DIFERRENT ASPECTS OF OROFACIAL PAIN
(PART IV) -
HEADACHE AS A CONSEQUENCE OF TRIGEMINAL NERVE AFFECTATION

RAZLIČITI ASPEKTI OROFACIJALNOG BOLA (IV DEO) -
GLAVOBOLJA KAO POSLEDICA OBOLJENJA TRIGEMINALNOG ŽIVCA

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Abstract

The trigeminal nerve is the principal afferent pathway for the sensory perception of headaches and facial pain. Neurogenic or vascular mechanisms are suspected in the pathogenesis of many "atypical" forms of orofacial pain, and emphasis has been placed on the possibility that vascular alterations might play an important role in some chronic orofacial pain (1). The relatively slow-conducting non-myelinated fibers mediate visceral type vascular pain. Evidence points to the existence of sensory axons that innervate the cephalic blood vessels, forming part of the so-called trigeminovascular system. Vascular orofacial pain can be due to altered non-myelinated trigeminal fibers (2). In this context, vascular pain would be transmitted by such axons (3) - particularly perivascular sensory axons. These trigeminal axons would thus transmit nociceptive information to the central nervous system (CNS), and would lead to neurogenic inflammation when subjected to antidromic stimulation. In addition to their afferent (sensory) function, the trigeminal sensory fibers play a neuroeffector role in the regulation of blood flow. These fibers likewise belong to the trigeminovascular system. The non-myelinated fibers contain potent vasodilating neuropeptides such as the Calcitonin Gene-Related Peptide (CGRP), substance P (SP) and neurokinin A (NKA). Type C non-myelinated fiber depolarization triggers peptide release in the vascular wall via calcium-dependent mechanisms (2, 3).

Key words

Headache, Trigeminal Nerve, Treatment

INTRODUCTION

The neuroeffector function of the trigeminal sensory system involves SP and NKA release from the distal tip of the stimulated non-myelinated fiber. The release of these substances is regulated via serotonergic receptors and causes vascular dilatation and oedema or neurogenic serosal inflammation of the vascular walls that are innervated by these fibers. The serosal inflammation in turn contributes to further sensitize these fibers and prolong pain. The efficacy of certain drugs in combating headache can be explained in terms of the correction of these physiopathological mechanisms. Serotonergic receptor agonists such as ergotamine and sumatriptan antagonize vasodilating neuropeptide release during headache crises, inducing vasoconstriction and preventing the development of serosal inflammation (2).

Both homolateral local and general autonomic manifestations (some sympathetic and others parasympathetic) develop in the course of a facial vascular pain episode. Increased lacrimation, nasal secretion or plugging and conjunctival injection may reflect local parasympathetic hyperactivity triggered through a reflex circuit consisting of a trigeminal afferent pathway and a parasympathetic efferent trajectory through the greater superficial petrosal nerve and the sphenopalatinal ganglion. Palpebral ptosis, miosis and sweat alterations are attributed to sympathetic involvement, while activity of the trigeminovascular system induces serosal inflammation of the carotid wall that in turn compresses the perivascular sympathetic fibers against the narrow bony canal through which its passes (4).

The cervical sympathetic trunk possesses visceral afferents that follow the branches of the external carotid artery to
innervate the depth of the mandible, the teeth and the auditory regions of the head. These afferents do not receive painful stimuli, though they may be activated by the sympathetic nerves. Direct stimulation of the superior cervical ganglion causes intense pain in the lower teeth and behind the ear of the same side. Compression of the carotid sinus likewise induces pain in the teeth and ear. Much remains to be learned of the relations between the sympathetic nerves and pain perception (5).

The non-myelinated trigeminal fibers establish connections with the cells of the solitary fasciculus and nucleus of the vagus. By means of a reflex arc possessing a trigeminal afferent component and efferents arising from these vegetative nuclei, bradycardia, syncopal conditions and sweat crises develop in the course of the pain episodes (2).

Myelinated trigeminal fiber alterations appear to be related to essential trigeminal neuralgia – a condition that involves intense, unilateral and momentary pain crises preferentially distributed through territories II and III of the trigeminal pathway (6). Carbamazepine and other antiepileptic drugs are the most effective medical treatment in such cases.

**TYPES OF TRIGEMINAL AUTONOMIC HEADACHE**

Orofacial vascular pain is of great diagnostic and therapeutic importance. The similarities with dental pain frequently cause diagnostic difficulties; knowledge of these conditions on the part of the odontologist and stomatologist is therefore important. Craniofacial vascular pain comprises facial migraine or headache in the lower half of the face, temporal arthritis, vascular pain of cardiac origin, cardiology and the styloid process syndromes, and the recently termed trigeminal autonomic headaches – of which particular mention will be made (7, 8).

Goadsby and Lipton (9) proposed a classification for trigeminal autonomic headache in a 1997 review. According to Benodie et al. that same year (1), orofacial vascular pain encompassing so-called atypical dental pain could well be added to this classification.

1. Cluster headaches

Cluster headaches (CH), or migrainous neuralgia, consists of intense unilateral pain manifesting as crises with duration of 15 to 180 minutes. The condition is associated to tearing, nasal blockage, ptosis, miosis and enophthalmos of the same side (10). The crises can occur one or more times a day for periods spanning weeks or months. CH is more frequent in young males, though it can afect individuals of either sex and in any age range - including the elderly. It tends to commence in the upper premolar zone, and the differential diagnosis must be established with dental pain. In a number of cases, these patients have been subjected to endodontic treatment and/or extraction of the premolars in an attempt to resolve the pain (11).

The term „cluster headache“ reflects the tendency of the pain to recur in the form of outbreaks or clusters. Most frequently, the crises appear over a period of 4-8 weeks, with a typical frequency of 1-3 crises per day. Most such crises occur at a particular time of day or night - a fact that has led to the term „alarm clock headache“. The crises often develop during sleep, and are said to be related to the onset of the rapid eye movement (REM) phase of sleep (12). Alcohol, histamine and cocaine are known triggering factors (13).

Hardebo (4) proposed a theory to explain the development of CH as a consequence of cavernous sinus infection. In this context, infection purportedly reaches the cavernous sinus through the ethmoidal and superior ophthalmic veins, which are in turn inflamed by an upper airways infectious process. Periodic changes in cavernous sinus drainage, related to inflammation of the carotid wall, could account for the appearance of the crises. Vasoconstriction, either spontaneous or induced by sumatriptan - which is highly effective as symptomatic treatment of such crises - would in turn eliminate the pain.

In the presence of a suggestive case history, the process should be confirmed by clinical exploration and complementary tests. During the actual pain crises the patient presents incomplete Horner’s syndrome (without anhydrosis) of the affected side. The clinical findings are typically normal between crises. Maxillary sinusitis and alterations of the paranasal and skull base sinususes must be discarded by means of radiological studies and computed tomography (14).

The differential diagnosis is from palpal pain (15), based on the repetitive nature of the crises and the associated vegetative manifestations. The condition may in some cases simulate trigeminal neuralgia - though in such situations the pain is briefer and no vegetative symptoms are observed (16). Raeder’s paratrigeminal neuralgia is similar to CH, though palpebral ptosis and miosis are sustained as a result of sympathetic nerve damage in the wall of the internal carotid artery - possibly reflecting the presence of a pericarotid tumor (17). Facial migraine is in turn differentiated from CH by its predominance among females, the longer duration of the crises with nausea and vomiting (but no tearing or nose block), and its periodic presentation (i.e., not in the form of clusters). The onset typically corresponds to young patients, though the crises may persist until advanced age (8).

**VARIANTS OF CLUSTER HEADACHE**

Cluster headache (CH) - trigeminal neuralgia. CH and essential trigeminal neuralgia (TN) are conditions with seemingly clearly distinct pathogenic, physiopathological, clinical and treatment characteristics. Curiously, however, some patients apparently suffer both disorders simultaneously, with pain associated to CH-type crises.

**Trigeminal neuralgias**

Trigeminal neuralgia refers to pain in the distribution area of one or more trigeminal branches. The typical presentation involves paroxysmal pain of sudden onset and a duration of only a few seconds. The pain is very intense and stabbing, in the way of electrical discharges, and may arise isolatedly or in waves. The number of attacks varies greatly from 2-3 episodes daily to subintrant continuous crises in the more severe forms, induced upon touching the corresponding trigger zones. During the crises the patient typically remains immobile; all activity ceases, and the affected side of the face contracts strongly. No pain is referred between crises.
In the atypical presentations the pain is dull or burning, and continuous: it can prolong for hours or even last all day. Women are more often affected than men. The pain is moderately intense - less so than in the typical presentations. Brief and more intense crises may superimpose upon the background pain, however (37). There are no trigger zones, and no autonomic manifestations are usually associated. The frequent nocturnal crises observed in patients with orofacial vascular pain are uncommon in this case. The course of the clinical picture is discontinuous and unpredictable, with periods of pain extending for days, weeks, months or years, and alternating with very long periods (months or - with luck - even years) of total remission (38).

Cluster headache - trigeminal neuralgia (CHTN), or cluster-tic syndrome, is a process of unknown cause associated to headache similar to CH and facial pain reminiscent of that observed in essential TN. The clinical picture is characteristic. The neuralgiform pain is located in the second and third trigeminal branches; the CH and neuralgias are usually not synchronous, though simultaneous manifestation is possible, generating three types of pain: that corresponding to CH, and pain representing the sum of both types of pain. More than 40 cases of this process have been documented in the literature to date (18).

In CHTN the headache and neuralgia always coincide on the same side of the face, and pain often develops in the same trigeminal root territory. This systematic coincidence suggests that the simultaneous presentation of both types of pain is no mere coincidence, and that both are intimately related.

Important semiological differences exist between TN, CH and CHTN. As an example, the neuralgic pain of CHTN predominates in the territory of the first trigeminal branch, while in TN the pain fundamentally affects the maxillary and mandibular branches. In turn, the CH crises usually last 15-90 minutes, and generally arise 1-3 times per day, while CHTN headache tends to be much briefer (1-5 min.) and may occur as often as 50 times in a single day. These data suggest that CHTN is a differential entity distinct to any other described to date.

The lesion underlying CHTN must affect the trigeminal nerve, for the disorder causes trigeminal neuralgic pain. The same lesion must in htm be responsible for the headache. The neuralgic pain is feasibly related to alterations in the myelinic trigeminal fibers, as has also been proposed for TN. The intervention of the non-myelinated fibers would in turn trigger vascular serosal inflammation, thereby contributing to sensitize the vessels and prolong the headache (19).

Cluster headache - migraine. Cluster headache - migraine is a poorly defined and infrequent atypical variant of CH, characterized by headache involving typical features of CH and certain characteristics of migraine - generally an aura, which may be visual, sensory or motor. The latter must be distinguished from the paresthesias that the patient can experience at the onset of the crisis in the region where pain develops, since this symptom may reflect participation of the trigeminal nerve in the CH. In some cases pain or loss of strength sensation may be referred in the arm or leg. The characteristic pain of CH subsequently develops (20).

Other variants. A series of unusual CH variants have been described secondary to treatment or ergotamine or steroid abuse (18). In this sense, idiopathic stabbing headache is a type of vascular headache mainly observed in women, and characterized by extremely brief, uni - or multifocal pain episodes (duration 1 sec. or less), with frequent changes in localization in one or both sides of the head. The orbit is the most commonly affected zone, and no triggering factors or accompanying symptoms are observed. The frequency of the paroxysmal attacks is highly variable, from one crisis a year to more than 50 in a single day. Under extreme circumstances a stabbing status with one crisis per minute can be observed. Indomethacin treatment usually affords considerable relief.

In terms of the average duration of the accesses of pain, idiopathic stabbing headache typically lasts 1 second, TN 1-5 seconds, SUNCT 1 minute, chronic paroxysmal hemianemia 13 minutes, CH 35 minutes, and facial migraine hours or even days (21, 22).

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2. Paroxysmal hemicrania
Chronic paroxysmal hemicrania (PH) is generally observed in females, with cases documented in patients aged 6 to 80 years. The pain is unilateral, and the same side is always affected; the ocular, frontal and temporal regions are the preferential localizations, and the pain may develop during the day or at night. The dysautonomic phenomena correspond to the side of pain. Numerous pain episodes (8 to over 30) develop during the day, with a duration shorter than in the case of CH - from 13 to 29 minutes (23). The response to indomethacin is typically absolute (24), though the inclusion of absolute response as a diagnostic criterion has recently been questioned (23).

Episodic PH refers to the temporal pattern of the disorder, involving a series of painful crises or „active periods“ arising in succession, and separated by pain-free intervals (25, 26). Patients with continuous crises or constantly active periods are said to suffer chronic PH (2). Benodiel and Sharav (23), in their 1998 review, reported 111 such cases referred in the literature.

The main differential diagnostic difficulty is posed by CH. Both conditions involve very intense, unilateral pain associated to eye and nose dysautonomic manifestations. Chronic PH should be suspected in females, and involves much more frequent (but also shorter) pain episodes than CH. Therapeutic performance may also serve to distinguish the two conditions; thus, the former responds to oxygen, ergotamine tartrate and sumatriptan, while the latter is amenable to ergotamine (24). On the other hand, PH should also be distinguished from TN; in this sense, some authors have reported the simultaneous presentation of both disorders in the same patient (27).

PH has also been described secondary to organic maxillary alterations - specifically, maxillary sinusitis and a maxillary cyst. In the patient with the maxillary cyst, the PH crises resolved over a 22-month follow-up period after surgical treatment of the cyst (28). This observation suggests the peripheral activation of the trigeminovascular system by local alterations that would induce neurogenic inflammation. On the other hand, there have been recent reports of symptomatic chronic PH due to a parasellar hypophyseal micro-adenoma and a maxillary cyst (29).

3. Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)
The SUNCT syndrome is characterized by brief, paroxysmal episodes of facial pain accompanied by homolateral autonomic manifestations (generally conjunctival injection and lacrimation). There are marked similarities to TN, though autonomic manifestations are not normally associated to neuralgias (1).

The crises typically manifest in the daytime and only very rarely at night. The duration is 15-120 seconds, though some episodes have been reported to last up to two hours. The frequency in turn varies from several attacks daily to several per hour. The mean number of crises according to Pareja et al. is 28 daily (21). The pain is quite intense and can be triggered by touching trigeminal innervation zones. The localization is unilateral, with characteristic involvement of the ocular and periorcular zones. By definition, SUNCT is accompanied by marked conjunctival injection and tearing. It exhibits a clear female predominance (7:1 over males), and a distinguishing characteristic is its resistance to anticonvulsive and vasoactive drugs (23).

SUNCT is distinguished from TN by its marked predominance among females, associated autonomic signs and resistance to anticonvulsive medication. In CH the crises are longer lasting, less frequent and often nocturnal. In SUNCT, pain is characteristically briefer, and treatment is scanty effective - with no response to indomethacin (24).

4. Hemicrania continua
Hemicrania continua (HC) is characteristically unilateral and continuous, persisting from the time the patient gets up in the morning until bedtime. The severity of pain is moderate to intense, and few associated autonomic manifestations are observed. There are no triggering factors, and the condition responds well to salicylates. The response to indomethacin is absolute and persistent (30).
The 1994 review by Newman et al. (31) reported 34 cases, with continuous pain but involving major fluctuations over time; moreover, many patients suffered increased intensity paroxysms that could last from 20 minutes to several days. Nocturnal exacerbation episodes were reported in one half of cases.

HC is not usually episodic, though remittent forms exist. The condition can arise in the context of analgesics abuse - which may in turn alter the clinical characteristics and response to treatment (9).

5. Orofacial vascular pain

According to Benodiel et al. (1), orofacial vascular pain (OVP) includes patients with vascular headache presenting a primary intraoral component (teeth or mucosa). They described 29 patients with a mean age of 42 years; the pain was characteristically intense, unilateral and in most cases lasted minutes or hours. In one half of cases there were concomitant homolateral autonomic vegetative phenomena. In turn, the pain was seated within the primary dentoalveolar process in 62% of patients (teeth and adjacent gums), and proved more diffuse with involvement of the mucosa beyond the periodontal structures in 38% of cases. In one third of the patients the condition was accompanied by peri orbital pain, with periauricular pain in another third. Almost 40% received dental treatment to achieve pain relief (1).

OVP has been referred to as phantom tooth pain - a term that implies the existence of underlying traumatic neuropathic mechanisms (32, 33). The condition would in turn correspond to Brooke’s „atypical odontalgia“ (34) though it remains debatable whether the pain is vascular or neurogenic. Many patients suffer continuous pain, in contrast to the classical types of vascular pain. According to Benodiel et al. (1), atypical odontalgia - which manifests as intense, episodic and generally pulsatile pain without accompanying symptoms or manifest organic causes - constitutes a type of vascular pain best referred to as orofacial vascular pain (OVP). In the event the pain is constant and burning, these authors suggest the existence of neuropathic mechanisms and propose the term „orofacial neuropathic pain“ to describe the condition. Possibly, in some cases OVP coexists with neuropathic type pain - particularly in patients who have undergone multiple dental interventions with the aim of treating the pain.

The teeth possess a potent nociceptive capacity that serves to warn of possible structural damage. In this sense, the teeth are „visceral structures“ that function as part of the masticatory musculoskeletal system. Pain of dental origin is described 29 patients with a mean age of 42 years; the pain was seated within the primary dentoalveolar process in 62% of cases (teeth and adjacent gums), and proved more diffuse with involvement of the mucosa beyond the periodontal structures in 38% of cases. In one third of the patients the condition was accompanied by peri orbital pain, with periauricular pain in another third. Almost 40% received dental treatment to achieve pain relief (1).

Effective treatment of orofacial vascular pain starts with an adequate diagnosis. In this sense, Benodiel et al., in 1997, recorded an average period of three years until correct diagnosis (1).

The symptomatic treatment of the crises in patients with CH is based on vasoactive drugs such as ergotamine and sumatriptan. Due to the frequency of the crises, the use of ergotamine drugs is limited by the hypertensive effects of ergotamine. The onset of the outbreak can be aborted by administering corticoids for brief periods of time. The crises tend to respond to the inhalation of oxygen for 15 min. In cases where the attacks are severe or arise more than once a day, prophylactic treatment may be provided in the form of ergotamine, calcium antagonists, indomethacin, propanolol clonazepam, corticoids, methysergide, sodium valproate and sumatriptan (39). In turn, different surgical treatments have been described, including trigeminal rhizotomy, neurectomy of the superficial petrosal nerve, or decompression of the intermediary nerve. The benefit derived from these procedures can be estimated at about 50% (7).

Carbamazepine is used in cluster headache - trigeminal neuralgia (CHTN), at a dose of 400-1200 mg daily. In cluster headache - migraine, the symptomatic treatment of choice is sumatriptan, with combined calcium antagonists and ergotamine tartrate for prophylactic purposes (2). In idiopathic stabbing, headache, indomethacin usually secures considerable relief (19).

In patients with chronic paroxysmal hemicrania, indomethacin is the first choice, starting with doses in the range of 50-75 mg/day and reaching a maximum of 150 mg/day if necessary (23). The response to indomethacin tends to be absolute - unlike in the case of CH, where the response is usually not very good. Other nonsteroidal antiinflammatory drugs (NSAIDs) have been found to be less effective. Amitriptyline, which is still widely used to treat...
other types of chronic orofacial pain, has also been reported to offer benefit in such patients (1, 40).

A distinctive feature of SUNCT is its total refractoriness to both anticonvulsive drugs and vasoactive medication - though remissions in response to carbamazepine and corticoids have been reported (1).

Hemicrania continua (HC) responds well to indomethacin - a fact considered by some to constitute an inclusion criterion for the condition - and piroxicam has also been reported to be effective (30).

In turn, orofacial vascular pain (OVP) responds favorably to nonsteroidal antiinflammatory drugs but not particularly well to indomethacin. Amitriptyline at doses above 50 mg also provides relief; this drug is an effective analgesic in the management of masticatory orofacial pain, and is usually provided when patients suffer associated muscle pain (40).

The rest of the orofacial vascular pain variants are effectively treated with non-steroidal anti-inflammatory drugs. Indomethacin and naproxen have been found to afford good symptoms relief (1). Amitriptyline is in turn effective as prophylaxis against vascular pain (41); moreover, since it offers good results in cases of orofacial muscle pain, it is usually administered in patients with associated muscle pain (as commented above: 40). Finally, valproic acid provides effective prophylaxis against both migraine and CH.

Sažetak

REFERENCES