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Persistent idiopathic facial pain, a challenging diagnostic entity: clinical series from a third-level headache center

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ABSTRACT

Background: Persistent idiopathic facial pain (PIFP) is a rare and disabling disease, often misdiagnosed. In this paper, we describe clinical phenotypes and histories of our patients with PIFP.

Methods: Clinical information about pain, treatment histories, previous diagnoses, and MRI findings were assessed during the visit and collected retrospectively.

Results: We observed a total of 44 females and 19 males, with a median age of 63 years. The patients had previously received diagnoses of trigeminal neuralgia, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), and migraine, and some had a diagnosis of PIFP. The quality of pain was described mostly as continuous, stabbing, or burning. The distribution of the pain was referred to as the trigeminal territory, mostly with a second-third branch distribution. Eighteen patients underwent dentistry procedures before the pain started. Pregabalin and carbamazepine were the most frequently prescribed treatment. In 18 patients, a neuro-vascular conflict was found, and all underwent invasive procedures with poor outcomes.

Conclusions: PIFP is a challenging orofacial pain entity, often misdiagnosed. Knowledge of the disease is the first step toward better management. A methodological and systemic approach like that applied to neuropathic pain would be suitable. We suggest a multidisciplinary approach, including medications combined with non-pharmacological options.

Key words: persistent idiopathic facial pain, trigeminal neuralgia, neuropathic pain.

Introduction

Persistent idiopathic facial pain (PIFP), previously known as atypical facial pain, is defined by the International Headache Society in the new International Classification of Orofacial Pain-1st edition (ICOP) as a facial and/or oral pain recurring daily for more than 2 hours per day for at least 3 months, with pain that has the characteristics of being poorly localized, not following the distribution of a peripheral nerve, and dull, aching, or nagging quality in the absence of clinical neurological deficit or radiological findings and with other causes excluded by appropriate investigations. Moreover, ICOP further subdivides PIFP into PIFP with or without somatosensory changes investigated with quantitative sensory testing (QST). (1) It is a rare disease that typically occurs between the ages of 30 and 60 years and scores a prevalence of 0.3% in the general population with female predilection. (2-4)

The pain is fluctuating, typically present during the day, sparing the night, affecting only one side of the face at the onset of the disease and only later expanding to the contralateral midface. Pain is felt primarily in the cheeks and upper jaw but may also radiate to the lower jaw, occipital, and ear, and have no concomitant autonomic symptoms, and is not associated with negative sensory symptoms (hypoesthesia, anesthesia), even if some evidence suggests a neuropathic component in its pathogenesis. (5,6)

While a subtype of PIFP was previously called "atypical odontalgia", it has been redefined by ICOP as a separate entity, called persistent idiopathic dentoalveolar pain (PIDAP), a dental alveolar pain, usually involving only one site, with variable pain characteristics (deep, dull, pressure-like in quality), recurring daily for more than 2 hours/day for at least 3 months, without clinical or radiographic findings. (1) In fact, the first attempt for relief by these patients is often with the dentist, to treat the area or tooth presumably responsible for the pain. Transient improvement may occur after dental procedures but is not lasting. The onset of the pain may be closely related to dental procedures, leading to a vicious cycle of invasive interventions, which can worsen the situation in the long run, with increased pain intensity. (4,5,7)

A frequent misdiagnosis of PIFP is trigeminal neuralgia (TN), especially in the form associated with concomitant persistent background pain, (4) but findings support that PIFP is a clinically and etiologically separate entity from TN, as the most common pathogenetic process of the classical form of TN, neurovascular compression (NVC), is not associated with PIFP. (7-9)

No randomized clinical trials have been performed on this disease, so chronic pain treatment, usually a combined therapy of antidepressants and anti-epileptic drugs, is prescribed, with some recent evidence for behavioral approaches that can help to improve the clinical benefit obtained from medication. Further invasive procedures should be avoided, as they usually lead to worsening pain. (6,10) PIFP clinical presentation is not always easy to manage, and treatment is a challenge. The aim of this paper is to describe the clinical phenotype and clinical history of our outpatients with PIFP.

Results

We enrolled 63 patients out of 180 who met the criteria for PIFP at our outpatient service dedicated to facial pain. Forty-four were females and 19 males, with a median age of 64 years. Neurological examination did not reveal any abnormalities, nor were any deficiencies in sensory or motor components of the cranial nerves found.

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The patients had previously received several different diagnoses: trigeminal neuralgia (70.4%), short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) (11.1%), and migraine (3.7%); only 14.8% had received the diagnosis of PIFP.

The quality of pain was described as: continuous at 20.3%, stabbing at 20.3%, burning at 20.3%, shaking at 18.8%, a sensation of pins and needles (paresthetic) at 12.5%, painful anesthesia-like at 4.7%, and gravitative at 3.1%. The distribution of pain was defined in the trigeminal nerve territory for almost the entire sample (58 out of 63 patients): 6% I branch, 9% II, 12% III, 6% I-II, 27% II-III, 34% I-II-III, 6% other (ear, occipital, mastoid areas) (**Figure 1**). Within the trigeminal territory, the most reported was the second-third branch distribution.

45 out of 63 patients reported worsening factors for pain: chewing 28.9%, speaking 24.4%, brushing teeth or using dental floss or mouthwash 15.6%, swallowing 8.9%, pillow face contacts 8.9%, face washing 4.4%, opening the mouth 4.4%, smiling 2.2%, and wearing glasses 2.2%.

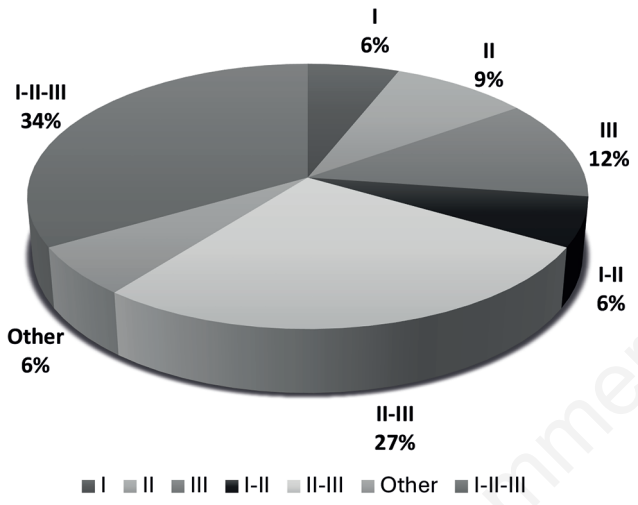

Figure 1. Distribution of Pain (I-II-III are referred to first, second, and third trigeminal branches; other refers to ear, occipital, or mastoid areas).

Of 63 patients, 18 underwent dental procedures before the pain started.

Patients received different types of treatments before presenting to our center, with poor or no improvement of pain: pregabalin and carbamazepine were the most prescribed treatments, with 22.5% each, followed by lamotrigine 8.8%, gabapentin 7.5%, duloxetine 7.5%, amitriptyline 6.3%, clonazepam, tapentadol 5%, and other accounting for 13.9% (phenytoin, paroxetine, trazodone, valproic acid, oxcarbazepine) (**Table 1**).

Of 63 patients, 41 had already performed an MRI angiography imaging with detection of neurovascular contact in 18 out of 41, with no evidence of morphological changes in the trigeminal root. All patients underwent invasive procedures, mostly Gamma Knife (33.3%), thermolysis (27.8%), or neurovascular decompression (11.1%), and others, such as radiofrequency of Gasser ganglion, alcoholization with ethanol of Gasser ganglion, stereotactic thalamotomy, or glycerol Gasser ganglion infiltration, 5.6% each.

Discussion

The ICOP classifies facial pain syndromes, (1) among which: orofacial pain attributed to disorders of dentoalveolar and anatomically related structures, myofascial orofacial pain, temporomandibular joint pain, orofacial pain attributed to lesions or disease of the cranial nerves, orofacial pains resembling presentations of primary headaches, and idiopathic orofacial pain. (1) Non-dental facial pain could be subclassified into two broad groups of orofacial pain: "attack-like pain", such as neuralgias and facial headaches (less frequent variants of primary headaches), and "persistent pain", such as neuropathic or idiopathic pain. (11)

From our data, even using the criteria of the ICOP, (1) patients with PIFP appear to be difficult to diagnose: only 14% of our patients had received a correct diagnosis before coming to our center; consequently, they might have received many inadequate treatments, sometimes even invasive procedures, and delays in diagnosis.

The diagnosis most frequently mistaken with PIFP is trigeminal neuralgia (70.4%), often prescribed with an aggressive pharmacological treatment, as there was little response, and sometimes even invasive approaches (18 of 63 patients) without a sustained response, despite the fact that TN has well-defined diagnostic criteria and a clinical definition that should not confound pain experts. (4,8) The clinical picture of PIFP has some differ-

Table 1. Sample characteristics, quality of pain referred, drug treatments failed, previous diagnoses, and worsening factors.

Sample characteristics		Drug treatments failed	*n*	Previous diagnoses	%	Worsening factors	*n*
Age (y)	64±9	Pregabalin	18	Trigeminal neuralgia	70	Chewing	13
Sex (M : F)	19:44	Carbamazepine	18	Persistent idiopathic facial pain	15	Speaking	11
Mean age at onset (y)	57±7	Lamotrigine	7	SUNCT	11	Oral hygiene (brushing teeth or mouthwash)	7
Quality of pain		Gabapentin	6	Migraine	4	Swallowing	4
Continuous	20%	Duloxetine	6			Pillow face contacts	4
Stabbing	20%	Amitriptyline	6			Face washing	2
Burning	20%	Tapentadol	4			Opening the mouth	2
Shaking	19%	Clonazepam	4	-		Smiling	1
Dysesthesia	13%	Phenytoin	4	-		Wearing glasses	1
Painful anesthesia	5%	Valproic acid	2	-			
Gravative	3%	Trazodone	2	-			
		Paroxetine	2	-			
		Oxcarbazepine	1	-			

SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

Table 2. Clinical features of painful clinical symptoms and possible differential diagnosis with PIFP.

Clinical characteristics	PIFP	Trigeminal neuralgia	SUNA/SUNCT	Migraine
Pain duration	Constant, at least 2 hours per day	1 to 200 attacks/day - lasting 1sec to 2min	3 to 200 attacks/day - 1 to 600 sec	4 to 72 hours
Pain location	Poorly localized, can cross midline	Usually unilateral, among I, II, III trigeminal branches	Orbital, supraorbital, temporal, trigeminal	Usually unilateral, frontotemporal
Pain characteristics	Dull, aching or nagging	Electric, stabbing, sharp shooting	Single stab, groups, serrated	Pulsating or throbbing
Associated symptoms	None	None	Tearing, conjunctival injection	Sensitivity to light and sound, nausea, and vomiting
Preventive treatments	Amitriptyline, Gabapentin, Pregabalin, Carbamazepine, Duloxetine	Carbamazepine, Oxcarbazepine, Gabapentin, Lamotrigine	Lamotrigine, Topiramate, Gabapentin, Pregabalin	Betablockers, Amitriptyline, Topiramate, Candesartan, Flunarizine, mAbs anti-CGRP, Gepants

ences from TN. In PIFP, the pain is often constant, localized to the jaw, not closely related to a well-defined branch of the V cranial nerve, and may also change localization, usually with a not-well-defined character (dull, deep, or pins-and-needles), without accompanying symptoms; in contrast, in NT the pain presents with a dull sensation and a defined duration in time, localized more closely to the course of the V cranial nerve, described as excruciating (*i.e.,* electrical, stabbing), without accompanying symptoms. Accompanying symptoms such as photophobia/phonophobia, conjunctival injection, and lacrimation are useful elements for differential diagnoses with other pathologies, such as the trigeminal autonomic cephalalgias (TACs) family, including SUNCT, which in our case series were misdiagnosed in 11% of cases (**Table 2**). (11)

To note, MRI angiography imaging detected, in 18 out of 41 patients, neurovascular compression, even if, according to literature, PIFP is not associated with neurovascular conflicts, such as TN, and clinical presentation was not suggestive for TN. PIFP is not associated with the presence of neurovascular conflict, meaning when trigeminal root dislocation or atrophy is present, but it might be associated with neurovascular contact in the trigeminal nerve root, a nonspecific finding sometimes present in both TN and healthy subjects. Microvascular decompression procedures or any other invasive procedures should not be part of treatment proposals in this cohort of patients. (1,7).

The anamnestic element of a dental procedure (18 of 63 patients) places this disorder in continuity with the "painful post-traumatic trigeminal neuropathy" caused by significant insult to the peripheral nerves (13.1.2.3 ICHD3), (4,12) with neurophysiological or imaging evidence of the nerve injury, making the clinical picture even more complex and nuanced. In fact, many patients, having already sought dental care, persist in the search for odontogenic causes of pain, resulting in additional, sometimes invasive, procedures in the hopes of resolving the pain. (4,11)

The drugs most often used in our sample were pregabalin and carbamazepine, often in combination with antidepressant-type drugs (duloxetine and amitriptyline), as for many chronic pain conditions, resulting in only suboptimal pain control. The treatment of this complicated form of facial pain is under debate; no randomized clinical trials are available, and poor evidence is available from case series or open studies. The most commonly used drugs are antidepressants, *i.e.,* amitriptyline or duloxetine, and antiepileptic drugs, *i.e.,* gabapentin or pregabalin, or even sodium channel blockers like carbamazepine or oxcarbazepine. A multidisciplinary approach is suitable, comparable to other holistic approaches for many chronic primary headaches, including non-pharmacological treatments. (4, 11)

Our study has some limitations. First, as stated in the new ICOP, a QST should be performed for diagnosis; however, we did not propose this to the patients. Second, additional neurophysiological tests, such as blink reflex and masseter inhibitory reflex, to rule out possible trigeminal neuropathy were not performed. Third, there is a bias associated with retrospective studies.

Conclusions

Persistent idiopathic facial pain is a challenging orofacial pain entity, often misdiagnosed. Correct diagnosis is the first step towards better treatment of patients who frequently follow a path of treatment attempts and sometimes invasive procedures, with a significant waste of medical and social resources.

We believe that these patients deserve more attention from clinicians and the scientific community. A methodological and systemic approach like that applied to neuropathic pain should be applied. Possible comorbidities and psychological variables, such as anxiety or depression, often found in these patients, must be evaluated to prescribe the best treatment plan. Further studies are needed to define a better diagnostic pathway and evaluate the most effective therapeutic interventions; it is likely that the most suitable approach is a multidisciplinary approach that includes medication combined with nonpharmacological options.

Materials and Methods

We enrolled patients from our Neurology Department – Headache Center at IRCCS Besta Institute from 2019 to 2022, seen at the outpatient service where they presented for clinical consult at the service dedicated to "facial pain". Sixty-three out of the 180 patients enrolled met the PIFP criteria, according to our neurology examination. The patients were evaluated by expert neurologists at Besta Institute, and a deep neurological examination was performed during the visit. Clinical information about type, pattern, site, and onset of pain, treatment received, previous diagnoses determined, MRI findings, and clinical histories were assessed during the visit and collected retrospectively.

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