Tooth be or not tooth be? Demographic and clinical phenotype and response to treatments of migraine with isolated facial pain

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Abstract

Background:

Migraine presenting with facial pain is considered rare and diagnostically challenging given its clinical overlap with other orofacial pain conditions. Sparse evidence have detailed its clinical phenotype and response to treatment. Here we aim to describe the demographic and clinical phenotype of patients with migraine presenting with isolated facial pain who attended our clinic.

Methods:

Between 2014 and 2019, patients with migraine with isolated facial pain were identified from our multidisciplinary facial pain service and demographic, clinical characteristics and response to treatments were analysed as a clinical audit.

Results:

Of 3900 patient datasets, 1248 (32%) were diagnosed with a primary headache disorder. Of these, 58 (4.6%) (F=, age) were diagnosed with migraine with location of pain episodes over the maxillary, mandibular and intra-oral regions. Migraine with isolated facial pain is predominant in female, often precipitated by orofacial surgical treatments, with strictly unilateral pain centred over the V2 distribution associated with cranial autonomic features. The majority of cases present with an episodic pattern, but a chronic daily pattern can occur. Migraine with isolated facial pain responds to triptans and to migraine preventive treatments. Indometacin tests are important to rule out indometacin-sensitive headaches in unilateral cases with continuous pain. Migraine with isolated facial can occur in comorbidity with other facial pain disorders, increasing the level of complexity.

Conclusions:

Isolated migraine facial pain is a rare condition that frequently undergoes misdiagnosis resulting in delayed presentation and multiple inappropriate courses of antibiotic and dental

and or ENT treatments. Isolated V2 and V3 migraine should be taught as a possible differential diagnosis to these groups.

Introduction

Chronic facial pain encompasses numerous conditions including dental causes and non-dental causes, namely primary headache disorders that can present with facial pain, temporo-mandibular joint dysfunction, trigeminal neuropathic causes and persistent idiopathic facial pain, amongst the most frequent (). Migraine with facial pain is considered rare but it is sometimes reported (). A thorough history taking, investigations and sometimes medications trials are often needed to correctly discriminate migraine with facial pain from other primary headaches or from other orofacial pain causes (). Migraine presenting with isolated facial pain (pain in V2 and or/V3) is considered extremely rare and its phenotype has not been described in full (). In view of the uncommon pain location, a high proportion of these patients are misdiagnosed for other more common conditions, namely pulpal disease, temporo-mandibular joint disorders (TMJD) and "sinus headache", frequently resulting in inappropriate surgical and medical treatments that themselves may complicate the presentation of the pain by changing its phenotype and further complicating diagnosis and timely management ().

Here we identified all patients with non-odontogenic continous and non-continuous facial pain attending our clinic and detail the demographic characteristics, clinical profile and response to treatments of those migraine patients with isolated facial pain.

Methods

This is a prospective clinical audit, part of a service evaluation, that took place at the King's Health Partner multidisciplinary facial pain service, which is a clinical and academic entity that include the Orofacial pain and skull base Neurosurgery services at King's College Hospital and the Headache Service at Guy's and St Thomas' Hospital. This service is dedicated to the diagnosis and treatment of complex facial pain patients. For this audit, data were collected from

consecutive patients referred at the Orofacial Pain (OFP) Service at Kings College Hospital between June 2013 to January 2018.

Participants were predominantly referred by dentists in view of lack of response to routine dental treatments. As per our service pathway, the initial clinical assessment was performed by the orofacial pain clinicians. Odontogenic, inflammatory, infective dental causes were excluded following clinical assessment and radiographic tests. When odontogenic causality was excluded, patients were assessed by the headache neurologist of our facial pain service (G.L.). Patients meeting the the International Headache Society (IHS) criteria for migraine presenting with isolated V2 and/or V3 trigeminal intra and/or extras oral facial pain were carefully phenotyped and included in the analysis. The diagnosis was reached after one of more face to face clinical assessments were conducted, further investigations were carried out when appropriate, outcome of certain medications trials were obtained and with the aid of headache diaries. The definition of facial pain proposed by the International Classification of Headache Disorders 3rd edition (ICHD-3) was used. It describes facial pain as pain below the orbitomeatal line, anterior to the pinnae and above the neck ().We also included patients with a previous personal history of episodic migraine with head pain; patients in whom the pain territory historically included V1, but at the time of the assessment was exclusively present in V2 and /or V3; patients with unilateral V2 and/or V3 migraine pain and other contralateral/bilateral tension-type headache provided that the patient was able to clearly discriminate between the two conditions. Conversely, patients with migraine pain centred over V2 and/or V3 and pain radiation to V1 territory were excluded. Data were collated in an electronic password protected spreadsheet.

Audit under current national guidelines does not require research ethics committee review (http:// www.hra-decisiontools.org.uk/research/).

Results

Over the audit period, 3900 patients were assessed, of which 1248 (32%) were diagnosed with a primary headache disorder. Of these, 58 (4.6%) patients had migraine with isolated facial pain.

Demographic characteristics

The patients were referred by dentists (n=28, 48.3%), general medical practitioner (n=18, 31.0%) and endodontists (n=7, 12.1%). The remaining five patients were referred by secondary care specialists, respectively by: a pain specialist, an oral surgeon, a maxillofacial surgeon, an ear nose and throat (ENT) specialist and a neurologist. Table 1 summarises the demographic and clinical characteristics of the facial pain in our patients.

Our patients were predominantly female (F=46, 79.3%) of Caucasian ethnicity (n=38, 65%). The age at the time of the assessment ranged between 17-73 years (mean 49.0 years, ± 9.85). At the time of the interview, the duration of the migraine with isolated facial pain ranged from 3 months to 30 years (mean 59 months SD 12.15). Apart from migraine, the medical history of our patients was remarkable for hypertension (n=8), irritable bowel syndrome (n=6), hypothyroidism (n=4) lower spinal pain (n=1) and endometriosis (n=1). A previous personal headache history was reported by 37% of patients (n=29), some having cessated as long as 30 years before the assessment. A percentage of 19% (n=11) of patients reported ongoing headaches fulfilling the IHS criteria for episodic tension-type headache (); 31% of patients (n=18) reported no personal previous or current history of headache. A percentage of 24%

(n=14) reported temporo-mandibular joint disorder (TMJD) as a comorbid pain condition to migraine.

Facial pain onset: The pain initiated spontaneously, without any apparent precipitant factors in 53% of patients (n=31) all of whom initially sought advice from dentists and had x-rays and a variety of dental interventions including antibiotics, simple analgesia and root canal treatments. In the reminder patients (47%, n=27), the pain began in temporal connection to surgical interventions, namely dental extractions (n=13), ENT procedures (n=6), dental implants (n=3), facial trauma, dental root canal treatment (n=4) and whiplash injury (n=1).

Episodic or chronic pattern: a percentage of 66% (n=38) of patients met the IHS criteria for episodic orofacial migraine. The remaining patients (34%, n=20) reported a daily facial pain with migrainous exacerbations, meeting the criteria for chronic orofacial migraine ().

Laterality of pain and site/s: the pain was unilateral side-locked in 79% (n=46) and bilateral in 16% of patients (n=12). The majority of patients reported unilateral left-sided pain (67%n=32). Pain was localised mainly in V2 territory (84.5%, n=49), followed by V2-V3 (10.3%, n=6) and V3 (5.2%, n=3). Four patients with pain in V2 reported temporal radiation.

Severity: in patient with non-constant pain the reported severity ranged between from 7-10/10 on the verbal rating scale (VRS). In patients with constant pain the background severity ranged between 3-5/10, whereas the more severe exacerbations ranged between 5-10/10.

Associated features: all but two patients reported at least one of nausea, vomiting, photo-phono- and/or osmophobia. Two patients experienced episodes of unilateral featureless throbbing facial pain without any associated symptoms. Thorough investigations rule out dental, TMJD and other cranio-facial pathology. A meaningful response to triptans supported the migraine biology of these episodes. Cranial autonomic signs/symptoms were reported by 45% (n=26) of our cohort. These ranged from just unilateral tearing (n=8) to multiple

autonomic signs/symptoms. No patients reported visual, sensory, speech or motor symptoms fulfilling the IHS criteria of aura.

Exacerbating and relieving factors: pain was triggered by stress (n=16) and alcohol (n=3). Exacerbation of the pain during menses was reported by 16 of 46 female patients. Twelve patients could not identify a trigger. Pain was made worse by eating in 11 patients who also had comorbid TMJD.

Previous ineffective treatments: multiple consultations was commonly reported by our patients. One patient had previously seen 28 consultants. The vast majority of patients (94.8%, n=55) had at least one course of antibiotics (one patient as many as 43 courses) to no avail. Ineffective dental treatments included; endodontics (n=21), multiple extractions (n=17), restorations (n=3) and bite raising appliances in 12 patients. Some patients tried as many as six different appliances. Patients reported no benefit from physiotherapy (n=4), Botulinum toxin type A (BoNT/A) injections (n=2), functional endoscopic surgery (n=4), temporomandibular joint surgery (n=1), pulsed radiofrequency and sphenopalatine block interventions (n=1). At the time of the assessment, 69% of patients (n=40) were taking daily non-steroidal antinflammatory drugs (NSAIDs), paracetamol- or codeine-based medicines with poor benefit. Of these, 20 patients were having daily facial pain and 20 were having episodic high-frequency episodic facial pain episodes.

Effective treatments: triptans were tried in all but eight patients (n=30/38) with episodic symptoms. In eight patients, due to hypertension, other abortive treatments were offered. The most frequently tried include sumatriptan 50mg, rizatriptan 10mg and zolmitriptan 2.5mg. Triptans were able to successfully and consistently abort the facial pain episodes in 77% of them (n=23). The discontinuation of daily intake of NSAIDs, led to an improvement of the facial pain symptoms in 40% (n=16/40) patients. However, all patients were offered preventive

treatments with evidence of efficacy in migraine in view of the frequency of symptoms. However not all patients decided to start them. Tricyclic antidepressants were reported to be effective in in 12 patients, propranolol in four, candesartan in nine, topiramate in four, gabapentin in three and pregabalin in one patient. Greater occipital nerve blocks perfomed every three months were effective in four patients and BoNT/A was effective four patients. Indometacin was used to exclude hemicrania continua in patients with unilateral side-locked facial pain with autonomic symptoms.

Discussion

Migraine presenting with isolated facial pain is considered to be very rare as shown in migraine population-based studies as well as in neurology clinical settings (Yoon 2009, Ziegler, 2019). Given its overlapping symptoms with dental and ENT pathologies, it is considered a clinical challenge to both neurologists who typically have limited knowledge of oral pain conditions and to dentists and ENT specialists who often have limited diagnostic skills in headache disorders phenotyping (Benoliel 1997). This has meant that to date only small cases series have attempted to describe the clinical characteristics of migraine with this rare pain location. Our multidisciplinary facial pain team is a one of its kind set up, including a orofacial pain specialist with a dental background, a headache neurologist, a neurosurgeon and a pain specialist with interest in facial pain. The level of specialisation provided along with the complexity of patients we are exposed to, may explain why we have been able to assess and diagnose such a large series of patients.

The demographic characteristics of our patients were similar to previous studies of facial pain in migraine, confirming the prominent female preponderance and a later age of onset compared to epidemiological data in migraine with head pain (Benoliel, 1997). The late age of onset has

been simply interpreted simply as a normal delay due to change in pain location in those with a previous history of migraine with head pain (Benoliel 1997). However, it may also be possible that accumulation of minor but multiple V2-V3 nerve ending injuries due to dental and/or sinus conditions and/or surgical procedures may have led to the expression of the migraine symptoms in sensitised areas of the trigeminal system in subjects with a migraine biology (personal and/or family history of migraine). Indeed, almost half of the patients in our cohort reported the onset of facial pain in temporal relationship with a cranio-facial procedure and a significant proportion of patients had previous history of dental treatments over the painful areas. Similar findings were reported in another series of 11 patients (Pennarocha, 2004). Whether this link is causal or a result of referral bias is difficult to establish at this stage.

The clinical phenotype of migraine patients with isolated facial pain that emerged from our analysis displayed some peculiarities which differ from migraine with head pain, namely the laterality of the pain and the proportion of patients with associated cranial autonomic features. The vast majority of our patients reported unilateral side-locked pain centred over the V2 trigeminal division, in particular the maxillary region with seldom radiation to the temple. Similar findings were observed in a series of 24 patients with migraine with isolated facial pain and subsequently in 76% of patients studied in a large population-based study (Daudia, 2020; Yoon 2010), but not in a small series of seven patients of whom only two had pain limited to V2 (Obermann 2007), possibly due to the small sample size. The high percentage of patients with V2 pain may only reflect a referral bias. Recurrent maxillary pain episodes are often misdiagnosed as “sinus pain” and often referred by ENT specialists to facial pain clinics (Eross 2007). Furthermore when migraine affects the facial territories seem to be more frequently associated with ipsilateral/bilateral cranial autonomic signs/symptoms compared to migraine with head pain, hence more often misdiagnosed as “sinus-pain” (Daudia, 2002). The presence of cranial autonomic signs/symptoms associated to the pain in our series (45%) was similar to

the one observed in a previous population-based study (48%) but also similar to studies conducted in non-neurological settings (Benoliel 1997). This consistency suggests that pain in V2-V3 may be able to recruit the parasympathetic nerve fibres of the trigemino-autonomic reflex more prominently than migraine pain in V1. It could also be possible that the autonomic overflow is due to the unilaterality of the pain rather than trigeminal territory distribution (). This would explain why unilateral migraine and unilateral side-locked headache disorders like the TACs, are more likely to be associated with ipsilateral cranial autonomic symptoms.

Migraine with isolated facial pain has been reported to largely respond to migraine specific abortive treatments as well as to preventive treatments used in migraine prophylaxis (Sharav, 2007, Benoliel 1997, Daudia 2002, Pennarocha, 2004). Our findings confirmed this trend. The response to triptans consistently demonstrated across the previous studies and confirmed by our results, apart from offering an effective abortive treatment option, could be used in some cases as a diagnostic aid for patients with complex/unclear presentations. Two of our patients presented with featureless facial throbbing pain episodes. Dental and other causes were excluded. A response to triptan confirmed the migraine biology of the pain episodes and allowed a tailored treatment plan, which otherwise would have been difficult. A similar response to triptan was reported in another series of patients diagnosed with neurovascular orofacial pain (Benoliel 1997). Some of those patients had unilateral featureless throbbing intraoral pain, which is still a debated entity (Sharav 2017) but others probably had orofacial migraine according to the integrated International Classification of Orofacial Pain (ICOP) (Benoliel 2019) and their pain episodes responded to triptans. The importance of understanding the extent of the contribution of migraine mechanisms becomes relevant in cases of migraine with isolated facial pain in comorbidity with other facial pain conditions for which specific treatments do not currently exist. Common examples include patients with orofacial migraine and trigeminal neuropathic pain or TMJD. In our cohort about 1/5 of the patients had TMJD in

comorbidity. This condition is known to often coexist with migraine () and can pose another level of diagnostic complexity and treatment outcomes can be poor if the two diagnosis are not disentangled, highlighting the importance of collaborative work between different specialties who see patients with facial pain.

This audit has limitations including the less rigorous methodology typical of an audit. However, the phenotyping and diagnostic processes were consistent and robust, based on multiple clinical assessments overtime, careful investigations and the use of diagnostic drugs trials such a triptan and indometacin trials.

Conclusions

We refined the demographic and clinical phenotype of a very rare subtype of migraine with isolated facial pain in a large series of patients. The characteristics are largely similar to migraine with head pain apart from a high proportion of cases precipitated by surgical oro-facial procedures, a high proportion of unilateral pain cases and of associated cranial autonomic features. Migraine with isolated facial pain responds well to triptans, to the commonly used migraine oral preventive treatments and to treatments injected away from the V2-V3 trigeminal territories. In view of its rarity, the diagnosis of orofacial migraine needs to be a diagnosis of exclusion after dental and sinus pathologies are excluded. However, dentists, ENT specialists and neurologists should be aware of this rare entity and carefully phenotype these patients or refer them to specialist multidisciplinary facial pain teams.

Clinical implications

- Migraine with isolated facial pain is a rare but treatable form of orofacial pain, often misdiagnosed by dentists and ENT specialists.
- Migraine with isolated facial pain is predominant in female, often precipitated by orofacial surgical treatments, with strictly unilateral pain centred over the V2 distribution associated with cranial autonomic features. The majority of cases present with an episodic pattern, but a chronic daily pattern can occur.
- Migraine with isolated facial pain responds to triptans and to migraine preventive treatments. Indometacin tests are important to rule out indometacin-sensitive headaches in unilateral cases with continuous pain.
- Migraine with isolated facial can occur in comorbidity with other facial pain disorders, increasing the level of complexity.
- The multidisciplinary approach is key for the diagnosis and treatment of this rare form of migraine and as an educational platform for physicians who treat patients with facial pain.

Contributors

All authors participated in the study design, implementation and/or conduct of the study. All authors contributed to the audit and approved the final manuscript.

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Declaration of conflicting interests

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