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Atypical Facial Pain: a Comprehensive, Evidence-Based Review

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Abstract
Purpose of Review The purpose of this article is to focus on an excruciating disorder of the face, named atypical facial pain or persistent idiopathic facial pain (PIFP). It is considered an underdiagnosed condition with limited treatment options. Facial pain can be a debilitating disorder that affects patients' quality of life. Up to 26% of the general population has suffered from facial pain at some point in their lives. It is important to highlight the different types of facial pain to be able to properly manage this condition accordingly.
Recent Findings Newer interventional modalities such as pulsed radiofrequency ablation (PFR) of the sphenopalatine ganglion, peripheral nerve field stimulators (PNFS), and botulinum toxin injections have promising results. In summary, more prospective studies such as randomized controlled trials are necessary to explore the possibility of their more widespread use as viable procedures for the treatment of PIFP.
Summary In this review article, we describe the workup and diagnosis of PIFP and highlight recent literature regarding the pathophysiology and treatment of PIFP. PIFP is an excruciating disorder of the face often misdiagnosed as trigeminal neuralgia (TN) However, unlike TN symptoms, the pain is persistent rather than intermittent, usually unilateral, and without autonomic signs or symptoms. When a clinician encounters a patient with neuropathic facial pain whose symptoms are incongruent with the more common etiologies, the diagnosis of atypical facial pain must be entertained. Treatment of PIFP is multidisciplinary. Unfortunately, few randomized controlled trials for the treatment of PIFP exist. However, there are a select number of pharmacological, non-pharmacological, and interventional treatment options that have proven to be moderately effective.

Keywords Facial pain · Persistent idiopathic facial pain (PIFP) · Trigeminal neuralgia · Orofacial pain · Cranial neuralgias

This article is part of the Topical Collection on *Other Pain*

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Introduction

Facial pain can be debilitating for any person's livelihood and wellbeing. 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. While the incidence of facial pain in the general population is difficult to judge accurately, some studies have shown that up to 26% of the general population has dealt with facial pain at some point in their lives [1].

Persistent idiopathic facial pain (PIFP), previously termed atypical facial pain, is an excruciating disorder of the face that is often compared to trigeminal neuralgia (TN) [2, 3]. Unlike TN, symptoms are persistent rather than intermittent, and the pain is usually unilateral without autonomic signs or symptoms. Patients typically describe the pain as a crushing sensation, a burning sensation, or a severe ache; however, upon examination and workup, no abnormality is noted [4].

PIFP is an underdiagnosed condition with an equally poor prognosis. Large studies on the subject are limited and effective

treatments are scarce. Unfortunately, even when the diagnosis is made, patients struggle with accepting a "catch-all" disorder such as this and often undergo unnecessary tests and procedures looking for alternative diagnoses. In light of these statements, this article will review the workup and diagnosis of PIFP and highlight recent literature regarding the pathophysiology and treatment of PIFP.

History and Physical Examination

Regardless of the etiology, a thorough history and physical should be given to every patient complaining of facial pain. The pain history needs to include key components in order to come up with a specific differential diagnosis. First, the timing of the pain needs to be determined including when the pain started, how long the pain lasts, and how often the patient experiences the pain. The location and radiation can be strong determinants of the source of pain. As such, an expert knowledge of dermatomes and nerve distribution is crucial. The clinician should then assess the quality and severity of the pain. Quality is usually documented with modifiers such as throbbing, stabbing, dull, or sharp. Severity can be assessed using pain scales, such as the visual analogue scale (VAS). The VAS ranges from 1 to 10, with 1 being minimal pain and 10 being the worst pain imaginable. Then, the physician should evaluate the relieving and aggravating factors of the pain. Next, the impact of the pain should be assessed and how the patient's quality of life is when dealing with this pain. The physician should ask if the patient can sleep with the pain, if the patient can concentrate and still perform at an adequate level at his or her job with the pain, and if the patient feels fatigued by the pain. As in all patients with chronic pain, a psychological assessment is important to attain as well as a full drug history. Finally, the physician should document a medical, family, and social history while ruling out any history of dental disease, orofacial disease, or surgery prior to the initial onset of symptoms [5].

Clinicians should then perform a comprehensive physical exam of the head and neck region on the patient. Visual inspection of the head and neck region should be noted for any skin lesions, color changes, or swellings. Palpation of the lymph nodes and salivary glands should be done to detect and rule any palpable masses present in this area. Then, the physician should examine the muscles of the head and neck for any tenderness or trigger points. Range of motion should also be tested in the muscles of mastication and the temporomandibular joints. A neurologic exam of the cranial nerves can also reveal the underlying pain. Next, an intraoral exam needs to be performed for any dental pathology. The hard palate, soft palate, teeth, and oral mucosa need to be examined for any lesions, decay, or abnormalities [5].

Classification and Differential Diagnosis

Facial pain can be broadly split into two categories: tooth-related and non-tooth-related oral pain [6]. Tooth-related facial pain is the most common type of pain people experience and can have a serious negative impact on a person's quality of life. Dental pain has a high prevalence in the pediatric population, especially for those of low socio-economic status who lack of access to dental care [7]. In adults, tooth-related pain is highly correlated with tooth decay due to untreated dental disease. This includes fractured teeth and exposed dentin due to various causes that can lead to severe facial pain [6]. The most often cause of unexplained orofacial pain is cracked mandibular molars due to reduced access to dental care [4]. Those who suffer from gum disease experience increasing pain scores throughout the course of the natural disease process if left untreated. Only about 6% of people with gingivitis have significant pain, but one in four people with periodontal disease experience pain due to a pocket abscess formation [8].

Most non-tooth-related orofacial pain stems from two major subtypes: Temporomandibular disorders (TMD) and neuropathic facial pain. Common symptoms of TMDs are pain in the temporomandibular joint or preauricular area and restrictions or deviations in the range of motion of the muscles of mastication [6].

Neuropathic facial pain is a general term for facial pain associated with nerve lesions or injuries. Trigeminal neuralgia (TN) is the most common and perhaps the most well-known form of neuropathic facial pain, but it is relatively low in incidence with approximately 5 in 100,000 people per year suffering from this disorder. Postherpetic neuralgia (PHN) is a long-term complication of the reactivation of a previous herpes zoster infection and has a similar incidence of TN [9]. Burning mouth syndrome is another type of neuropathic facial pain described as a burning oral sensation in the oral mucous membranes or the tongue without any abnormal clinical findings or diagnostic cause. This syndrome is more common in middle-aged and older women with prevalence rates ranging from 0.6 to 12.22% [10, 11].

While a clinician may only encounter a fraction of the aforementioned disorders and may diagnose them with relative ease, other less common types of facial pain also need to be taken into account. Oral mucosal lesions, sinonasal diseases, and headaches are all common complaints that can lead to facial pain. Psychosomatic disorders such as stress and anxiety can cause a myriad of symptoms including muscle tenderness, vague pains, and sleep disturbances [12, 13]. One prospective population study of 1735 subjects in 2010 revealed that 7% of those complaining of chronic orofacial pain had coexisting anxiety disorders [14]. Non-neoplastic salivary gland diseases, most commonly sialadenitis, can also cause pain and inflammation radiating to the face [15].

When a clinician encounters a patient with neuropathic facial pain whose symptoms are incongruent with the more common etiologies, the diagnosis of atypical facial pain must be entertained.

Diagnosis

Persistent idiopathic facial pain (PIFP), formerly known as atypical facial pain, is a pain along the territory of trigeminal nerve but does not fit in the criteria of other cranial neuralgias. The etiology of PFIP is unknown, and its diagnosis is given to patients who have persistent facial pain with no known pain mechanism or underlying cause of pain. The pain is deep, poorly localized, and typically unilateral, often in the nasolabial fold or side of the chin. The pain does not follow dermatomal patterns and may spread to the upper or lower jaw or a wider area of the face of neck. Unlike TN, PIFP is usually continuous and persistent with no periods of remission. Additionally, there are no autonomic symptoms associated with PIFP.

The Headache Classification Subcommittee of the International Headache Society defines PIFP as follows [4].

- Pain is in the face.
- Pain is present daily and persists for all or most of the day.
- Pain is confined at onset to a limited area on one side of the face and is deep and poorly localized.
- In addition, the pain is not associated with sensory loss or other physical signs, with no abnormalities in laboratory or imaging studies.

Upon examination and work up, no abnormalities are noted. Women in their forties are most likely to have PIFP, and 6% of patients receiving a root canal have this diagnosis [16, 17].

Pathophysiology

Previous literature has suggested that persistent idiopathic facial pain, previously termed atypical facial pain, may be the result of hyperactive central neuronal activity secondary to damage of primary afferent neurons; however, it is more likely a combination of both biological and psychological factors [6].

Interestingly, recent literature suggests that PIFP is characteristically similar to trigeminal neuropathic pain (TNP) and that the two disorders could simply be on different points of a continuum [18]. In the last decade, studies using quantitative sensory testing (QST) and functional brain imaging have been able to demonstrate specific sensory abnormalities in PIFP that could shed light on the relationship between the disorder and certain neuronal etiologies [18–20]. Most of these pathophysiologic studies highlight the significance of dopaminergic pathways in PIFP and related clinical pain conditions. Specifically, it is the hypofunction of dopaminergic pathways in the basal ganglia that may contribute to PIFP [21–24].

The pathophysiology of PIFP remains poorly understood, and patients often present with oral and other psychological complaints. The association between PIFP and certain psychiatric comorbidities is well documented, but a causal link between the two remains equivocal [25, 26]. Like many idiopathic pain syndromes, the most commonly associated symptoms are those of depression and anxiety, but discerning the psycho-physiologic relationship between these symptoms and PIFP will require further epidemiologic, physiologic, and psychiatric research. The prevalence of psychiatric symptoms in patients with PIFP also stresses the need for interdisciplinary cooperation in both research and patient care.

Treatment

As of yet, there are no curative therapies for persistent idiopathic facial pain. Thus, patients often have a hard time accepting these diagnoses, which can make management difficult. Patients are frequently convinced that their pain stems from perhaps an infection or a tumor, or that provider lacks the ability to diagnose their ailment properly. These misconceptions typically lead patients to seek out multiple providers from various specialties in search of a more satisfying diagnosis. Subsequently, they may receive invasive and unnecessary procedures with little to no relief from their pain. Situations like these are all too common and stress the need for thorough patient education when delivering a diagnosis like PIFP. Furthermore, the management of these patients' pain is frequently complicated by both physical and psychological comorbidities. Therefore, multidisciplinary communication between medical, dental, neurological, psychological, and psychiatric specialist is crucial when caring for these individuals.

Unfortunately, few randomized controlled trials for the treatment of PIFP exist which makes the utilization of evidence-based practices difficult at best. However, there are a select number of pharmacological, non-pharmacological, and interventional treatment options that have proven to be moderately effective.

Pharmacological Management

Pharmacological approaches to PIFP have changed little in recent years. The current mainstay of treatment is a low-dose tricyclic antidepressant. If not contraindicated, amitriptyline remains the primary drug of choice at an initial dose of 25 to 100 mg per day [27]. If TCAs are contraindicated or ineffective, there are a selection of second-line pharmacologic treatments that have proven effective including certain SSRIs, SNRIs, and anticonvulsants. Among the second-line antidepressants, venlafaxine and fluoxetine are preferred [27, 28]. With regards to the anticonvulsants, a trial of pregabalin and gabapentin may be tried [29]. Of note, cognitive behavioral therapy (CBT) as an adjunct to antidepressant therapy has been shown to obtain better outcomes than antidepressant therapy alone [6, 30, 31].

Non-pharmacologic Management

For patients and physicians not ready or unable to explore other treatment options, the use hypnosis has shown some promising data for those suffering from PIFP. In a controlled, patient-blinded study of 41 patients with atypical facial pain, Abrahamsen and colleagues compared the effects of active hypnosis for five 1-h sessions with simple relaxation. Their results showed significant pain reduction, albeit with a variety of psychosocial variables that were unaccounted [32]. Therefore, when considering this option, it is important to include stress-coping strategies and unresolved psychological problems in the management plan [33•].

Another novel proposal has been the utilization of cannabinoids as a therapeutic avenue for PIFP [34•]. Large data studies in rat models have shown that cannabinoids target the same dopamine pathways that may serve as the physiologic backbone of PIFP [28, 35].

Other non-pharmacologic approaches such as acupuncture, biofeedback, and dental splinting have been proposed, but evidence of their effectiveness in the management of atypical facial pain is insufficient thus far.

Interventional Management

In patients with PIFP to conservative management, interventional approaches should be considered. By far, the most studied approach with the most document success is the use of pulsed radiofrequency (PRF) treatment. A sphenopalatine ganglion block using the infrazygomatic approach should be attempted first. If adequate but temporary relief is achieved after the block, then PRF should be considered. In a retrospective study, PRF of the sphenopalatine (pterygopalatine) ganglion was performed in patients with chronic facial pain syndromes, including PIFP. Of the patients who received the treatment ($n = 30$), 21% reported complete pain relief, and 65% had subjectively rated their pain relief between good and moderate. Furthermore, more than half of the patients reported a 50% reduction in their opioid medication use [36]. Secondary to the positive results of similar studies using this method, PRF is currently the recommended interventional treatment for persistent idiopathic facial pain [27, 37, 38••]; however, most of these studies are observational, and strong evidence-based studies are scarce.

While there is a need for more randomized controlled trials of PRF, there are other promising interventional approaches warranting further exploration. In a small study of note ($n = 10$), Klein and colleagues implanted peripheral nerve field stimulators (PNFS) in patients with intractable facial pain secondary to trigeminal neuralgia, trigeminal neuropathic pain, and PIFP. After implantation, six of the ten patients were pain-free, and two showed marked improvement in their perceived pain. Additionally, those eight patients experienced lasting significant improvement at follow-up times of up to 28 months [39••].

Botulinum toxin injections are also being explored as treatment options for PIFP. In a small study by Cuadrado et al., four patients with atypical odontalgia, a subtype of PIFP, were treated with several local injections of botulinum neurotoxin type-A (BoNTA) at the site of the pain and the surrounding tissue. Although there was a latency period of 3–14 days, all patients experienced significant relief with complete or near complete resolution of their pain [40••]. The results of this study are promising, but as with PNFS, they suffer from very low sample sizes.

PNFS and BoNTA injections have been studied and proven efficacious in other neuropathic pain syndromes as well [41, 42••]. However, more prospective studies such as randomized controlled trials are necessary to explore the possibility of their more widespread use as viable procedures for the treatment of PIFP.

Conclusion

As described in this review, persistent idiopathic facial pain remains a condition that requires interdisciplinary cooperation in both treatment and research. The condition is debilitating for patients, and their quest for a satisfying diagnosis often leads to unnecessary procedures and costs. Furthermore, understanding the differential of atypical facial pain is crucial to avoid delaying diagnosis and treatment. Finding new, more effective treatments for PIFP will rely heavily upon the further understanding of its underlying pathophysiology. Regarding treatment modalities, developing larger controlled trials of current therapies and continuing to investigate novel ones should remain top priorities.

Compliance with Ethical Standards

Conflict of Interest Austin L. Weiss and Ken P. Ehrhardt declare that they have no conflict of interest. Reda Tolba declares personal fees from AstraZeneca for serving as a speaker.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Macfarlane TV, Blinkhorn AS, Davies RM, et al. Oro-facial pain in the community: prevalence and associated impact. Community Dent Oral Epidemiol. 2002;30(1):52–60.
2. Obermann M, Holle D, Katsarava Z. Trigeminal neuralgia and persistent idiopathic facial pain. Expert review of neurotherapeutics. 2011;11(11):1619–29.

3. Mueller D, Obermann M, Yoon MS, et al. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: a population-based study. Cephalalgia. 2011;31(15):1542–8.
4. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9): 629–808.
5. Zakrzewska JM. Differential diagnosis of facial pain and guidelines for management. Br J Anaesth. 2013;111(1):95–104.
6. Vadivelu N, Vadivelu A, Kaye AD. Orofacial pain: a clinician's guide. Switzerland: Springer; 2014.
7. Slade GD. Epidemiology of dental pain and dental caries among children and adolescents. Community Dent Health. 2001;18(4):219–27.
8. Brennan DS, Spencer AJ, Roberts-Thomson KF. Quality of life and disability weights associated with periodontal disease. J Dent Res. 2007;86(8):713–7.
9. Manzoni GC, Torelli P. Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci. 2005;26 Suppl 2:s65–7.
10. Suzuki N, Mashu S, Toyoda M, et al. Oral burning sensation: prevalence and gender differences in a Japanese population. Pain Pract. 2010;10(4):306–11.
11. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med. 1999;28(8):350–4.
12. Penna PP, Recupero M, Gil C. Influence of psychopathologies on craniomandibular disorders. Braz Dent J. 2009;20(3):226–30.
13. Abetz LM, Savage NW. Burning mouth syndrome and psychological disorders. Aust Dent J. 2009;54(2):84–93. quiz 173.
14. Aggarwal VR, Macfarlane GJ, Farragher TM, et al. Risk factors for onset of chronic oro-facial pain-results of the North Cheshire orofacial pain prospective population study. Pain. 2010;149(2):354–9.
15. Mohan H, Tahlan A, Mundi I, et al. Non-neoplastic salivary gland lesions: a 15-year study. Eur Arch Otorhinolaryngol. 2010;268(8): 1187–90.
16. Zakrzewska JM. Facial pain: an update. Curr Opin Support Palliat Care. 2009;3(2):125–30.
17. Melis M, Lobo SL, Ceneviz C, et al. Atyical odontalgia: a review of the literature. Headache. 2003;43(10):1060–74.
18. Forssell H, Jaaskelainen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological mechanisms related to idiopathic orofacial pain conditions with implications for management. J Oral Rehabil. 2015;42(4):300–22.
19. Jääskeläinen SK, Forssell H, Tenovuo O. Electrophysiological testing of the trigeminofacial system: aid in the diagnosis of atypical facial pain. Pain. 1999;80(1):191–200.
20. Lang E, Kaltenhäuser M, Seidler S, Mattenklodt P, Neundörfer B. Persistent idiopathic facial pain exists independent of somatosensory input from the painful region: findings from quantitative sensory functions and somatotopy of the primary somatosensory cortex. Pain. 2005;118(1):80–91.
21. Jääskeläinen SK, Rinne JO, Forssell H, et al. Role of the dopaminergic system in chronic pain—a fluorodopa-PET study. Pain. 2001;90(3):257–60.
22. Hagelberg N, Forssell H, Aalto S, et al. Altered dopamine D2 receptor binding in atypical facial pain. Pain. 2003;106(1):43–8.
23. Hagelberg N, Forssell H, Rinne JO, et al. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. Pain. 2003;101(1):149–54.
24. Wood PB. Role of central dopamine in pain and analgesia. Expert review of neurotherapeutics. 2008;8(5):781–97.
25. Taiminen T, Kuusalo L, Lehtinen L, et al. Psychiatric (axis I) and personality (axis II) disorders in patients with burning mouth syndrome or atypical facial pain. Scandinavian Journal of Pain. 2011;2(4):155–60.
26. Zakrzewska JM, Hamlyn PJ. Facial pain. In: Crombie IK, editor. Epidemiology of pain. Seattle: IASP Press; 1999. p. 171–202.
27. Cornelissen P, van Kleef M, Mekhail N, Day M, van Zundert J. Evidence-based interventional pain medicine according to clinical diagnoses. 3. Persistent idiopathic facial pain. Pain Pract. 2009;9(6):443–8.
28. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain. 2004;18(2):131–7.
29. Sommer C. Patientenkarrieren. Der Schmerz. 2004;18(5):385–91.
30. Zakrzewska JM. Multi-dimensionality of chronic pain of the oral cavity and face. J Headache Pain. 2013;14(1):37. -2377-14-37.
31. Harrison S, Glover L, Maslin L, Feinmann C, Pearce S, Harris M. A comparison of antidepressant medication alone and in conjunction with cognitive behavioural therapy for chronic idiopathic facial pain. In: Jensen G, Turner JA, Weisenfeld-Hallin Z, editors. Proceedings of the 8th World Congress on Pain: progress in pain research and management, vol. 8. Seattle: IASP Press; 1997. p. 663–72.
32. Abrahamsen R, Baad-Hansen L, Svensson P. Hypnosis in the management of persistent idiopathic orofacial pain—clinical and psychosocial findings. Pain. 2008;136(1–2):44–52.
33.• Zakrzewska JM. Chronic/persistent idiopathic facial pain. Neurosurg Clin N Am. 2016;27(3):345–51. **Stress coping strategies and treatment of underlying psychological disorders is a key factor for multimodal management of patients with PIFP**.
34.• McDonough P, McKenna JP, McCreary C, Downer EJ. Neuropathic orofacial pain: cannabinoids as a therapeutic avenue. Int J Biochem Cell Biol. 2014;55:72–8. **Cannabinoids treatment has been a hot topic of interest for treatment of chronic painful conditions, including PIFP**.
35. Dalton VS, Zavitsanou K. Differential treatment regimen-related effects of cannabinoids on D1 and D2 receptors in adolescent and adult rat brain. J Chem Neuroanat. 2010;40(4):272–80.
36. Bayer E, Racz GB, Miles D, Heavner J. Sphenopalatine ganglion pulsed radiofrequency treatment in 30 patients suffering from chronic face and head pain. Pain Practice. 2005;5(3):223–7.
37. Narouze SN. Interventional management of head and face pain: nerve blocks and beyond. New York: Springer; 2014.
38.•• Akbas M, Gunduz E, Sanli S, Yegin A. Sphenopalatine ganglion pulsed radiofrequency treatment in patients suffering from chronic face and head pain. Braz J Anesthesiol. 2016;66(1):50–4. **Novel techniques such as pulsed radiofrequency ablation of the sphenopalatine ganglion have been studied and used for treatment of PIFP as well as other forms of facial pain**.
39.•• Klein J, Sandi-Gahun S, Schackert G, Juratli TA. Peripheral nerve field stimulation for trigeminal neuralgia, trigeminal neuropathic pain, and persistent idiopathic facial pain. Cephalalgia. 2016;36(5):445–53. **Emerging technologies in the field of neuromodulation such as peripheral nerve stimulation are promising options for patients suffering from IPFP**.
40.•• Cuadrado ML, Garcia-Moreno H, Arias JA, Pareja JA. Botulinum neurotoxin type-A for the treatment of atypical odontalgia. Pain Med. 2016. **Injection of neurotoxins such as botulinum toxins could be a promising treatment option for patients suffering from facial pain**.
41. Pessoa BL, Escudeiro G, Nascimento OJ. Emerging treatments for neuropathic pain. Curr Pain Headache Rep. 2015;19(12):1–9.
42.•• Mittal SO, Safarpour D, Jabbari B. Botulinum toxin treatment of neuropathic pain. Seminars in Neurology. 2016;36(01):073–83. **Injection of neurotoxins such as botulinum toxins could be a promising treatment option for patients suffering from facial pain**.