Diagnostic Dilemma in Atypical Facial Pain: A Review

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Abstract:

Atypical Facial Pain, also known as Persistent Idiopathic Facial Pain (PIFP), is an excruciating disorder of the face considered an underdiagnosed condition with limited treatment options. It is often diagnosed when the clinician has exhausted all possible alternatives that are within his knowledge base, thus is considered as a 'diagnosis of exclusion.' This literature review aims to provide an overview about this rare condition, and discuss about the diagnostic dilemma and challenges the physicians face, and the treatment considerations.

Keywords: Atypical facial pain, persistent idiopathic facial pain, orofacial pain, trigeminal neuralgia, neuropathic pain

Introduction:

Pain is a symptom of the disease to be diagnosed and treated and gravely impairs the lives of millions of people around the world. The task force on taxonomy of the International Association for the Study of Pain (IASP) recently defined pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[(1)] Orofacial pain (OFP) conditions occur due to complex pathophysiology, often associated with psychological co-morbidities, and may have a significant impact upon quality of life and daily functioning.[(2)] OFP is the presenting symptom of various spectrums of diseases which may be of orofacial origin itself, or musculoskeletal, nervous system origin, intracranial pathology, psychological abnormality, or pain referred from cervical muscles. It can also occur without any known reason and might have normal physical, imaging or laboratory findings. Some of the OFP disorders are easily diagnosed and treatable, but others are difficult to classify and unresponsive to routine methods of treatment.[(3)]

In 1924, Frazier and Russell determined that 10% to 15% of patients presented with chronic facial pain with symptoms that differed from the characteristic clinical pattern of trigeminal neuralgia and failed to respond to neurosurgical treatment, leading them to coin the term, atypical neuralgia.[(4)] This was recorded as the first known diagnosis of Atypical Facial Pain (AFP), also called as Persistent Idiopathic Facial Pain (PIFP) which is an excruciating disorder of the face considered an underdiagnosed condition with limited treatment options.[(5)]

Owing to the fact that patients with this disorder experience pain that neither follows the distribution of the peripheral nerve nor responds to antiepileptic agents or antidepressants or analgesics, this condition was labelled as 'atypical' to distinguish it from the typical trigeminal neuralgia. Because of the poorly understood etiology and loose diagnostic criteria, AFP is usually misdiagnosed and susceptible to invasive treatment that can worsen the condition of the patients. Thus, it is important that physicians take every patient's complaint of facial pain seriously by gathering a thorough differential diagnosis from the patient's history and performing a complete physical, imaging, and laboratory investigation for pain.[(6)]

As there is no definite etiology and pathophysiology that are described in literature, PIFP is often diagnosed when the clinician has exhausted all possible alternatives that are within his knowledge base, thus is considered as a 'diagnosis of exclusion'. This may include a number of less recognized regional pain syndromes that were misdiagnosed as PIFP in the past.[(7)]

Because of this reason, PIFP has tended to include a heterogeneous group of patients. This may be the reason why the treatments which were effective in some PIFP patients were ineffective in other PIFP patients. Despite this, the clinical reality of this group of patients remains, and we should be therefore obliged to continue our endeavours to elucidate the pathophysiology, outline a clear clinical phenotype, differentiate between similar clinical entities, and establish evidence-based treatment recommendations.[(7)]

This literature review thus aims to provide an overview of the last considered condition called Atypical Facial Pain and discuss about the treatment outcomes that were noted in these patients. This will help in forming a homogenous group of diagnosed AFP/PIFP cases who will respond to a definite treatment protocol structured for the same, thus providing a ray of hope to this hapless group.

Definition:

In 1988, the International Headache Society proposed the first diagnostic criteria for PIFP. In the latest edition of the International Classification of Headache Disorders, PIFP is defined as persistent facial and/or oral pain with varying presentations, recurring daily for more than 2 hours per day over more than 3 months, in the absence of clinical neurological deficit or preceding causative event.[8]

Prevalence:

According to a population study conducted by Mueller et al in 2011, the estimated lifetime prevalence of PIFP is around 0.03%. [9] A study in primary care in the Netherlands in 2009 found an incidence rate of 4.4 per 100,000 person-years with 75% predominance in women and a mean age of 45.5 years.[10] These data clearly indicate that that PIFP is a rare disorder. In orofacial pain clinics, PIFP may account for around 10–21% of the patient population. In a neurological tertiary care centre, about 21–27% of the patients referred for facial pain had persistent idiopathic facial pain, while only 3% of patients with side-locked unilateral headache and facial pain presenting to a neurology outpatient clinic were diagnosed with PIFP.[11] Clinical case series indicate a preponderance of middle-aged or older women [8].

Etiopathogenesis:

In spite of having many case reports and studies and innumerable data in literature, the etiopathogenesis of PIFP still remains inconclusive and an unsolved mystery. Several causal theories have been proposed, but little evidence has been found to support these theories. It has been suggested that it could be a consequence of deafferentation and central sensitization but is still not clear if peripheral or central mechanisms are involved. The underlying causes may be associated with injury to the trigeminal nerve, peripheral central demyelination, or minor trauma, such as a dental extraction. Some literature suggests of the possibility of an abnormal sensitization of the trigeminal nociceptive system. On the other hand, it has been suggested that PIFP is likely a combination of both biological and psychosocial elements. It could be a centrally mediated pain and may even be psychological in origin because they have found associations with underlying psychological disorders, such as depression and anxiety. [4,12]

1. Trigeminal nerve neuropathy:

Some researchers suggested that the underlying causes of AFP are associated with injury to the trigeminal nerve since it is possible that an abnormal sensitization of the trigeminal nociceptive system play a crucial role in the onset of AFP.[4] Studies have postulated that in patients with PIFP there is local pathology (inflammation) of the distal branches of the trigeminal nerve.[13] Unlike trigeminal neuralgia, PIFP often spreads to a wider area, not conforming to a specific dermatome. In addition, the pain is typically continuous with no periods of remission and there are no signs or symptoms of autonomic involvement. As demonstrated by Nicholas Moser et al in their four cases, abnormal findings were not noticed in clinical examination or additional investigations apart from sensitivity to palpation and tension along the course of the nerve, thus as a result, the diagnosis of PIFP is the one of exclusion.[13]

2. Role of Dopaminergic system:

N. Hagelberg et al. in 2003 conducted a study to evaluate the nigrostriatal dopaminergic system in patients with atypical facial pain using positron emission tomography PET. There was a tendency of increased D2 receptor availability in the left putamen and the D1/D2 ratio in the putamen was decreased bilaterally in patients when compared to controls. This implies that alterations in the striatal dopaminergic system as evaluated by PET may be involved in chronic orofacial pain conditions.[14]

3. Role of Psychology:

It is suggested that there is involvement of central sensitisation pain mechanisms in PIFP. Patients may demonstrate greater incidence of psychiatric co-morbidities such as depression and obsessive-compulsive personality characteristics. They also have identified brain dopaminergic hypofunction in PIFP patients, in a similar way to other chronic pain conditions.[2] As such, PIFP would therefore be considered a neuropathic pain syndrome. While the psychogenic pain hypothesis has not been substantiated, a relationship is likely to exist with primary idiopathic headaches, and a neurovascular mechanism. Moreover, this chronic morbid condition causes severe disability in working or personal activities and seriously reduces the quality of life of sufferers.[15] Psychological factors that are identified could also be a consequence of having chronic pain, lack of diagnosis, and attitude of health care professionals.

Clinical Features:

PIFP is a poorly localised pain condition that may be felt as deep or superficial, may be radiating, the initial location of pain is most often unilateral that spreads out over a larger territory with time and up to one-third of the patients (40%) may experience bilateral pain. The pain is described as aching, burning, stabbing, throbbing, or pressing. Pain intensity varies from moderate to severe, and is usually continuous but often fluctuates in intensity, may be aggravated by emotional stress, and there may be pain free periods.[8] Most PIFP patients report persistent, long lasting daily pain extending up to years, that tends to spread, in a non-dermatomal pattern with time. Accompanying neurological

signs are not obvious, but there may be subjective feeling of altered sensation, such as dysesthesia and paraesthesia, with subtle sensory deficits in meticulous clinical sensory tests. Although there should be no clinically evident neurosensory deficits in PIFP, hypoesthesia has been reported in studies using quantitative sensory testing (QST).[11]

The ICHD diagnostic classification for PIFP includes the features described previously, with the addition of normal clinical neurological examination and exclusion of a dental cause.[16]

A thorough clinical examination including a detailed dental and oral examination, palpation of the masticatory and cervical muscles, and cranial nerve examination is essential. To detect subclinical cranial neuropathies that may occur in PIFP patients, sensitive neurophysiological recordings, and quantitative sensory tests (QST) are recommended to improve diagnostic accuracy. In addition to conventional radiographic examination of the pain site, head MRI examination is recommended to exclude intra-cranial and extracranial structural pathology.[8]

Table 1: Diagnostic criteria for Persistent Idiopathic Facial Pain (Section 13.12). ©International Headache Society.[11]

	Diagnostic criteria	Notes
A	Facial and/or oral pain fulfilling criteria B and C	This is the current term for what was previously termed Atypical Facial Pain or its intraoral counterpart, Atypical Odontalgia
B	Recurring daily for >2 hours per day for >3 months	It can have sharp exacerbations, and is aggravated by stress
C	Pain has both of the following characteristics: 1. Poorly localized, and not following the distribution of a peripheral nerve 2. Dull, aching or nagging quality	Pain may be described as either deep or superficial. With time, it may spread to a wider area of the craniocervical region
D	Clinical neurological examination is normal	A continuum seems to exist from PIFP induced by insignificant trauma to painful post-traumatic trigeminal neuropathy caused by significant insult to the peripheral nerves. PIFP may be initiated by a minor operation or injury to the face, maxillae, teeth, or gums without any demonstrable local cause. However, psychophysical, or neurophysiological tests may demonstrate sensory abnormalities.
E	A dental cause has been excluded by appropriate investigations	The term atypical odontalgia has been applied to a continuous pain in one or more teeth or in a tooth socket after extraction, in the absence of any usual dental cause. This is thought to be a sub form of PIFP, although it is more localized, the mean age at onset is younger and genders are more balanced
F	Not better accounted for by another ICHD-3 diagnosis	Persistent idiopathic facial pain (PIFP) may be comorbid with other pain conditions such as chronic widespread pain and irritable bowel syndrome. In addition, it presents with high levels of psychiatric comorbidity and psychosocial disability

Based on the first edition of International Classification of Orofacial Pain (ICOP)© [17] by International Headache Society, Persistent Idiopathic Facial Pain is coded as 6.2, and subdivided into:

1) 6.2.1 Persistent idiopathic facial pain without somatosensory changes
2) 6.2.2 Persistent idiopathic facial pain with somatosensory changes
3) 6.2.3 Probable persistent idiopathic facial pain

Table 2: Subdivisions of PIFP, International Classification of Orofacial Pain (ICOP)© by International Headache Society[17]

Description	Diagnostic criteria
6.2.1 Persistent idiopathic facial pain without somatosensory changes	
Persistent facial pain, with variable features, recurring daily for more than 2 hours per day for more than 3 months, unaccompanied by somatosensory changes and in the absence of clinical neurological deficit or preceding causative event.	A. Facial pain fulfilling criteria for 6.2 Persistent idiopathic facial pain B. Somatosensory changes are not present on qualitative or quantitative somatosensory testing
6.2.2 Persistent idiopathic facial pain with somatosensory changes	
Persistent facial pain, with variable features, recurring daily for more than 2 hours per day for more than 3 months and accompanied by negative and/or positive somatosensory changes, in the absence of clinical neurological deficit or preceding causative event	A. Facial pain fulfilling criteria for 6.2 Persistent idiopathic facial pain B. Somatosensory changes are present on qualitative and/or quantitative somatosensory testing. **Note:** Negative (e.g. hypaesthesia and/or hypalgesia) and/ or positive (e.g. hyperalgesia and/or allodynia) sensory symptoms and/or signs.
6.2.3 Probable persistent idiopathic facial pain	
Facial pain, with variable features, recurring daily for more than 2 hours per day but for less than 3 months, in the absence of clinical neurological deficit or preceding causative event.	A.Facial pain fulfilling criteria for 6.2 Persistent idiopathic facial pain except that it has been present for <3 months **Note:** Once 3 months have elapsed, the diagnosis becomes 6.2 Persistent idiopathic facial pain (or one of its subtypes) **Comment:** Sub forms are not formally classified but may be coded 6.2.3.1 Probable persistent idiopathic facial pain without somatosensory changes or 6.2.3.2 Probable persistent idiopathic facial pain with somatosensory changes according to the criteria above.

Investigations

Examination and diagnostic study usually reveal no clear abnormality nor elevation in inflammatory markers.[18] Clinical neurophysiology, neuropathological, quantitative sensory testing (QST) and functional brain imaging provide objective and quantitative information and are sensitive and accurate diagnostic tools for detailed investigation of the mechanisms involved in different clinical pain conditions. But these are technique-sensitive and not always easily accessible for orofacial pain patients.[8]

The methods used include:

- Electroneuromyography (ENMG)
- Brainstem reflex recordings (blink reflex (BR), masseter reflex and masseter silent period)
- Estimation of habituation and excitability of the BR, tactile, pinprick, vibratory
- Thermal quantitative sensory testing (QST, with psychophysical methods)
- Somatosensory (SEP), Laser (LEP) and Contact Heat (CHEP) evoked potential recordings
- Quantification of epithelial nerve fibre density (ENFD) from skin or mucosal biopsies
- Positron Emission Tomography (PET)
- Functional magnetic resonance imaging (fMRI) of the brain.
- Psychophysical methods: If qualitative sensory testing and neurophysiological recordings are abnormal, it is important that these patients have some form of psychological testing, the easiest of which are psychometrically tested questionnaires such as the Brief Pain Inventory– Facial, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, and Chronic Graded Pain Scale. These tests often show high levels of disability.[19]

Diagnostic Dilemma:

Practical difficulties in timely and accurate diagnosis of patients with PIFP is due to:

- Firstly, the clinical presentations of PIFP are nonspecific, symptoms of PIFP overlap with other pain syndromes, the diagnostic criteria are not precise enough and precise diagnostic tools are lacking.
- Secondly, the epidemiological characteristics of PIFP still lack adequate research and published data are also controversial.
- Thirdly, despite several proposed theories and hypotheses, the etiology and pathological mechanisms are not well understood.
- Fourthly, there are no standardized treatment protocols established and the effectiveness of medication lacked support from high-level evidence.[20]

Hassona et al. in 2019 conducted a study to explore the diagnostic and therapeutic challenges encountered by patients with PIFP and to investigate factors influencing its delayed diagnosis. The average amount of time elapsed between the onset of pain to the correct diagnosis (i.e., diagnostic delay) was 19.3 ± 11.1 months. In patients with extraoral pain, the average diagnostic delay was 16.1 months ± 9.3, whereas it was significantly longer in patients with intraoral pain (22.6 ± 7.4 months). General dental practitioners were the most commonly consulted health care professionals, followed by maxillofacial surgeons, general medical practitioners, ENT surgeons, endodontists, neurologist; but interestingly, none of the patients consulted or was referred to a pain specialist or an orofacial pain specialist before the correct diagnosis was achieved. Dental pain, including pulpitis, apical periodontitis, tooth sensitivity, cracked tooth, failed root canal treatment, postoperative pain, and occlusal trauma were the most frequent diagnoses. Others included sinusitis, TMJ dysfunction, migraine, myofascial pain, burning mouth syndrome, osteomyelitis, neuralgia, and iatrogenic nerve trauma.[21]

The common clinical conditions with which PIFP gets misdiagnosed are Trigeminal Neuralgia, Atypical Odontalgia, Temporomandibular disorder, Burning Mouth Syndrome, Traumatic trigeminal neuropathies, Regional myofascial pain, Atypical neurovascular pains, and Atypical neuropathic pain. [22]

Other diagnostic considerations are multiple sclerosis, apical fenestration, bilateral atypical facial pain caused by Eagle's Syndrome, intractable facial pain secondary to metastatic lung cancer. [23,24,25,26]

These are clear examples of the importance of proper investigations and search for the exact diagnosis, as the cause of atypical kind of facial pain can be hidden anywhere in the CNS, and thus misdiagnosis and neglect can cause serious detrimental impact on the lives of these patients.

Treatment:

Randomised controlled treatment trials performed in PIFP patients are very few, and this makes an evidence-based treatment decision difficult. There are no definitive curative treatments available for idiopathic orofacial pain, and patients may frequently have difficulties in accepting these diagnoses and their management. During this quest for a diagnosis, they may potentially receive a number of invasive dental and surgical treatments without the desired pain relief. Such unnecessary invasive treatments should of course be avoided because they carry the risk of pain aggravation. This stresses the need for patient education during the presentation of the diagnosis.[8]

In view of the overtly neuropathic nature of PIFP, one could consider consulting the NICE guidelines for neuropathic pain[27] – which suggest first line management with either: amitriptyline, duloxetine, gabapentin or pregabalin. If sufficient benefit is not achieved, then it is suggested that patients may change to one of the alternative medications or take a combination therapy. Moreover, one may also include the intermittent use of tramadol (an opioid) for breakthrough pain. However, solely using medications may be insufficient for managing PIFP, as patients with PIFP may also present with significant distress, psychiatric co-morbidities, and impaired quality of life. It is important to consider a holistic approach, incorporating patient education and psychological therapies to facilitate self-management.[2]

The recommended biomedical management of neuropathic pain is systemic pharmacologic treatment. Initially, topical/local approach can be initiated, but if desired effects are not attained, pharmacological treatment should be considered. [8]

Following the treatment algorithm for peripheral neuropathic pain, tricyclic antidepressants (TCA) such as amitriptyline, duloxetine, venlafaxine are the first choice – if not contraindicated. Amitriptyline (50–100 mg/d) or nortriptyline (20–50 mg), can be effective if used for at least 6 months. [28]

If TCA is contraindicated or ineffective, anticonvulsants such as gabapentin, pregabalin, or carbamazepine are next in line. Their molecular mechanisms are varied, but typically involve action at the level of cell membrane ion channels.[29]

Opioids such as tramadol or oxycodone might be considered if pain relief cannot be obtained otherwise. The opioids are

thought to be less effective in neuropathic pain conditions and carry with them serious adverse effect profiles including respiratory depression, hypotension, seizures, paralytic ileus, and dependency. [29]

Because of its safety profile with fewer side effects, topical analgesics may be considered a first-choice treatment over systemic treatment. In one uncontrolled trial, a mixture of lidocaine and prilocaine (topical local anaesthetic EMLA cream) and topical application of capsaicin showed some promise. Topical application of capsaicin alone or in combination with topical local anaesthetics may be helpful. Unfortunately, side effects, such as a burning sensation, may cause the patients to discontinue capsaicin use.[8]

Botulinum toxin A (Botox) has been suggested in cases in which masticatory hyperactivity is present. The mechanism of action of botulinum toxin in neuropathic pain is multifactorial, inhibiting the release of nociceptive agents from nerve endings and dorsal root ganglion, inhibition of sodium channels, anti-inflammatory actions, and central and peripheral sensitization.[30]

A questionnaire sent to 240 UK specialists dealing with PIFP showed that 78% of the specialists used antidepressants as first choice treatment. The other specialists used anticonvulsants as first choice drug. Second choice and alternatives to these compounds consisted of many drugs and techniques, the most used being NSAIDs, benzodiazepine, psychiatric therapy, and physiotherapy. Nineteen specialists stated they kept these patients under observation without treatment.[28]

Studies have reported that behavioural therapies such as patient education, counselling and self-management therapies are beneficial complements to biomedical approaches. In a randomised placebo-controlled study, hypnosis, acupuncture, biofeedback, and dental splints have been proposed, but evidence of efficacy in the pain management is so far lacking. [8]

Facial pain syndromes can be refractory to medical management and often need neurosurgical interventions. The neurosurgical management of PIFP can be broadly divided into Neuromodulatory and Neuroablative techniques and have been implemented in the management of intractable facial pain.

1.Neuromodulatory procedures: Trigeminal nerve stimulation (TNS), Motor cortex stimulation (MCS), Nerve blocks.

2. Neuroablative procedures: They are largely reserved for PIFP that is refractory to reversible and less invasive procedures. They are irreversible with a limited efficacy and high rates of pain exacerbation.[3]

Other non-pharmacological methods include targeted intraoral vibration therapy, pulsed radiofrequency, Transcutaneous electrical stimulation (TENS), *Spinal cord stimulation (SCS),* Low-level energy laser therapy, Gamma Knife surgery, Deep brain stimulation, sphenopalatine ganglion block, and Stellate ganglion block.

Discussion

Patients with PIFP have increased vulnerability to chronic pain and will present with many other medically unexplained symptoms and personality disorders. PIFP is a long-term condition especially if not managed early, and patients need to be positively reassured that they are believed to have real pain, but its cause currently remains unknown. A systematic review showed weak evidence for psychological therapy on its own but one RCT showed that when combined with antidepressants, improved outcomes are possible. [32,33]

Facial pain can be debilitating for any person's livelihood and wellbeing. This is accompanied by an economic impact with high personal expenses. It is important that physicians take every patient's complaint of facial pain seriously. This includes gathering a thorough differential diagnosis from the patient's history and performing a complete physical examination for pain. PIFP is an underdiagnosed condition with an equally poor prognosis. Large studies on the subject are limited and effective treatments are scarce.[34]

Certainly, some leeway should be allowed so as to closely examine "atypical" cases of PIFP. This may enlighten us as to the range of presentations that may be consistent with a diagnosis of PIFP. Based on these studies we should attempt to establish modified criteria, striving to make these positive inclusion criteria rather than a "diagnosis of exclusion".[11]

Conclusion

The pain of these patients is beyond explanation and perception is different among every patient. Oral physicians should gain good understanding of the orofacial pain, their diagnosis and management, which can itself minimise the span of traumatic experience such a patient can experience both physically as well as mentally. Advanced diagnostic measures recording the electrical activity in brain and periphery may help to clarify the pain mechanisms in individual patients and lead to more carefully targeted treatment options for AFP. Integrated treatment approach with pharmacological and non-pharmacological management have proven benefits to PIFP patients. The cause could be hidden anywhere, and thus misdiagnosis and neglect can cause serious detrimental impact on the lives of these patients.

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