Neurovascular Orofacial Pain

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Abstract

Referral of pain to facial and oral structures is common in neurovascular craniofacial pain (NVCP). Pain quality in NVCP often resembles dental pathologies so dental practitioners often encounter these patients. The commonest NVCPs, migraines and trigeminal autonomic cephalgias (TACs), are classically located around the ocular and frontal regions. Yet, isolated primary neurovascular-type pain in the lower two thirds of the face has been reported. These patients are not easily classified and have been termed facial migraine, or lower-half migraine. Often these isolated facial pains present with a clinical phenotype that, other than the location, may be diagnosed as a migraine or TAC variant. However, a primary facial neurovascular pain possibly separate from migraines or TACs may exist, called "neurovascular orofacial pain" (NVOP). These diagnostic entities are of high importance in the differential diagnosis of oral and facial pain and will avoid misdiagnoses as sinusitis and/or dental pulpal pathology.

In addition to the location outside the conventional boundaries of migraine and TACs, NVOP presents with a distinctive combination of clinical signs and symptoms. Thus, the rational for introducing NVOP is based on specific features that segregate it from other primary neurovascular-type craniofacial pain. Due to its intraoral and perioral location NVOP has great diagnostic and therapeutic importance in differentiating it from dental pathology. A clear classification and terminology will avoid misdiagnosis and dental mutilation. A brief description of NVCP and its underlying pathophysiology is introduced to give a framework for a better understanding of NVOP.

Keywords

Migraine • Trigeminal autonomic cephalgia • Neurovascular craniofacial pain • Trigemino-autonomic reflex

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Introduction

Neurovascular Craniofacial Pain (NVCP)

Definition and Classification

The best classification for headaches is that published by the International Headache Society (IHS) (Olesen 2013). In this classification the primary headaches include migraines, tension-type headaches, and the trigeminal autonomic cephalgias (TACs). The suspected etiology of the pain in migraines and TACs is considered to result, at least partly, from an interaction between the nervous and vascular systems (Goadsby 2001). Therefore, as a group, these are termed neurovascular craniofacial pain (NVCP).

Although sharing pathophysiological pathways, including activation of the trigeminovascular system, and many signs and symptoms, NVCPs are individually classified based on well-defined criteria of location, attack frequency, duration, accompanying signs or symptoms, and treatment response. Migraines may occur with and without aura and these are the most common, but there are a number of rare migraine syndromes classified by the IHS (Olesen 2013). The TACs include cluster headache (CH), paroxysmal hemicrania (PH), the short-lasting neuralgiform headache attacks (SUNHA), and hemicrania continua (HC) (Olesen 2013).

Migraines and TACs are classically located in the frontal and periocular regions. Yet, referral of pain to oral structures is common in NVCPs and may complicate diagnosis. More rarely only a facial or oral pain may occur in NVCPs, and these are often mistaken for regional pathologies such as sinusitis and dental pulpal disease. Furthermore, pain quality often resembles inflammatory processes (such as sinusitis and dental pathologies) so that patients with NVCP are often encountered in otolaryngology, dental, and orofacial pain clinics (van Vliet et al. 2003; Benoliel et al. 2008; Van Alboom et al. 2009; Benoliel et al. 2010). Specifically, pain location over the malar (or maxillary sinus) region as part of the migraine and TAC phenotype may confuse the diagnosis with both dental pain and sinusitis causing even further misdiagnosis (Klapper et al. 2000; Lipton et al. 2001; van Vliet et al. 2003; Schreiber et al. 2004; Eross et al. 2007; Kari and DelGaudio 2008; Jones 2009; Rossi et al. 2009; Van Alboom et al. 2009; Foroughipour et al. 2011; Patel et al. 2013; Viana et al. 2013).

Differential Diagnosis of NVCP in the Lower Part of the Face

Primary neurovascular craniofacial pain (NVCP) in the lower two thirds of the face (lower NVCP) is not easily classified with the IHS criteria (Benoliel et al. 1997; Penarrocha et al. 2004; Obermann et al. 2007). These have been termed facial migraine, lower-half facial migraine, or neurovascular orofacial pain (NVOP) (Benoliel et al. 1997; Daudia and Jones 2002; Penarrocha et al. 2004; Lance and Goadsby 2005; Dodick 2007; Gaul et al. 2007; Obermann et al. 2007; Benoliel et al. 2008, 2010). In the authors' experience many patients with lower NVCP can be diagnosed, based on accompanying signs and symptoms and features other than location, as either atypical migraines or atypical TACs. However, a third group not fitting the criteria for either atypical migraines or TACs, termed neurovascular orofacial pain (NVOP), has been observed (Fig. 1).

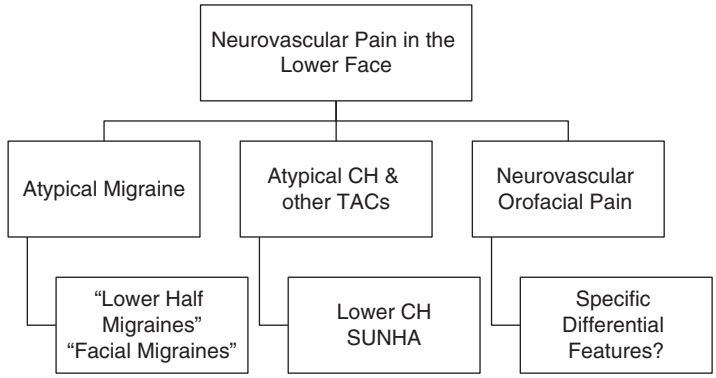

Fig. 1 Differential diagnosis of neurovascular pain in the lower face. These are often atypically located migraines or trigeminal autonomic cephalgias (TACs), particularly cluster headache or short-lasting unilateral neuralgiform headache attacks (SUNHA). A third group that does not neatly fit diagnostic criteria for migraine or a TAC is termed neurovascular orofacial pain. Currently research is investigating whether there are specific differentiating features that justify separate classification

In addition to an atypical location, NVOP's clinical features contain a distinctive combination of signs and symptoms, common to both migraine and TACs. Thus, the rationale for introducing NVOP is based on specific features that segregate it from other primary neurovascular-type craniofacial pain (NVCP), and due to its intraoral and perioral location that have great diagnostic and therapeutic importance for differentiating NVOP from dental pathology (Benoliel et al. 1997; Czerninsky et al. 1999; Benoliel et al. 2008, 2010). The authors have previously collected cases with NVCP and, applying IHS criteria, found that 52% were unclassifiable. These have subsequently been grouped into an entity termed neurovascular orofacial pain (NVOP) (Benoliel et al. 1997; Czerninsky et al. 1999), hypothesizing that a primary neurovascular pain, separate from migraines or TACs, may exist (Benoliel et al. 1997).

As many of the features of NVOP and response to therapy are similar to those of migraine without aura (MWoA), or chronic migraine as well as to TACs, in particular cluster headache (CH), the following section will briefly focus on the main features of MWoA, chronic migraine and CH.

Migraine

Migraine is a common disabling primary headache disorder and has two major subtypes.

(1) Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms. (2) Migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, and depression; cravings for particular foods; repetitive yawning; fatigue; and neck stiffness and/or pain.

Migraine affects a relatively small part of the population, but due to its long duration, severe pain and debilitating neurological symptoms is a major healthcare concern. The two most common types of migraine headaches are migraine without aura (MWoA) and migraine with aura (MWA) (Olesen 2000).

Epidemiology: The percentage of the adult population with an active migraine is 11% and 42% for active tension-type headache (Stovner

et al. 2007). New cases of migraine are uncommon among males but relatively common among females in their late 20s with the highest rates found in the 25–34 year age group (males 6.5, females 22.8 per 1000) (Stewart et al. 1991). Consequently, 50% of patients have migraine before the age of 25, and by 35 years of age 75% of migraine patients are affected (Stewart et al. 2008). Among both males and females under the age of 30 years, the incidence rate for migraine with visual aura appears to peak earlier than MWoA (Stewart et al. 1991). Both MWoA and MWA peak earlier in boys and explain why in childhood males have a higher prevalence of migraine than girls (Lipton and Bigal 2005). At age 11 a female preponderance appears, possibly linked to female hormones. In most studies MWoA is more prevalent than MWA (Rasmussen and Olesen 1995a).

Location: Headache is typically unilateral with no side preference, but is reported bilaterally in some patients (Rasmussen et al. 1991; Rasmussen and Olesen 1995a; Kelman 2005). Migraine that occurs persistently in the same side (side-locked migraine) has been observed in up to half of migraineurs (Kelman 2005). A single location is rarely encountered and commonly migraines occur in the ocular, temporal, and frontal regions. The occipital and neck regions are also commonly involved while the vertex and diffuse location are rarer (Kelman 2005).

In 1963 Harold Wolff observed: "The sites of migraine headache are notably temporal, supraorbital, frontal, retrobulbar, parietal, auricular, and occipital. However... they may occur as well in the malar region the upper and lower teeth, at the base of the nose, in the median wall of the orbit, in the neck" (Wolff 1963). Atypical locations around and in the mouth have therefore been known for some time. In a population-based sample, 8.9% of patients reported migraine pain in the head and the lower half of the face (Yoon et al. 2010). Patients with facial pain suffered more trigemino-autonomic symptoms than migraine patients. Rarely isolated facial pain is the only presentation of migraine (Eross et al. 2007; Yoon et al. 2010). In 0.2% (one case) isolated facial pain without headache was the leading symptom of migraine (Yoon et al. 2010). Facial pain is therefore not unusual in migraine, whereas isolated facial migraine is rare.

Quality: Typically pain is throbbing or pulsating (47–82%) but may be occasionally pressing (Rasmussen et al. 1991; Russell et al. 1996; Stewart et al. 2003). Pain intensity is moderate to severe with an average visual analog scale rating (VAS) of 7.5 (Steiner et al. 2003). Pain intensity is not uniform; mild to moderate (VAS 3–6) and moderate to severe (VAS 7–8) pain is reported by about 40% of migraineurs each and 15% report very severe pain (VAS 9–10) (Stewart et al. 2003). Some patients (24%) describe exacerbations of pain within an attack (Stewart et al. 2003). Others report interictal short, sharp periorbital pain, often described as icepick pains (Rasmussen and Olesen 1995b).

A feature of MWoA is that it is almost invariably (95%) aggravated by routine physical activity such as walking or climbing stairs (Rasmussen et al. 1991; Russell et al. 1996). Many patients report that even moving the head, coughing, or breath holding will accentuate their headaches. Premonitory symptoms may begin hours or even a day or two before the other symptoms of a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning, and pallor. Additionally hyper- or hypoactivity, depression, and food cravings are reported. Some of these signs have been found to be predictive of headache: speech difficulty, reading/writing difficulty, yawning, emotional changes, blurred vision, and phonophobia (Giffin et al. 2003). Most premonitory signs are actually part of the migraine complex and not a trigger.

Associated signs and symptoms: On average, 50% of migraineurs vomit during an attack, 80% report nausea, and more than 80% report photophobia or phonophobia (Rasmussen et al. 1991; Rasmussen and Olesen 1995a). Associated signs are more prominent and common in severe headaches (Rasmussen et al. 1991). However, not all headaches are accompanied by the same signs, even within patients (Stewart et al. 2003). Migraine may present with ipsilateral autonomic signs (AS), most usually lacrimation (≈50%),

demonstrating significant correlation with unilateral and severe attacks (Kaup et al. 2003). Migraine patients with facial pain suffer significantly more trigemino-autonomic symptoms (conjunctival injection, tearing, miosis, ptosis, eyelid edema, nasal congestion, facial flush) than patients without facial pain (47.8 versus 7.9%) (Yoon et al. 2010). Remarkably, the majority of *pediatric* migraineurs (62%) had one or more cranial autonomic symptom, and symptoms tended to be bilateral. Age, gender, laterality of headache, presence of aura, and whether migraine was episodic versus chronic did not influence the likelihood of having cranial autonomic symptoms (Gelfand et al. 2013).

Temporal Pattern: Migraine is a periodic headache lasting 4–72 h, and longer lasting attacks are considered "status migrainosus" (Olesen 2013). In about half of migraineurs pain duration was 5–24 h, in a third more than 25 h, and in a small number (16.4%) less than 5 h (Stewart et al. 2003). The headache resolution phase is gradual in most patients (Giffin et al. 2003). For most migraineurs headache frequency is less than one per month (Pryse-Phillips et al. 1992; Steiner et al. 2003), but vary considerably from 6–12 per year (46%) to 1–2 per month (20%), up to 2–4 per month (16%) (Stewart et al. 2003). Clinic populations report more frequent headaches with a third suffering more than four attacks monthly (Magnusson and Becker 2003). MWoA has a higher average attack frequency and is usually more debilitating than MWA. Seasonal or cyclic patterns have been associated with migraine attacks, often correlating with light hours (Alstadhaug et al. 2005).

Chronic Migraine

Chronic migraine (CM) is defined as headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month, and/or respond to migraine-specific treatment, occurring in a patient with a lifetime history of at least five prior migraine attacks and no medication overuse (Olesen 2013). Results of electrophysiologic and functional imaging studies indicate that chronic migraine is associated with abnormalities in the brainstem that may be progressive. Additionally, chronic migraine is associated with a greater degree of impairment in cortical processing of sensory stimuli than in episodic migraine, perhaps due to more pervasive or persistent cortical hyperexcitability (Aurora et al. 2011). Because of these distinctions it is critical to focus on chronic migraine as a unique condition, even though its relationship to episodic migraine, primarily as a predisposing condition, is acknowledged (Aurora et al. 2011).

Epidemiology: The 1-year gender stratified prevalence for CM is 1.3% for women and 0.5% for men. CM prevalence rates vary by age, and are highest for women (1.9%) and men (0.8%) in the age range of 40–49 years. CM represents 7.7% of the total migraine population (Natoli et al. 2010). Yet, about 3% of individuals with episodic migraine progress to chronic migraine.

Location: Typically the headache location is bilateral in the frontotemporal region, but up to half may be strictly unilateral.

Quality and temporal patterns: Headache is mostly mild to moderate with a dull and pressing quality. Truly continuous headache is observed in under half of patients, and although most patients do not awaken with a headache, many will develop it during early morning. Night-time arousals due to headache are reported particularly by women (Krymchantowski and Moreira 2001). The clinical evolution appears to occur gradually over months or years, with some individuals progressing from infrequent attacks (2–104 headache days/year) or frequent episodic attacks (105–179/y) to chronic migraine (Bigal and Lipton 2008). Factors associated with the progression of episodic to chronic migraine include female gender, lower socioeconomic status, and marital status (unmarried). Other factors include obesity, snoring, other pain syndromes, previous neck or head injury, stressful life events, caffeine intake, and acute headache medication use. Sleep disorders, psychopathology (especially anxiety and depression), and gastrointestinal disorders also occur more frequently in those with chronic migraine than in those with episodic migraine

(Scher et al. 2008). Additionally MWoA is most prone to accelerate to CM with frequent use of symptomatic medication, resulting in a new headache termed *medication-overuse headache* (Olesen 2013). After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and should be rediagnosed accordingly (Olesen 2013). Medication overuse is defined as intake of simple analgesics (e.g., aspirin, acetaminophen, ibuprofen) on more than 15 days per month or the intake of combination analgesics, opioids, ergots, or triptans on more than 10 days per month (Diener et al. 2011). Acute pain medication overuse or overuse of specific migraine medication is reported in about 66–75% of adults with CM (Schmid et al. 2013).

Trigeminal Autonomic Cephalgias (TACs)

The trigeminal autonomic cephalgias (TACs) are a group of pain disorders that share the clinical features of headache, which is usually lateralized, and accompanied by prominent cranial parasympathetic autonomic features, which are again lateralized and ipsilateral to the headache.

TACs are characterized by a shared clinical phenotype of trigeminal pain accompanied by prominent autonomic signs (AS) suggesting a shared pathophysiology (Olesen et al. 2013). Common diagnostic features of TACs include: episodic pain that is unilateral, pulsatile or sharp, of severe intensity, accompanied by AS (e.g., tearing and rhinorrhea) and often wakes from sleep (Olesen et al. 2013). TACs have been individually classified based on well-defined criteria of location, attack frequency, duration, and accompanying signs and symptoms with a specific and distinctive response to therapy.

Pain quality in TACs, particularly cluster headache (CH), and dental pulpitis are similar and oral health care providers are often the first health care providers consulted (Benoliel et al. 1997; van Vliet et al. 2003; Bahra and Goadsby 2004).

Cluster Headache

CH is the typical TAC, with severe pain and major autonomic activation (Olesen et al. 2013). Many CH patients describe toothache like pain (Gaul et al. 2012), and incorrect diagnosis may lead to dental treatment that is both misguided and unjustified; 15% of CH patients report having dental extractions in an attempt to treat their pain (Rozen and Fishman 2012).

Epidemiology: Several studies indicate that CH is a relatively rare syndrome predominantly affecting men (Ekbom et al. 2002; Tonon et al. 2002). The closest approximation to actual CH one-year prevalence is 0.53% (Fischera et al. 2008; Robbins and Lipton 2010). The male to female ratio to 4.3:1 (Fischera et al. 2008), with an increasing female proportion being reported in later studies. This is postulated to be associated with the proliferation of alcohol and tobacco use among females but may also be due to increased recognition of CH in females (May 2005; Robbins and Lipton 2010).

Location: CH is considered unilateral but attacks may change sides in about 20% of cases (Dodick et al. 2000; Black et al. 2006; Gaul et al. 2012), and bilateral CH may occur in about 3% of patients (Rozen and Fishman 2012). Attacks that alternate sides are more common between clusters than between attacks in the same cluster (Dodick et al. 2000). Peak pain intensity in CH is classically felt periorbitally or in the eye (Dodick et al. 2000; Bahra et al. 2002).

"Lower" and "upper" subtypes of CH have been reported. Pain in "lower CH" is ocular, temporal, and suboccipital with radiation to the teeth, jaws, and neck (Dodick et al. 2000; Cademartiri et al. 2002). Intra/perioral radiation of pain includes the jaws (37%), teeth (maxillary: 50%, mandibular: 32%), and the cheeks (45%) (Bahra et al. 2002; van Vliet et al. 2003). In "upper CH" pain is periorbital but radiates to the forehead, temporal, and parietal regions (Dodick et al. 2000). Note that radiation to the teeth (44%), the jaws (37%), and the ear (28%) is extremely common, irrespective of subtype (Rozen and Fishman 2012).

In one recent series about 40% of CH patients described their pain as "toothache-like" and may partly explain the extensive misdiagnosis with dental pain (Gaul et al. 2012).

Quality: CH is severe and rated as 8–10 on a 10-point VAS (Dodick et al. 2000; Torelli and Manzoni 2003). Nearly all patients describe their pain as sharp (Rozen and Fishman 2012) and less frequently throbbing or pressure-like (Torelli and Manzoni 2003; Black et al. 2006). A small number describe combined characteristics of sharp and throbbing pain. Descriptions of a "hot poker" or a "stabbing" feeling in the eye are common (Dodick et al. 2000; Bahra et al. 2002). The extensive descriptors used by patients attests to the wide variety of presentations (Torelli and Manzoni 2003). In addition, sudden jabs of intense pain are often felt and may be an integral part of some CH variants (Black et al. 2006). Restlessness during attacks is so frequent (>80%) that it is now included as a diagnostic criterion for CH (Torelli and Manzoni 2003; Marmura et al. 2010; Gaul et al. 2012). Patients are agitated (Rozen and Fishman 2012), move around, change body position, and this is particularly prominent during severe attacks. This is in sharp contrast to the quiet-seeking behavior observed in migraine.

Autonomic Signs (*AS*): Ipsilateral AS are very common in CH, with lacrimation being the most frequent and occurring in up to 90% of cases (Bahra et al. 2002; Gaul et al. 2012; Rozen and Fishman 2012). AS overwhelmingly occur with the headache rather than before or after (Lai et al. 2009). About 50–75% may have multiple AS such as conjunctival injection, nasal congestion, ptosis and/or miosis, and rhinorrhea (Bahra et al. 2002; Gaul et al. 2012). AS are transient and resolve with the headache but rarely ptosis and miosis (partial Horner's syndrome) may persist. Forehead sweating may be observed and this is usually bilateral (Lai et al. 2009; Rozen and Fishman 2012). "Lower CH" patients were found to report not only a higher overall rate of AS but also a higher predominance of nasal congestion, ptosis, and forehead and facial sweating (Cademartiri et al. 2002).

A small proportion of CH patients (3–7%) may not have AS during attacks, and this may make diagnosis difficult (Torelli et al. 2001; Martins et al. 2005). CH with AS is significantly more painful than CH without AS (Goadsby et al. 2001; Martins et al. 2005). Additionally AS are significantly more frequent in males and in episodic rather than chronic CH, but is probably related to differences in pain intensity (Martins et al. 2005).

Temporal Pattern: CH attacks tend to occur in clusters that last for a variable period of time (weeks to years) (Dodick et al. 2000). Based on the distinct temporal patterns of these cluster periods two clinical presentations of CH are described. Most CH patients (80–85%) suffer from the episodic type characterized by considerable pain free periods between clusters. The IHS defines episodic as "at least 2 cluster periods lasting 7–365 days and separated by pain-free periods of ≥1 month." In chronic CH repeated attacks recur over more than a year without remission or with remission periods lasting less than one month.

Episodic CH commonly occurs at least once daily for a period of weeks. At low frequencies, CH attacks tend to occur at the same time of day or night with surprising clock-wise regularity (Dodick et al. 2000). Active periods (average 6–12 weeks) are followed by a temporary remission or an inactive period that may last from weeks to years (average 12 months). Attacks tend to be shorter and less severe at the beginning and towards the end of each cluster period (Black et al. 2006). Particularly at the initial onset of CH, active periods are seasonal, occurring around spring or autumn (Dodick et al. 2000; Rozen and Fishman 2012; Lee et al. 2014). Correlation between daylight hours and CH occurrence and frequency has also been noted. However, as CH develops the active periods become less predictable and variations in the length of both active and inactive periods are apparent (Dodick et al. 2000).

Nearly half of patients report that the most common time for a CH is around 2 a.m. and a further one third at 1.00 or 3.00 a.m. (Rozen and Fishman 2012). Peak intensity is usually reached

within 9–10 min of onset but may develop more rapidly, within 3 min (Torelli and Manzoni 2003). Most attacks last 30 min to 1 h (average 45–90 min, range 15–180 min) but rarely may last from 3–48 h (Dodick et al. 2000; van Vliet et al. 2003; Gaul et al. 2012). The most common attack frequency is 2 per day but may reach 8 per day (Rozen and Fishman 2012). Most patients report daily attacks during active clusters (Rozen and Fishman 2012).

Neurovascular Orofacial Pain (NVOP)

Epidemiology

In 1997 it was reported (Benoliel et al. 1997) that out of 55 patients with neurovascular facial pain, 29 presented primary intraoral pain with characteristics of isolated neurovascular craniofacial pain. Based on location and unique characteristics and features, not fitting any of the IHS classifications, the latter was termed "neurovascular orofacial pain" (NVOP). The average age was 42.6 years (range 17–66) with a high female preponderance (F/M = 2.6:1). A later study (Penarrocha et al. 2004) identified 11 patients whom they called lower-half migraine. The mean age of this group was 35 years (range, 22–57 years), with 10 women and 1 man. In an additional study (Obermann et al. 2007) of a cohort of 7 patients (6 women), the mean age was 55.4+/−3.2 years (range 46–68), with a mean duration of illness of 12.4+/−3.9 years (range 3–29). In a later study, the authors (Benoliel et al. 1997) surveyed an additional 23 patients diagnosed as NVOP with a mean onset age of 39+/−13.7 years. This group consisted of seven men (mean onset age 33.4+/−11 years) and 16 women (40.8+/−14 years). Recently, an additional 61 patients with NVOP were studied (unpublished data), the mean age was 40.3 and the female to male ratio was 3.8:1. Based on a total of 131 NVOP patients, summarized from various studies, the mean age is 40.9 and the female to male ratio is 3.2:1 (Table 1). These data are in sharp contrast to a much earlier onset age in migraine, where 50% of patients have migraine before the age of 25, and by 35 years of age 75% are affected (Stewart et al. 2008) and the female to male ratio is 2:1 (Russell et al. 1995; Victor et al. 2010).

Clinical Features

Location: Some studies report mostly unilateral pain (Benoliel et al. 1997, Obermann et al. 2007). However, one of the studies used unilaterality as an inclusion criterion, and in later studies the same group found that close to half of patients had bilateral pain (Benoliel et al. 2008) (and unpublished data). Pain occurs primarily intraorally, with a number of teeth affected, usually around the alveolar process (62%) and mucosal sites (32%) (Benoliel et al. 1997; Penarrocha et al. 2004). In 35% of cases pain referral was to perioral structures (lips, chin, etc.), to the infraorbital region in 35% and to the preauricular region in 30% (Benoliel et al. 1997). In a later study conducted on 23 NVOP patients, 16 (70%) reported unilateral pain and 7 (30%) bilateral (Benoliel et al. 2008). To conclude, in about half of NVOP patients pain is bilateral, but in about two thirds of these there is a dominant more painful side.

Quality and Temporal Pattern: NVOP is characterized by moderate to strong, pulsating pain (Benoliel et al. 1997; Czerninsky et al. 1999; Penarrocha et al. 2004; Obermann et al. 2007; Benoliel et al. 2008). In 48% of cases the pain throbs and in 35% woke the patient from sleep (Benoliel et al. 1997, 2008). Of 23 patients studied (Benoliel et al. 2008) seven were episodic and 16 were of a daily or nearly daily pattern. Episodic cases were characterized by long attack duration (17.4+/−16.2 h) and a frequency of <15 days per month (6.3+/−3.3 days). Mean verbal pain report for NVOP cases was 8.3+/−1.4. Reported pain intensity was not different between unilateral (8.3+/−1.5) and bilateral (8.3+/−1.1) cases. Bilateral pain was marginally more frequent (43%) in cases that reported pain onset following trauma ($n = 7$) than in cases classified as primary NVOP. In another study (Penarrocha et al. 2004) pain was described as moderately intense in 64% and severe in 36%. The duration ranged from 1 to 4 days in 55% of the patients, and from 12 to 24 h in 45%. In another group (Obermann et al. 2007)

Table 1 Age and sex distribution in NVOP patients

	N	Age	Female/male	Terminology
Benoliel et al. 1997	29	42.6	20/9	NVOP
Peñarrocha et al. 2004	11	35	10/1	Lower half facial migraine
Obermann et al. 2007	7	55.4	6/1	Isolated facial migraine
Benoliel et al. 2008	23	39	16/7	NVOP
Haviv et al. Unpublished data	61	40.3	48/13	NVOP
Total	**131**	**40.9**	**100/31 (3.2:1)**	**NVOP**

NVOP neurovascular orofacial pain

of patients the mean attack frequency was 2.9+/−0.46 attacks (range 1–4) per month.

To summarize, about a third of cases are characterized by a chronic pattern reminiscent of chronic migraine.

Accompanying Phenomena: Pain can be accompanied by various local AS, and these were found in 36% of cases (Penarrocha et al. 2004). Specifically tearing (10%), nasal congestion (7%), a feeling of swelling or fullness (7%) particularly in the cheek, and a complaint of excessive sweating (7%) were reported (Benoliel et al. 1997). Other phenomena such as photo- or phonophobia (14%) and nausea (24%) are observed (Benoliel et al. 1997; Penarrocha et al. 2004; Obermann et al. 2007). Often patients report dental hypersensitivity to cold leading to diagnostic confusion (Czerninsky et al. 1999; Benoliel et al. 2010). Pain may be aggravated by physical activity (Obermann et al. 2007). On the whole, patients with neurovascular facial pain suffer more trigemino-autonomic symptoms than migraine patients with no facial distribution (47.8% versus 7.9%, $P < 0.001$) (Yoon et al. 2010). Similar results were observed in two other studies (Penarrocha et al. 2004; Obermann et al. 2007); pain was associated with local autonomic signs on the affected side (e.g., lacrimation, facial flushing, and rhinorrhea) and with systemic manifestations (nausea, vomiting, photophobia, and phonophobia).

The positive (PPV) and negative predictive values (NPV) of the clinical features in NVOP have been examined (Benoliel et al. 2008). Individually the presence of some of the features, such as tearing, is highly suggestive of NVOP (high PPV). However, since such features are often seen in other diagnoses the NPV was usually low. Combining a number of features improved the diagnostic criteria for NVOP with good PPV (0.71) and NPV (0.95) values. Based on this review these criteria have been modified as outlined in Table 2. These require further research and validation.

The pathophysiological mechanisms are detailed under etiology and pathophysiology. However, it is suspected that the mechanisms operating in "NVOP related toothache" are most probably inflammatory in nature, and often respond, at least temporarily, to analgesics or to tooth pulp extirpation. However, in the long run this is certainly not the appropriate treatment, and as later discussed under patient management, these patients require management with medications similar to those used for episodic or chronic migraine. Often teeth may over-react to clinical tests (e.g., cold application) similarly to teeth with pulpitis. Clinicians should be very attentive to the patient's complaint and the lack of local dental pathology that would explain such symptomatology.

Patient Management

Most patients with NVOP will need pharmacological management, either abortive (acute, symptomatic) or preventive (chronic, prophylactic). Abortive treatment is taken as early as possible before attack onset with the aim of stopping the pain attack. Prophylactic medication is taken on a daily basis in order to reduce the severity, duration, and frequency of pain attacks. As most cases on NVOP are chronic in nature or even when episodic of frequent, often daily occurrence, the prophylactic approach is warranted most of the

Table 2 Criteria for Neurovascular orofacial pain (NVOP)

Diagnostic criteria		Notes
A	At least 5 attacks of facial pain fulfilling criteria B–E	
B	Severe, uni/bilateral oral, and/or perioral pain	May refer to orbital and/or temporal regions. Side shift may occur. Bilateral location is reported in up to 50% of cases
C	At least one of the following characteristics: 1. Toothache with no local pathology 2. Throbbing 3. Wakes 4. Cold sensitivity in adjacent teeth (cold allodynia)	Frequently, painful vital teeth will be hypersensitive to cold stimuli. Some of the teeth in the painful region may have undergone root canal therapy with no long-lasting pain relief
D	Episodic or chronic attacks lasting 60 min to days	Chronic unremitting cases (around 30%) have been observed Subclassification into episodic and chronic forms may therefore be needed
E	Accompanied by at least one of the following: 1. Ipsilateral lacrimation and/or conjunctival injection 2. Ipsilateral rhinorrhea and/or nasal congestion 3. Ipsilateral cheek swelling 4. Photo- and/or phonophobia 5. Nausea and/or vomiting	See positive and negative predictive value calculations in text above
F	Not attributed to another disorder	Dental pathology may be very difficult to differentiate and needs careful assessment

times. Nonfrequent episodic NVOP can be managed abortively, but these are the minority of patients.

Abortive treatment: Abortive therapy is usually utilized when there are less than four attacks per month. Additionally abortive drugs are often used to supplement prophylactic regimens that do not totally eradicate pain; in these situations the drugs are often referred to as "escape" medications. The first line medication will often be a relatively inexpensive analgesic with a good safety profile. Efficacy of abortive therapy is maximized when an appropriate dose is initiated as early in the course of the attack as possible. Analgesics and anti-inflammatory drugs are to be considered first, and if these are not effective triptans should be utilized. Analgesics such as 1000 mg acetaminophen are good first-line in the acute treatment, if these fail, ibuprofen 400–800 mg or 550–825 mg naproxen sodium can be trialed (Matchar et al. 2000; Tfelt-Hansen et al. 2000). However, since most of these analgesics and NSAIDs can be obtained over the counter (OTC), they are associated with overuse and the risk of serious side effects such as gastric complications, and kidney or liver failure. If drug abuse is suspected or pain is chronic or more frequent the prophylactic approach is to be preferred. Prophylactic treatment is usually indicated due to daily or almost daily pain and the high sensitivity to cold food ingestion. Sometimes, trial triptan treatment should be considered in the more complicated cases in order to confirm the diagnosis of NVOP. Successful treatment with triptans might subsequently lead to implementation of prophylaxis (Obermann et al. 2007).

Prophylactic treatment: Prophylactic medication is taken on a daily basis in order to reduce the severity, duration, and frequency of pain attacks. In 2012 a Quality Standards Subcommittee of the American Academy of Neurology (AAN) and the American Headache Society provided an updated evidence-based recommendation for the preventive treatment of migraine headache (Silberstein et al. 2012). These guidelines appear to serve well in the treatment of NVOP. Level A medications,

with established efficacy include antiepileptic: Divalproex sodium, Sodium valproate or Topiramate, and beta blockers: Metoprolol or Propranolol. Level B medications, probably effective, are antidepressants: Amitriptyline or Venlafaxine and beta blockers: Atenolol or Nadolol. Clinicians should be familiar with these medications and be aware of their side effects in order to effectively and safely treat their patients.

A recent Cochrane review points to the efficacy of acupuncture for migraine prophylaxis, that is as effective as, or possibly more than, prophylactic drug treatment, and has fewer adverse effects (Linde et al. 2009). Acupuncture has not been tried in patients with NVOP, but its utilization alone or as adjuvant therapy to prophylactic drug treatment may serve as an attractive alternative.

NVOP: Differential Diagnosis

These include irreversible pulpitis and cold stimulus, or "ice-cream" headache. Cold stimulus headache occurs particularly in individuals with a history of migraine and is not associated with dental pathology (Fuh et al. 2003). Pain follows the passage of cold material over the palate and posterior pharyngeal wall and does not originate in the teeth; facial pain is produced in the mid-frontal region or around the ears, referred probably by the trigeminal and glossopharyngeal nerves, respectively. No treatment other than sensible caution is needed. Prolonged gingival cold allodynia should be considered in patients with atypical odontalgia (Zagury et al. 2011). With accumulated experience it has become apparent that many patients with NVOP have marked allodynia when a cold stimulus is applied to the vestibular mucosal area of the affected side. It has become now a standard test in suspected NVOP patients who complain about pain to cold drinks or food. A situation that may be particularly misleading is when after root canal therapy pain to cold drinks continue to exist, which may lead to more unnecessary dental treatment, when the source of pain stems from the mucosal area. Additionally, trial triptan treatment should be considered in more complicated cases. Although initially pulpal pain may resemble NVCPs, careful history and examination should easily differentiate between them (Table 3).

Classification Issues

Isolated neurovascular facial pains may form a distinct subdiagnosis and deserve careful examination (Benoliel et al. 1997, 2008, 2010). Until recently no attempt had been made to characterize or categorize these patients (Benoliel et al. 1997; Penarrocha et al. 2004; Obermann et al. 2007; Benoliel et al. 2008, 2010). It is tempting to assign these to the "migraine family" and remain with a term such as "lower-half migraine" (Penarrocha et al. 2004). However, *isolated* facial migraine is exceptionally rare (0.2%) (Yoon et al. 2010). It is suggested that the term be updated to neurovascular orofacial pain (NVOP) in keeping with current thought on the mechanisms underlying migraines and TACs. There are enough differentiating factors to distinctly classify NVOP and segregate it from migraine (Table 4). The most prominent are: oral and perioral or midface (Daudia and Jones 2002) location, late age of onset, and a neurovascular "pulpitis" (Benoliel et al. 1997; Czerninsky et al. 1999; Penarrocha et al. 2004; Dodick 2007; Obermann et al. 2007). In addition, migraine is predominantly episodic while NVOP emerges as largely chronic. While chronic migraine is mostly *bilateral* chronic NVOP is mostly *unilateral.* If NVOP is a migraine variant, one would expect to see the majority of patients with longer pain attacks, a younger onset and more photophobia, phonophobia, and nausea (Benoliel et al. 1997; Obermann et al. 2007). Some NVOP patients describe a history of episodic migraine suggesting similarities to CM (Benoliel et al. 1997; Penarrocha et al. 2004). However, unlike CM exacerbations of pain in NVOP are not characterized by more prominent or typical migrainous features and they differ in treatment response.

The similarities to the CH group are limited by the fact that there is an overwhelming female preponderance, and treatment response is not similar. Treatment of NVOP with classical antimigraine drugs has been successful and firmly

Table 3 Differential diagnosis between NVOP and irreversible pulpitis

Parameter	NVOP	Irreversible pulpitis
History of:		
Migraine	+	–
Past endodontics	+	–
Autonomic/systemic signs	+	–
Treatment/effectiveness:		
Endodontics	–	++
NSAIDs	+	+/–
Anticonvulsant	++	–
Amitriptyline	++	–
β-adrenergic blocker	+	–
Triptans	+	–
Clinical Signs:		
Teeth		
Hypersensitive to cold	+	+++
Tender to percussion	–	++
Change location/side shift	+	–
Carious (clinical/radiological)	–	++
Soft tissues		
Cheek swelling	+	–
Cheek redness	+	–

establishes an association with migraine (Benoliel et al. 1997; Czerninsky et al. 1999; Penarrocha et al. 2004; Obermann et al. 2007). In chronic cases, there have been very good results with prophylactic propranolol, divalproex, or, when muscle tenderness is prominent, amitriptyline. Some episodic cases respond quite well to NSAIDs, particularly naproxen sodium. Similarly, some cases respond well to triptans, but the response rate may be lower than in typical migraine (Benoliel et al. 2008). A summary of migraine and NVOP features is presented in Table 4.

To conclude, although the head and face are intimately related, diagnostic classifications of headache and orofacial pain are not sufficiently integrated. Although, the International Headache Society (IHS) has the most widely used classification system for headaches (Olesen 2013), it does not adequately cover currently accepted orofacial pain entities (Benoliel et al. 2008). As a result it states that "a subset, of otherwise typical patients, has facial location of pain, which is called "facial migraine" in the literature; there is no evidence that these patients form a separate subgroup of migraine patients" (Olesen 2013). Regrettably, the bibliography of the 2013 edition (Olesen 2013) on "Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure" is limited to references no later than 2001. Definitely, some newer data is required in order to make a prudent decision on the classification of NVOP.

Etiology and Pathophysiology

Pathophysiology of Migraine

In order to comprehend the etiology and pathophysiology of NVOP, one must first understand the pathophysiology of NVCP and in particular that of the most studied ones, migraine and CH.

It is thought that migraine headache is a manifestation of a brain state of altered excitability capable of activating the trigeminovascular system in genetically susceptible individuals (Noseda and Burstein 2013). Advances in in vivo and in vitro technologies indicate that cortical

Table 4 Differential diagnosis between migraine and neurovascular orofacial pain (NVOP)

	Migraine	NVOP
Onset (age)	20–40	40–50
M:F	1:2	1:3.2
Location (mostly unilateral)	Forehead, temple	Intraoral/lower face
Duration	Hours to days	Hours to days
Time course	Mostly periodic	Periodic but many with underlying chronic pain
Character of pain	Throbbing Deep	Throbbing Paroxysmal
Pain intensity	Moderate to severe	Moderate to severe
Precipitating factors	Stress, hunger, menstrual period, etc.	Cold stimuli applied to teeth
Associated signs	Nausea, photophobia, visual aura	Cheek swelling and redness, tearing

spreading depression (CSD) and activation of the trigeminovascular system and its constituent neuropeptides, as well as neuronal and glial ion channels and transporters, contribute to the putative cortical excitatory/inhibitory imbalance that renders migraineurs susceptible to attack (Pietrobon and Moskowitz 2013).

The trigeminovascular system: The trigeminovascular system consists of trigeminal neurons (mainly ophthalmic) and the blood vessels (usually cerebral) they innervate. The peripheral axons synapse with cranial structures, craniofacial blood vessels (predominantly pain-producing large cranial vessels) and the centrally projecting fibers synapse in the trigeminal nucleus caudalis and the upper two cervical divisions, the trigeminocervical complex (Goadsby and Hoskin 1997). The peripheral fibers contain substance P (SP) and calcitonin gene-related peptide (CGRP), released when the trigeminal ganglion is stimulated (Goadsby et al. 1988). Nerve fibers vary in their neuropeptide content; sensory fibers are rich in SP, CGRP, nitric oxide (NO), and neurokinin A; parasympathetic fibers contain vasoactive intestinal polypeptide (VIP) and NO; and sympathetic fibers express neuropeptide-Y (Tajti et al. 1999a, b). These peptides (NO, SP, CGRP, VIP) induce vasodilatation and plasma extravasation and are released into the blood stream and therefore can be assayed as indicators of trigeminal and autonomic nerve fiber activation.

Neurogenic Inflammation: Neurogenic inflammation (NI) occurs when trigeminal afferents are stimulated antidromically and release vasoactive neuropeptides that induce mast cell degranulation and plasma extravasation, which play a central role in the initiation of neurovascular type headaches. The fibers releasing these neuropeptides are characteristic of thin, unmyelinated C fibers. When released, the neuropeptides initiate a cascade of events including mast cell degranulation, platelet aggregation, vasodilation, and plasma extravasation (Izumi 1999), i.e., neurogenic inflammation (NI).

The headache phase of migraine depends on the activation and sensitization of trigeminal nociceptors that innervate the large blood vessels in the meninges. These processes then lead to sequential activation (and, in most patients, sensitization) of second- and third-order central trigeminovascular neurons, which in turn activate different areas of the brain stem and forebrain, resulting in pain and other migrainous symptoms (Pietrobon and Moskowitz 2013). Additionally, the vasodilatatory effect is thought also to be partly mediated by reflex activation of the parasympathetic system and the release of VIP (Goadsby and Edvinsson 1994).

However, vasodilation of meningeal and/or extracranial arteries is neither necessary nor sufficient to cause migraine pain. NI is one key mechanism that may underlie the activation and sensitization of perivascular meningeal nociceptors, but the endogenous processes promoting the inflammation during migraine attacks remain unclear (Pietrobon and Moskowitz 2013).

Central pain activation and modulation: Increasing evidence from animal studies supports the idea that cortical spreading depression (CSD) can cause sustained activation of meningeal nociceptors and central trigeminovascular neurons and can thus initiate the headache mechanisms. Also, in the period between attacks, migraineurs show abnormal processing of sensory information due to dysfunctional regulation of cortical excitability (Pietrobon and Moskowitz 2013). A central noxious event activates trigeminal afferents (i.e., pain) with reflex parasympathetic activation. Parasympathetic nerve section attenuates vasodilatation but not plasma extravasation (Bolay et al. 2002). Plasma extravasation is thus clearly shown to be under trigeminal nerve control while vasodilatation seems to be dependent on intact trigeminal and parasympathetic systems suggesting involvement of a trigeminoparasympathetic reflex (TPR, see below). A wide variety of symptoms that are associated with migraine headache, such as irritability, fatigue, sleepiness, exaggerated emotional responses, nausea, and loss of appetite, may appear before or after the onset of the headache. Most likely, the symptoms that appear before the onset of migraine (i.e., prodrome) are related to abnormal neuronal activity in cortical, diencephalic, and/or brainstem structures. In contrast, the most likely explanation for symptoms that appear after the onset of migraine is the bombardment of supramedullary brain structures involved in sensory, affective, endocrine, and autonomic functions by intracranial pain signals originating in the meninges (Noseda and Burstein 2013).

Migraine-like headaches are induced when peri aqueductal grey (PAG) areas are electrically stimulated (Veloso et al. 1998), or triggered by structural pathologies affecting the PAG (Goadsby 2002). Iron homeostasis in the PAG has been demonstrated to be progressively impaired in MA, MO, and chronic headache (Welch et al. 2001). These results support the hypothesis that the PAG is a major element in the pathophysiology of migraine attacks, possibly acting as a central generator or as a permissive dysfunctional control of trigeminovascular nociception.

Observed widespread allodynia is consistent with third-order neuronal sensitization such as in thalamic neurons clearly supporting a CNS component to the pathophysiology of migraine (Burstein et al. 2004). The establishment of sensitization is a crucial negative factor in determining the outcome of triptan treatment, so that early and aggressive intervention is advised; migraine attacks in humans treated with triptans prior to the onset of allodynia respond significantly better than those with allodynia (Burstein et al. 2004).

Pathophysiology of TACs

The three major features of CH are trigeminal pain, rhythmicity, and autonomic signs.

Pain

Fundamental to the pathophysiology of neurovascular headaches is the trigeminovascular system, described above. The distribution of pain in TACs implicates activity of the trigeminal nerve, particularly the ophthalmic branch.

Peripheral nerve activation explains pain and, when affecting the trigeminal nerve, may initiate reflex autonomic manifestations. Nociceptor activation was thought to originate from dilated blood vessels that stimulate trigeminal afferents directly. However, it seems likely that the vascular changes are an epiphenomenon of activation of the trigeminovascular system (May et al. 2001; Matharu and Goadsby 2002). Trigeminal and autonomic activation, as evidenced by increased levels of CGRP and VIP in the cranial circulation, as well as increased levels of NO, are seen in CH (D'Amico et al. 2002; Costa et al. 2003).

Observed ptosis and miosis, suggestive of sympathetic dysfunction, may be secondary to neuropaxic effects of carotid edema on the sympathetic plexus or may signify a generalized sympathetic dysfunction (Stillman and Spears 2008). Indeed, a dysfunction in the central control of the autonomic system in CH has been proposed (Boes et al. 2006).

Case descriptions of continued tearing with no pain in CH patients following surgical section of the trigeminal nerve establish the role of central

mechanisms in the TAC phenotype (Lin and Dodick 2005). A 59-year-old man with a 14-year history of left-sided CH underwent surgical section of the ipsilateral trigeminal root but continued to suffer *both* headaches and AS (Matharu and Goadsby 2002). The patient also continued to respond to sumatriptan in spite of nerve sectioning. Clearly in this case CNS structures only were necessary to induce CH, express the full phenotype and therapeutic response so it seems that pain need not originate peripherally. Current thinking is that primary headaches occur with no substantial peripheral pathology (Ekbom and Hardebo 2002; Goadsby et al. 2002).

It is increasingly clear that pain distribution in CH involves not only other branches of the trigeminal nerve but extra-trigeminal regions such as the ear, neck, shoulder, and arm (Boes and Dodick 2002; Cademartiri et al. 2002; Boes et al. 2006; Cohen et al. 2006; Cittadini et al. 2008; Prakash and Patell 2014).

The Hypothalamus

The trigeminal system has a two-way connection to the hypothalamus via the trigeminohypothalamic tract (May et al. 2006; Leone and Bussone 2009). Structural connections have been identified between the hypothalamus and the medullary dorsal reticular nucleus, a supraspinal system that gives origin to a descending projection that facilitates pain perception and other major structures involved in the affective and cognitive aspects of pain (Holle et al. 2011). Accumulating data therefore indicate involvement of the hypothalamic ventricular nucleus in antinociception (Miranda-Cardenas et al. 2006) and studies with orexins, hypothalamic peptides located in the posterior hypothalamus, have established that the posterior hypothalamus is a modulator of trigeminal nucleus caudalis activity (Bartsch et al. 2004a; Leone et al. 2005; Holland and Goadsby 2009).

The hypothalamus is therefore a prime candidate to initiate and "manage" CH. However, hypothalamic stimulation does not induce CH attacks (Schoenen et al. 2005; Bartsch et al. 2008; Leone et al. 2013) and will not abort an ongoing attack (Leone et al. 2006). Current thinking places the hypothalamus as playing a prime role in terminating attacks so that hypothalamic dysfunction may act in a permissive manner (Matharu and May 2008; Leone and Bussone 2009). Activation from brain areas other than the hypothalamus may be a primary event triggering headache (Bolay et al. 2002).

A role for the hypothalamus in CH is supported by functional and morphometric neuroimaging. During CH, but not in experimental pain, there is marked activation of the hypothalamus, ipsilateral or contralateral to pain in CH (May et al. 1998a, 1998b, 1999, 2000, 2001; Matharu et al. 2004, 2006; Cohen 2007). Studies with magnetic resonance spectroscopy demonstrate specifically impaired metabolic activity of the hypothalamus of CH patients indicating neuronal dysfunction (Lodi et al. 2006; Wang et al. 2006). Within headaches and interictally, PET morphometric studies reveal a significant structural difference (increased volume) in the inferior posterior hypothalamus of CH patients.

Dysfunction of the descending pain modulatory system has been suggested in the pathophysiology of headaches (Moulton et al. 2008; Holland 2009). Involvement of the opioid system and other top-down controls has been demonstrated in CH (Sprenger et al. 2006, 2007). These studies are supported by imaging findings of significant structural changes in pain modulation areas of CH patients (Yang et al. 2013). Neurophysiologic testing of CH patients confirms defective supraspinal controls and facilitated temporal processing of pain, but whether these are a cause or a result of pain is unclear (Perrotta et al. 2013). Patients with CH demonstrate significantly increased interleukin (IL)-2 receptors (Empl et al. 2003). Elevated IL-2 receptors indicate T cell and immune activation during CH. IL-2 is known to activate the hypothalamus and stimulate the release of corticotropin-releasing factor (CRF), potentially acting as a link between immune activation, CH, hypothalamic activation, and hormonal imbalances (Empl et al. 2003; Stillman and Spears 2008).

Rhythmicity

The periodicity and sleep association in CH suggests involvement of central sites involved in the control of the human "biological clock." In humans these are located in the suprachiasmatic nucleus. Hypothalamic regulation of the endocrine system involves rhythmic and phasic homeostatic modulation of the hypophyseal hormones and melatonin. In CH, changes have been observed in melatonin, cortisol, follicular-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone (Leone and Bussone 1993; Stillman and Spears 2008).

Autonomic Signs

The blood vessels of craniofacial tissues are innervated by three sets of nerves: the cranial parasympathetic, the superior cervical sympathetic, and the trigeminal sensory nerves. Cranial parasympathetic fibers arise in the superior salivatory nucleus (SSN) and innervate part of the craniofacial structures via the oculomotor, facial, glossopharyngeal, or vagal nerves. These efferents synapse in the ciliary, pterygopalatine, submandibular, lingual, or otic ganglia, and postganglionic fibers project to specific craniofacial targets such as the lacrimal, nasal mucosa and salivary glands as well as the craniofacial vasculature. Parasympathetic stimulation induces lacrimation and rhinorrhea as observed in CH. Elevated plasma VIP levels confirm the activity of the parasympathetic system in CH; in migraine this occurs only if AS are present.

Painful experimental stimuli in areas innervated by trigeminal nerve divisions 1 and 2 will cause ipsilateral lacrimation and local sweating, signs similar to those observed in TACs (Frese et al. 2003). Following trigeminal nerve stimulation decreased carotid artery resistance was observed, an effect blocked by trigeminal section. These effects are largely considered secondary to initiation of a parasympathetic reflex via trigeminal nerve activation; the trigeminoparasympathetic reflex (TPR). Existence of a TPR is established by anatomical and functional connections at brainstem level between the trigeminal complex and the SSN (Knight et al. 2005).

The autonomic system is regulated by hypothalamic nuclei acting through the nucleus tractus solitarius (Goadsby 2005). Specifically the TPR is also actively modulated by higher centers, including the hypothalamus (Goadsby 2005). Injection of a γ-aminobutyric acid (GABA) antagonist intravenously elicits a parasympathetic response similar to a reflex and supports the existence of a tonically active GABA-mediated inhibition of the TPR (Izumi 1999). Furthermore electrical stimulation of the anterior hypothalamus attenuates lip vasodilation in response to lingual nerve stimulation, an effect abolished by administration of a GABA antagonist (Izumi 1999). This confirms a role for hypothalamic modulation of TPR, in all branches of the trigeminal nerve. The TPR may therefore be pathologically disinhibited in TACs.

Pathophysiology of Neurovascular Orofacial Pain (NVOP)

Primary NVCP in the lower two thirds of the face accompanied by systemic and AS raises various issues relating to mechanisms. The pathophysiology of NVOP may be based on migraine and/or CH. If so, there is the possibility that neurogenic inflammation (NI) occurs in the oral and perioral tissues and may play a possible role in the phenotype of NVOP.

Neurogenic inflammation in oral tissues and the dental pulp: Nerve fibers entering the dental pulp have been identified as unmyelinated C-fibers and autonomic nerves, myelinated A-δ, and A-β fibers. Nerve fibers exhibiting SP and CGRP positive immunoreactivity are present in the dental pulp and oral mucosa in several species including humans (Tajti et al. 1999b). Following antidromic electrical nerve stimulation, neurogenic inflammation has been demonstrated in the dental pulp of dogs and in the dental pulp, lower lip, and oral mucosa of rats (Izumi and Karita 1991; Ohkubo et al. 1993). Involvement of adjacent teeth suggests that collateral C-fiber innervation exists within the pulps of molar teeth in the same dental quadrant (Komorowski et al. 1996) and may partly explain referral patterns in primary

NVOP. The anatomical substrate for neurovascular tooth pain is therefore present.

Since neurogenic inflammation in the trigeminovascular system seems to play a central role in the genesis of NVCPs the same mechanism could function in the oral mucosa and teeth. It has been postulated that the trigeminovascular system causes some of its effects by neurovascular activation within the space limited by the skull, a closed system that may rapidly lead to pressure buildup and increased nociceptor activation. This system is replicated in the dental pulp that is similarly confined by the surrounding dental hard tissues, and it is feasible that pressure buildup plays a role in intrapulpal nociceptor activation. For example, A-δ fibers have been shown to be sensitive to the increased intrapulpal pressure following plasma extravasation (Byers and Narhi 1999). However, homeostatic mechanisms limit pressure buildup in the pulp following antidromic stimulation (Heyeraas and Kvinnsland 1992), probably by reabsorption into the circulation. This may explain clinical observations that in spite of pulpitis-like symptoms in teeth of patients with NVOP, spontaneous pulp necrosis is rare.

Additionally, activation of 5-HT-1B/1D receptors, by local injection of naratriptan into ventrolateral PAG, produces selective inhibition of trigeminovascular nociceptive afferent input but not facial afferents (Bartsch et al. 2004). This finding points to the possible distinctiveness of orofacial neurovascular pain from migraine, and may have important consequences for the treatment of other neurovascular pains located in the orofacial region such as CH and NVOP.

The trigeminoparasympathetic reflex in the orofacial region: The trigeminoparasympathetic reflex (TPR) is thought important in the clinical phenotype of both migraine and TACs. Trigeminal pain, particularly in the ophthalmic branch, initiates reflex activation of the parasympathetic afferents and induces autonomic signs (AS). In neurovascular orofacial pain (NVOP) isolated to the lower face the question arises if the TPR is also activated.

Experimentally the TPR has been shown in animals after stimulation of the lingual nerve (Mizuta and Izumi 2004). Stimulation of the infraorbital nerve and the maxillary buccal gingiva in cats (Izumi 1999) and painful stimulation of tooth pulp in humans induces an increase in ipsilateral lip blood flow (Kemppainen et al. 1994).

An oral TPR is therefore apparent that is activated by intradermatomal stimuli. However, some cases of NVOP present with tearing and mandibular pain, i.e., cross-dermatomal activation of the TPR. Cross-dermatomal activation has been experimentally demonstrated in cats (Izumi 1999). Such cross-dermatomal reflexes could therefore explain clinical reports of lacrimation in mandibular and maxillary pain syndromes. However, there is no experimental evidence of ocular AS following peripheral stimuli to the mandibular region. Capsaicin injected into the forehead induces a rapid ipsilateral autonomic response, but injection of capsaicin into the mandibular region (third trigeminal division) does not (Frese et al. 2003). In mild to moderate experimental pain in the mandibular branches of the trigeminal nerve, no reflex lacrimation is found (unpublished observations). Experimental ophthalmic pain will induce vasodilatation in the internal carotid artery while mandibular pain will not (May et al. 2001). From this data we conclude that cases with pain in the distribution of the mandibular divisions accompanied by ocular AS such as lacrimation are not driven via peripheral activation of the TPR, and central mechanisms are therefore likely candidates. This may also explain the relative paucity of AS in NVOP.

Conclusions and Future Directions

Present knowledge indicates that NVOP is a possible variant of facial migraine, yet with enough segregating factors to justify a discrete diagnostic entity. The definition of NVOP is of paramount clinical importance, in particular for the dental profession, taking into account that intraoral neurovascular pain has many signs and symptoms suggestive of pulpitis.

While many features of NVOP have been described, and are summarized in Table 2, the hierarchy, or importance, of the different

symptoms is not yet well established. A better definition of patients' profiles is needed, in order to determine the most prevalent combination of signs and symptoms in each patient. This could be achieved as more patients are identified. As is the case with many "new" diagnostic entities, once they are defined, new cases begin to accumulate faster, ensuring a more well-founded definition of NVOP.

Cross-References

- ▶ Classification of Orofacial Pain
- ▶ Headache
- ▶ Neurophysiology of Orofacial Pain

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