Review

Orofacial Migraine

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Posted Date: 13 August 2024

doi: 10.20944/preprints202408.0928.v1

Keywords: migraine; headache; facial pain; cluster headache; orofacial pain; dental pain

Review

Orofacial Migraine

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Abstract: The diagnosis of migraine is based on clear criteria outlined in the International Classification of Headache Disorders version 3 (ICHD-3). Notably, the criteria in ICHD-3 omit the location of migraine. There are increasing reports of migraine in the facial region.[1–3] Facial presentations of migraine are not easy to diagnose as they appear in the lower 2/3rd of the face, often in the maxillary sinus region, around the ear, the upper/lower jaws and teeth.[4] Moreover, the symptomatology of these facial representations of these headaches often resembles sinusitis and dental pathology. We will review these presentations, their diagnosis and possible pathophysiology.

Keywords: migraine; headache; facial pain; cluster headache; orofacial pain; dental pain

Introduction

Migraine is a common primary headache with an additional number of rarer related syndromes. [1] The combination of high prevalence, severe pain, and debilitating neurological symptoms increases the social impact of migraine beyond that of other primary headaches. The two most common types of migraine headaches are migraine without aura (migraine) and migraine with aura (MWA), often confused in the clinic and in the literature. [5]

The diagnosis of migraine is based on clear criteria outlined in the International Classification of Headache Disorders version 3 (ICHD-3). Notably, the criteria in ICHD-3 omit the location of migraine, which is unlike the system used for other primary headaches and attests to the variability in pain location. Of relevance, are reports of migraine in the facial region.[1–3] Similarly facial pain resembling Trigeminal Autonomic Cephalgias (TACs) has also been reported [2,6–20], most recently in a large patient cohort. [3]

Facial Presentations of Primary Headaches

The publication of the recent International Classification of Orofacial Pain, 1st edition (ICOP),[21] bridges the classification gap for various orofacial pains (OFP) not included in ICHD-3. Section 5 of ICOP deals with orofacial presentations of primary headaches. Of relevance to this chapter, ICOP clearly classifies orofacial presentations of primary migraine and trigeminal autonomic cephalgias (TACs) in Tables 2–4. The TACs equivalents are beyond the scope of this review Table 1.

These facial representations are not easy to diagnose as they appear in the lower 2/3rd of the face, often in the maxillary sinus region, around the ear, the upper/lower jaws and teeth.[4] Moreover, the symptomatology of these facial representations of these headaches often resembles sinusitis and dental pathology. Clearly these cause significant diagnostic difficulties.

 doi:10.20944/preprints202408.0928.v1

On the Relation between Head and Face Pain in Patients

ICOP is not only a classification of orofacial pains but a true bridge between the intimately related subjects of oral, face and head pain. On the topic of orofacial pains resembling presentations of primary headaches, ICOP underscores that in clinical practice we often see three types of patients who seem to typify the overlap between headache and orofacial pain. Type 1: Headache patients who report additional facial pain during, and usually ipsilateral to, the headache attacks. Facial pain may often occur independent of the co-occurrence of headache. Type 2: Headache patients whose headache attacks have stopped and been replaced by facial pain attacks of the same quality, length and intensity, including occurrence of the associated symptoms of the former headache. Type 3: Headache naive patients who develop de novo orofacial pain attacks that resemble one of the primary headache types in pain character, duration and intensity, with or without the associated symptoms of these headache types.

Table 1. Orofacial pains resembling presentations of primary headaches.

ICOP Coding	Diagnosis	Subcategory Diagnosis/Time pattern	Time pattern
5.1	Orofacial migraines		
5.1.1		Episodic	
5.1.2		Chronic	
5.2	Tension-type orofacial pain		
5.3	Trigeminal autonomic orofacial pains		
5.3.1		Cluster Orofacial Attacks	
5.3.1.1			Episodic
5.3.1.2			Chronic
5.3.2		Paroxysmal hemifacial pain	
5.3.2.1			Episodic
5.3.2.2			Chronic
5.3.3		Short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic symptoms (SUNFA)	
5.3.3.1			Episodic
5.3.3.2			Chronic
5.3.4		Hemifacial continuous pain with autonomic symptoms	
5.4	Neurovascular orofacial pain		
5.4.1		Short-lasting	
5.4.2		Long lasting	

 doi:10.20944/preprints202408.0928.v1

Table 2. Episodic orofacial migraine (ICOP 5.1.1)

	Criteria	Comment
A.	At least five attacks fulfilling criteria B–D	Episodic or chronic pain exclusively in the orofacial region, without head pain, with the characteristics and associated features of 1. Migraine described in ICHD-3
B.	Facial and/or oral pain, without head pain, lasting 4–72 hours (untreated or unsuccessfully treated)	Orofacial pain otherwise meeting the criteria for any of the subtypes or subforms below, but accompanied by head pain, should be classified according to ICHD-3 under 1. Migraine.
C.	Pain has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe intensity 4. aggravation by, or causing avoidance of, routine physical activity (e.g. walking or climbing stairs)	Displays the typical characteristics of 1.Migraine headache as defined in ICHD-3 A group of patients with attacks of intraoral pain of varying duration, with atypical migraine-like features, have been described. These may be unrelated to migraine, and are described under *Neurovascular orofacial pain.*
D.	Pain is accompanied by one or both of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia	Orofacial migraine with aura has not, to our knowledge, been described, and is excluded from ICOP until better evidence of it accumulates.
E.	Not better accounted for by another ICOP or ICHD-3 diagnosis	

Table 3. Chronic orofacial migraine (ICOP 5.1.2).

	Criteria	Comment
A.	Facial and/or oral pain, without head pain, on ≥15 days/month for >3 months and fulfilling criteria B and C below	Characterization of frequently recurring OFP generally requires a pain diary to record information on pain and associated symptoms day-by-day for at least 1 month. The occurrence of the equivalent of *medication overuse headache* in the facial region has not been reported but drug abuse should be considered in chronic facial pain.
B.	Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 5.1 Episodic orofacial migraine	
C.	On ≥8 days/month for >3 months, fulfilling either or the following:	Displays the typical characteristics of Migraine Headache as defined in ICHD-3

 doi:10.20944/preprints202408.0928.v1

	1. criteria C and D for 5.1.1 Episodic orofacial migraine 2. believed by the patient to be orofacial migraine at onset and relieved by a triptan or ergot derivative	
D.	Not better accounted for by another ICOP or ICHD-3 diagnosis	

Table 4. Diagnostic Criteria for Neurovascular orofacial pain (NVOP).

	Diagnostic criteria	**Notes and comments**
A	At least five attacks of unilateral intraoral pain of variable duration, without head pain, fulfilling criteria B–D	Although essentially an intraoral pain, there may be referral and/or radiation to adjacent sites, particularly when pain is severe.
B	Pain has both of the following characteristics: 1. moderate or severe intensity 2. either or both of the following qualities: a) toothache-like b) pulsating	Side shift may occur, although pain is mostly unilateral, bilateral cases are reported in up to a third of cases.
C	Pain is 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. photophobia and/or phonophobia 5. nausea and/or vomiting	There are reports of abnormal sensitivity to cold, both interictally and during attacks.
D	Pain is unexplained by any local cause, and clinical and radiographic examinations are normal	Frequently painful vital teeth will be hypersensitive to cold stimuli.
E	Not better accounted for by another ICOP or ICHD-3 diagnosis	

Facial Presentations of Migraine: Orofacial Migraine

There have a been several sreports on migraine-like pain in the lower two thirds of the face [2,3,9,11,17,22]. There were no clear and consistent criteria for the diagnosis and different terms were assigned such as; orofacial migraine, lower half migraine, migraine with isolated facial pain [23], or migraine presenting as isolated facial pain, [24].

The phenomenon, still poorly recognized, is not new. In 1963 Woolf [25] wrote "*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 and....*" In this light, it is surprising that this presentation has caused diagnostic difficulties. As stated above careful examination of the ICHD-3 criteria for migraine reveals that the location of pain is unspecified [1]. In the footnotes for migraine the following appears;

 doi:10.20944/preprints202408.0928.v1

"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".

Ours and the experience of others confirms this and further suggests, that in addition to an orofacial component in migraine attacks, orofacial migraine (OFM) can be totally isolated from head pain.[2,9,11,17,22,24] Often these isolated facial pains present with a clinical phenotype that, other than the location, may be diagnosed as a migraine. The unusual location, both in migraines and TACs, often leads to erroneous diagnoses relevant to our discussion, such as oral pathology or sinusitis. [2,8,9,14,16,18–20,26–32] Patients with self-reported sinusitis that are migraine will respond well to sumatriptan [33]. Whether due to increased education or interest the diagnosis of head and face pain there are signs of improved diagnosis, [34].

There is little data specifically on the features of OFM. However other than location the clinical phenotype should be the same as in migraine – otherwise the diagnosis of OFM cannot be established. ICOP has defined episodic and chronic OFM (Tables 2 and 3).

4.1. Clinical Features

Location/Severity. The vast majority of patients report moderate to severe unilateral pain [24]. Pain occurs primarily in the midface but also in the lower face, over the mandible [3,11,16,24]. Location may resemble sinusitis.[14] In a recent study including 1,983 migraine patients 44 had a facial component (2.3%).[3] Only one patient had a totally isolated OFM and five had a 'relocated' migraine. The rest (n=38) had both ongoing migraine with an orofacial component. The most common facial involvement was reported in the maxilla, often involving dental pain. The mandible was affected in only 4 cases of facial involvement (9.3%).[3]

Quality and Temporal Pattern. Pain is usually throbbing and mimics inflammatory pathologies of the maxillary sinuses and the teeth. One would assume that duration is the same as in migraine, but the variability has not been described. Although migraine is typically episodic there are case series displaying a chronic course; up to 66% in the Lambru et al series [24]. This is like that seen in NVOP, see below.

Accompanying Phenomena. Research has shown that patients with isolated orofacial migraine report significantly more CAS, including conjunctival injection, tearing, miosis, ptosis, eyelid oedema, nasal congestion and facial flushing than in other migraine patients (47.8% vs. 7.9%; $P<0.001$) [24,35]. Also, it is important to emphasize that these facial presentations of headache disorders, with mixed migraine and trigeminal autonomic characteristics, are often misdiagnosed and many times mistreated as dental or otolaryngological problems [11,24,28]. No aura has, at this point, been reported in OFM (type 2 or 3).[3]

Treatment. Migraine therapy should be effective in OFM but we are still lacking data.

Epidemiology

A population-based study demonstrated that facial pain was not unusual in migraine (8.9%), yet *isolated* facial migraine was exceptionally rare (0.2%) [35]. However, Yoon et al. [35] were aware of some limitations of their study. Their screening question studied only migraine sufferers with respect to additional or isolated facial pain. Therefore, those having isolated facial pain without any other migraine symptoms could be neglected. Recently, Lambru et al. [24] found that out of 1176 patients with migraine 58 were defined as isolated facial migraine. The studied cohort is in our opinion a mixed one of both OFM and NVOP. Their pain location was restricted to intra- or/and extraoral areas, and 65% of these patients underwent endodontic treatments or multiple dental extractions making these patients very similar to the NVOP phenotype. Thus, isolated OFM accounted for about 5% of their migraine patients. With the prevalence of migraine at 15.3% in the US adult population (males 9.7%, females 20.7%) [36], and the preponderance of females in the NVOP group (about 80%), we estimate that the prevalence of NVOP/OFM approximates about 1% of the population.

 doi:10.20944/preprints202408.0928.v1

Neurovascular Orofacial Pain

The ICOP classification defined OFP resembling presentation of primary neurovascular headache under 3 categories: orofacial migraine, orofacial TACs and NVOP. ICOP subdivided NVOP into short and long-lasting forms reflecting the phenotypes that have been reported Table 4, [2,9,37,38]. NVOP shares many migraine signs and symptoms such as pulsating quality, often accompanied by nausea and/or vomiting, photophobia and phonophobia. Additionally, NVOP includes signs and symptoms such as toothache and dental sensitivity to cold, CAS such as ipsilateral lacrimation and/or conjunctival injection ipsilateral rhinorrhea and/or nasal congestion. Further research is needed to define the relationship between NVOP and OFM.

The clinical data suggest that NVOP includes patients in the two categories as defined in ICOP; Type 2 are headache patients whose headache attacks have stopped and been replaced by facial pain attacks of the same quality, length and intensity, including occurrence of the associated symptoms of the former headache and type 3 who are headache naive patients that develop de novo OFP. It has been our experience that in some cases (mostly in postmenopausal women with a migraine history) dental intervention such as root canal treatment may result in "reemergence" or "remapping"[39] of an isolated orofacial migraine type pain at the site of intervention. Additionally, it should be noted that in some of the cases mentioned under Type 1 (OFP during a migraine attack) tooth ache in the ipsilateral area is a common complaint.

Up until the publication of ICOP differentiating between the clinical phenotype of OFM and NVOP was not an easy task. Therefore, in our discussions on clinical features and epidemiology here, and above under orofacial migraine, there is undoubtedly overlap and the cohorts are not 100% homogenous. Going forwards the relationship between OFM and NVOP needs further clarification. In the interim we consider the data presented as possibly representing a mixed cohort of OFM and NVOP.

3.1. Clinical Features

Table 4 summarizes the findings of NVOP, first described by us in 1997 [2], and up to the most recent reports [23,24,38]. So far 199 cases have been documented, establishing a database to calculate age and gender distribution, pain location and characteristics as well as response to treatment.

Location. The vast majority of patients report unilateral pain (76%), disregarding Benoliel et al. [2] and Obermann et al. [23] who restricted their data to unilateral cases only (Table 4). Pain occurs primarily intraorally, teeth often affected, around the alveolar process (62%) and mucosal sites (32%) [2,11,38]. In 35% of cases pain referral was to perioral structures (lips, chin etc.), to the periorbital region (usually infraorbital) in 35% and to the preauricular region in 30%. Pain location is typically different from that described for migraine, later discussed.

Quality and Temporal Pattern. NVOP is characterized by strong, pulsating pain (7-8 on VAS).[38] Pain may last from minutes to hours, and up to 3 days [24]. Most cases are episodic in nature (see Table 4), and are characterized by a high frequency, short duration pain pattern mostly exacerbated by cold food ingestion.[38] NVOP is subdivided into a short and long-lasting form, the latter account for about 40% of cases; both are largely recurrent and chronic in nature but further studies are needed (Tables 2–4). About 60% of cases are episodic, short-lasting in nature. In some series, most cases present a chronic course (up to 66% in the Lambru et al series [24].

Accompanying Phenomena. Pain can be accompanied by various CAS, and these were found in close to 80% of cases. Specifically tearing (10-20%), conjunctival injection (14%), miosis (14%), ptosis (3%), nasal congestion (7-40%), a feeling of facial redness or swelling (3-7%), and a complaint of excessive sweating (7%) were reported [2,24]. Other phenomena such as photo- or phonophobia (14%) and nausea (24%) are observed [2,23]. Very often patients report dental hypersensitivity to cold leading to diagnostic confusion [28,40]. Pain may aggravated by physical activity [23].

Treatment. Low dose amitriptyline, propranolol (see case 10-1) and anti-convulsant therapy have been a successful prophylactic strategy in NVOP patients [28,40]. Topiramate, an anti-convulsant, is a very effective prophylactic agent particularly for chronic type NVOP. Triptan as an abortive agent was reported in one study and was effective in all patients [23]. While abortive or prophylactic

 doi:10.20944/preprints202408.0928.v1

treatments could be considered, it has been our experience that prophylactic treatment is generally indicated in most NVOP patients due to daily or almost daily pain and particularly the high painful sensitivity to cold food ingestion.

3.2. Epidemiology

The onset of NVOP is around 40 - 50 years of age (mean 43.4 years), with a female/male ratio approaching 4:1 [2,9,23,24,38]. Time to diagnosis was around 34-101 months (range 1-528 months) attesting to the diagnostic difficulties presented by these patients [2,11]. In 30-65% of cases the pain was diagnosed as secondary to dental pathology and patients underwent dental treatment with no success. The population prevalence is discussed above under orofacial migraine.

3.3. Differential diagnosis

NVOP, which is intraoral by nature, may radiate extraorally and in terms of features is like orofacial migraine. Due to the dental thermal hypersensitivity observed in NVOP the differential diagnosis will include inflammation of the dental pulp (pulpitis, see Chapter 6) and cold stimulus, or "ice-cream" headache. Although initially pulpitis may resemble NVOP careful history and examination should easily differentiate between them. Additionally, trial triptan treatment should be considered in the more complicated cases in order to ascertain NVOP pulpal pain mechanisms [23]. Cold stimulus headache occurs particularly in individuals with a history of migraine and is not associated with dental pathology. Pain follows the passage of cold material over the palate and posterior pharyngeal wall and does not originate in the teeth. The evoked facial pain is 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. PTTN may be confused due to the prolonged gingival cold allodynia that so often accompanies pain.[41] However, PTTN's history of trauma, the sensory deficits on examination and pain quality and pattern are very different from that of NVOP [9,38,41].

Pathophysiology

Migraine headache is likely a manifestation of an altered brain excitability state capable of activating the trigeminovascular system in genetically susceptible individuals.[42] The premonitory phase appears to involve the hypothalamus and its functional connections to specific brainstem nuclei and cortical regions, whereas migraine headache pain involves increased sensory processing within peripheral and central trigeminovascular pathways. Current data indicate that cortical spreading depolarization (CSD) and activation of the trigeminovascular system and its constituent neuropeptides (resulting in neurogenic inflammation), as well as neuronal and glial ion channels and transporters contribute to the putative cortical excitatory/inhibitory imbalance that renders those with migraine susceptible to an attack. [43] The various symptoms and neurological disturbances observed during all phases of migraine are complex and wide-ranging. Disturbances of sensory function, affect, and cognitive and autonomic function may be experienced, suggesting involvement of multiple neural networks. [44]

Pathophysiology of Facially Located Neurovascular Pain

The mechanisms underlying facial pain presentations of neurovascular headache disorders are suspected to involve the mechanisms described above but remain unclear.[4] One common hypothesis relies on the intracranial and extracranial innervation patterns of the trigeminal nerves. The intracranial structures for pain perception, i.e., the dura mater, are primarily innervated with the V1 branch and very little from V2 and V3. There is direct anatomical communication between the intra- and extracranial innervations of the trigeminal nerve: In both rat and human dura mater, some intracranial fibers leave the skull through emissary canals and fissures to innervate the periosteum and extracranial tissue such as the pericranial muscles.[45] Therefore, the anatomical connection between the intracranial and extracranial fibers provide a route of how trigeminovascular activation

 doi:10.20944/preprints202408.0928.v1

of the dura extends to their extracranial counterpart, the V1 dermatome in the face.[46] However, the dura mater in the posterior cranium is innervated by V2, V3 and cervical branches.[47] Intracranial activation of V2/V3 fibers is therefore more likely to evoke posterior head pain whereas intracranial activation of V1 would evoke frontal headache. Extracranial activation of the trigeminal nerves may also lead to the intracranial activation of their counterparts. Neurogenic inflammation via intranasal administration of capsaicin and formalin increased plasma protein extravasation not only in the nasal mucosa, but also the dura mater.[48] Based on the anatomical and functional connection between different branches of the trigeminal system, it is surprising that facial presentation of headache disorders remains so rare. Primary neurovascular pain in the lower two thirds of the face accompanied by systemic and CAS raises various issues relating to mechanisms. The pathophysiology of NVOP may be based on migraine. If so, we need to analyze the possibility that neurogenic inflammation (NI) occurs in the oral and perioral tissues and consider its 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.[49] The levels of two sensory neuropeptides SP and CGRP and two endogenous opioids, methionine-enkephalin, and β-endorphin were studied in human dental pulps. After 24 hours of an intrusive stimulus, associated with discomfort, only SP significantly increased, clarifying the role of neurogenic inflammation in early injury response. [50] Analysis of human dental pulp revealed significantly greater expression of CGRP, SP and VIP, in permanent teeth relative to deciduous counterparts. [51] This may explain the lack of children in reports of NVOP. [2,11] Following antidromic electrical nerve stimulation, neurogenic inflammation (NI) has been demonstrated in the dental pulp of dogs and in the dental pulp, lower lip and oral mucosa of rats. [52,53] This effect is not attenuated following sympathectomy. [54] Involvement of adjacent teeth suggests that collateral C-fiber innervation exists within the pulps of molar teeth in the same dental quadrant [54] and may partly explain referral patterns in primary NVOP. The anatomical substrate for neurovascular tooth pain is therefore present.

Since NI in the trigeminovascular system seems to play a central role in the genesis of headache and facial pain, 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 build up 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 possible that pressure build-up 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. [55] However homeostatic mechanisms limit pressure build up in the pulp following antidromic stimulation, [56] probably by re-absorption 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. [57] This finding may have important consequences for the treatment of OFM and other neurovascular pains located in the orofacial region such as CH and NVOP.

Central Mechanisms

The central somatotopy of trigeminal nucleus caudalis (TNC) is onion-ring shaped with the center being the perioral region. However, fibers from the V1 branch project more to the caudal part of the TNC, whereas those from the V2 and V3 branches more to the rostral part of the TNC.[58] This distribution also provides the anatomical basis of why cervical modulation, e.g., greater occipital nerve (GON) block, may be effective in aborting headache disorders, since the V1 dermatome projects

 doi:10.20944/preprints202408.0928.v1

to the most caudal part of the TNC and locates directly adjacent to the secondary sensory neuron of the C2/C3 branches in the spinal cord.[59,60] It has recently been demonstrated that the stimulation of the V1 dermatome via capsaicin was able to modulate the pain threshold in the V2, V3, and GON dermatome; similarly, stimulation at the GON was able to change the pain threshold on all three branches of the trigeminal nerve, but with a stronger effect on V1, compared to V2/V3.[61] This study provided evidence that the functional interaction between different branches of the trigeminal nerve takes place at the pontomedullary level. There is a functional connection between the limbic system and the ophthalmic branch;[62,63] this functional connection explains why such attack-like pains in migraine are predominately in the head.[64] Following this thought the facial presentations would be a simple "spread" of the pontomedullary activation in type 1 and type 2 facial presentations of headache, whereas the isolated facial attacks resembling headaches (type 3) are due to (extremely rare) direct functional connections between the limbic system and the maxillary or mandibular brainstem nuclei. Further studies into this subject are clearly needed.

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