis *et al*., 2007; Cheuk *et al*., 2004; Hai *et al*., 2006).

If compared to less invasive procedures like GKS, MVD shows a high percentage of pain relapse (30-40% after 10 years or 20% according to Lewis *et al*. (2007) and Kuncz *et al*. (2005), respectively)).

The percentage of recurrence was higher (57%) if a venous compression was present (Kuncz *et al*., 2005). It is also noteworthy that a venous compression is rare in the TTN group but is seen in 31.2% of the cases of ATN (Kuncz *et al*., 2005). Wherus in another trial, 42.3% of the cases demonstrated after MRTA a venous microvascular compression (Hai *et al*., 2006).

Preoperative sensory loss in cases of ATN before MVD is a negative predictor factor. On the other hand, memorable onset and trigger points are positive predictor factors (Tyler-Kabara *et al*., 2002). A failure of the MVD can be related to penetrating arteries into the brainstem or through neurofibers or to a failure of the procedure to dissert vessel branches from the nerve (Hai *et al*., 2006). This finding indicates that a complete decompression is necessary for pain relief (Sindou *et al*., 2002). According to the above, MVD is still the first choice treatment for patients with TN having less morbidity, long-term cure and minimal pain recurrence (Henson *et al*., 2005).

GKS for TN: GKS is based on stereotactic focused radiosurgery where tissues are radiated with a precision of 0.5 mm. 201 beams of gamma radiation generated by ^{60}Co are focused on the target. Brainstem dose appears to be very important, affecting the results of GKS. A radiation normally focused anteriously to the REZ over 12 Gy (Regis *et al*., 2001) may result in a better treatment response in conjunction with side-effects.

Possible target for radiation is the area from the brainstem edge to the trigeminal ganglion. The hole procedure starts with the administration of a local aneasthetic and the placement of a stereotactic field. CT and MR are used for imaging. GKS for TN gained a new lease of life in the last years and many concerns where expressed dealing with the radiation dose, area and extension of radiation and the pros and cons of GKS.

Radiation dose and side-effects: The radiation dose mainly used is 70 Gy. A higher radiation is associated with facial numbness and paresthesia with the last appearing in less than 10% of the cases (Pollock *et al*., 2000). A higher dose although is also associated with completely pain relief in a high percentage of patients undergoing GKS. This approach is based on the hypothesis that oligodendrocyte myelin is more responsive than Schwann myelin to radiation (Cheuk *et al*., 2004). Exactly this point, the Obersteiner-Redlich zone, located 2-3 mm outside the TREZ is mostly affected by an offending vessel (Sindou *et al*., 2002).

Propably facial numbness may be <<desirable>> because patients experienced numbness have better pain relief (Cheuk *et al*., 2004). Facial numbness seems not to have a correlation with imaging quality (axial MRI plane), presence of compression or brainstem radiation dose in the trial of Cheuk (Cheuk *et al*., 2004) thus the result of GKS is not affected by these factors. But there is a

correlation between visuable through MRI compression of the nerve and treatment response. Patients with compression experienced a better treatment result (Cheuk *et al*., 2004).

It remains to be explained whether an atrophy of the trigeminal nerve explored in the operation plays a vital role in the pathogenesis of TN (Sindou *et al*., 2002). According to many researchers if the length of the nerve radiated increases this is associated with a higher percentage of patients experiencing side-effects after GKS.

Pain relief: Sheehan *et al*. (2005) reported pain relief in 44% of the patients and in 70% after 3 years, suggesting GKS as an option with less invasive approach and side-effects. According to Cheuk *et al*. (2004) 89.6% of the patients had an improvement in pain class. Pain relief ranging from 33-90% was reported by the National Institute for Health and Clinical Excelence in the UK (Melis and Secci, 2007).

Glycerol Rhizotomy (GR) versus GKS: According to a clinical trial of Henson *et al*. (2005) patients undergoing GR experienced:

- Pain relief after 24 h compared to GKS patients who experienced pain relief after a median time of 3 weeks
- GR patients experienced in 45-51% of the cases side effects, reported only in 7-14% of the GKS group, having also a higher morbidity than the GKS patients
- Treatment failures where also higher in the GR group.

CONCLUSION

The most important aspect in case of a trigeminal neuropathy is the correct diagnosis. In case of AO dental treatment is unnecessary and pharmaceutical treatment has a satisfactory result. TN is treated according to the medical history of the patients, classifying them with refractory to pharmaceutical approaches pain as candidates for GKS. If an immediate pain relief is wanted GR is also an option if the possible side-effects and failure of the procedure are taken into account. It depends on the medical skills of the physician to choose the right method and relief the patient from pain causing minimal side effects.

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