

INVITED REVIEW

A review of persistent idiopathic dentoalveolar pain (formerly PDAP/Atypical odontalgia)

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atypical odontalgia, non-odontogenic pain, persistent dentoalveolar pain, persistent idiopathic dentoalveolar pain

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Abstract

Introduction: Persistent idiopathic dentoalveolar pain (PIDP) is a persistent pain condition isolated to the dentoalveolar region and has previously been known as PDAP/Atypical odontalgia.

Presentation: The challenge in diagnosing PIDP means it is often confused for acute dental pain resulting in patients often receiving a number of dental interventions before a diagnosis is made. This highlights the need for practitioners to be aware of the signs of PIDP as early detection can reduce this risk.

Aetiology: The pathophysiology behind PIDP is a subject for much debate. Theories suggest that there may be a link to nerve injury. However, this is complicated by suggestions of links to psychological factors and not all patients reporting dental interventions at the outset. Furthermore it is difficult to determine if the pain has continued since before the intervention or resulted after it.

Treatment: Current first line treatment for PIDP revolves around the prescription of systemic medications. Whilst these have been proven to have some efficacy they are not universally effective and side effects can reduce compliance. Local treatments have been trailed to improve this, but further research is required and a gold standard has not been set.

Conclusion: Persistent idiopathic dentoalveolar pain an uncommon and poorly understood condition making its diagnosis and treatment challenging. Advances in research are required to the aetiology and treatment of the condition as well as an improvement in clinician's awareness of PIDP. This will hopefully reduce the associated burden on quality of life.

Introduction

Persistent idiopathic dentoalveolar pain (PIDP) is a persistent pain condition localised to the dentoalveolar region, which is neither odontogenic, musculoskeletal or psychological in origin. It has previously been described in the literature as 'persistent dentoalveolar pain disorder', 'atypical odontalgia' or 'phantom tooth pain' but following the international classification for orofacial pain disorders (ICOP) these terms were replaced by PIDP¹. As a new definition

there exists little evidence in the literature using the term PIDP, meaning much of this review is taken from papers using previous terms such as persistent dentoalveolar pain, phantom tooth and atypical odontalgia. Many of these definitions had two subtypes; that of primary in which no obvious cause could be found similar to PIDP and secondary which could be linked to a casual event, typically trauma². ICOP addresses secondary persistent dentoalveolar pain through the terminology post-traumatic trigeminal neuropathic pain (PTNP), which covers

persistent pain in the orofacial region following trauma to the trigeminal nerve. Unfortunately many papers reporting on persistent dentoalveolar pain, phantom tooth and atypical odontalgia do not make the distinction between the two disorders; if the diagnosis was thought to be primary or secondary in nature. This means whilst this review is primarily focused upon PIDP the reader should be aware that much of the current evidence is irrevocably tied to PTNP and represents the best of currently available data.

Impact

The prevalence of PIDP is difficult to estimate due to the challenges of diagnosis but has been reported to be as high as 2.1%³. This sample was taken from a university-based orofacial pain centre and so may not be representative of the wider population, but remains the only paper investigating the prevalence of the condition. Research has instead focused upon the incidence of PIDP which has been found to range between 0.3% and 1.6% following root canal treatment^{2,4} but this does not account for other treatments or those for whom a history of treatment is not present.

The painful and persistent nature of PIDP impacts upon patients' quality of life (QoL). An assessment of oral health related quality of life (OHRQoL) using OHIP-49 found patients with PIDP to have self-reported increases in worry, lower mood levels, greater difficulty relaxing and more episodes of painful aching of the mouth compared to healthy patients. This overall level of impairment was thought to be similar to other more established orofacial pain conditions such as temporomandibular joint disorder (TMD), acute dental pain and trigeminal neuralgia⁵. Studies assessing the general impact upon QoL of orofacial pain using generic QoL tool EQ-5D-5L showed orofacial pain impacted upon usual activities and discomfort to a level found to be similar to chronic conditions such as osteoarthritis and depression⁶. Although PIDP was not specifically reported within this cohort the results from investigations into OHRQoL may indicate this will also apply to PIDP.

Persistent idiopathic dentoalveolar pain can be confused by dental practitioners for common odontogenic pains such as irreversible pulpitis or symptomatic apical periodontitis due to its mimicry of odontogenic symptoms and its persistent nature. This confusion leads to a delay in diagnosis⁷ and frequently leads to the provision of unnecessary treatment which at its best provides no improvement for patients and at its worst can cause significant

exacerbations in the pain experienced^{8,9}. Practitioners, therefore, need to be aware of the similarities in presentation and the correct management of PIDP.

Presentation and diagnosis

Patients who present with PIDP often recall a history of pain for which they may have had multiple irreversible treatments to no relief in symptoms⁹. The common nature of odontogenic pain which has been estimated to account for roughly 60% of orofacial pain¹⁰ means a diagnosis of PIDP is frequently overlooked as practitioners look for inflammatory signs and symptoms. Therefore, it is commonly only after all other causes of pain have been explored and a referral made to tertiary care that a diagnosis of PIDP is made. This delay highlights the need for general practitioners to be aware of the signs of PIDP. Table 1 sets out warning signs, which if noted should raise suspicion of PIDP when screening patients for traditional odontogenic diseases. These signs help to direct clinicians toward the consideration of PIDP, however, for a true diagnosis to be made the following criteria are proposed:

1. A Unilateral or rarely multilateral intra-oral dentoalveolar pain
2. Recurring daily for >2 h per day for >3 months
3. Pain has both of the following characteristics:
 - a. Localised to dentoalveolar site or sites (tooth or alveolar bone)
 - b. Deep, dull, pressure-like quality
4. Clinical and radiographic examination are normal and no local cause may explain the pain¹.

This classification developed as part of ICOP a newly proposed diagnostic criteria for facial pains which brought diagnosis inline with the

Table 1 A table detailing clinical signs and symptoms which if seen or reported should lead the examiners to consider that a PIDP may be present

Possible signs of PIDP

- Patient may have difficulty localising pain (may affect multiple teeth).
- No obvious source of local pathology.
- Pain described as burning or electric shock.
- Numbness or tingling present.
- Failure of local anaesthetic to provide pain reduction.
- Pain extending beyond the usual timeframe of healing.
- Repeated treatments which have failed to resolve pain.
- Pain has unusual triggers and abnormal response to usual odontogenic pain triggers i.e. percussion or temperature changes.
- History of past trauma to the area.
- Pain does not disturb patient's sleep.

International Classification of Headache Disorders 3rd edition (ICHD-3)¹¹ allowing consensus within diagnostic terminologies. Within ICOP PIDP was further split into those associated with somatosensory changes and PIDP without somatosensory changes. This was done to account for those cases which exhibit signs of such as dysaesthesia but did not follow defined sensory nerve distributions. Whilst not essential, splitting the diagnosis further differentiates cases of PIDP and identifying these subgroups clinically may help account for any subtle differences in aetiologies or treatment outcomes.

The full diagnostic criteria for PIDP is listed in Table 2 along with the criteria for two conditions listed in ICOP which may cause confusion during diagnosis of PIDP; PTNP and Idiopathic trigeminal neuropathic pain (ITNP)¹. PTNP is closely associated with PIDP in previous literature, but there is the potential for PTNP and ITNP to produce pain isolated only to the dentoalveolar region of the trigeminal nerve which is thought to be PIDP. To clarify this it must be remembered that PIDP is idiopathic and despite its links to injury which are discussed later in this paper the current definition requires no signs of local causes in contrast to PTNP and ITNP which require the presence of a peripheral trigeminal nerve lesion. This means that if a persistent pain is isolated to the dentoalveolar region and no local cause can be found PIDP should be considered the primary diagnosis.

Aetiology and pathophysiology

Unfortunately, as PIDP is essentially a diagnosis of exclusion, the aetiology behind the condition is poorly understood. Many papers have reported PIDP to be associated with a history of trauma, endodontic treatment or tooth extraction^{12–14}. However, this is based upon previous definitions and so these papers may have been investigating PTNP. The difficulty with applying this is for a true PTNP a diagnostic test confirming a peripheral trigeminal nerve lesion is required, which is often not available meaning a diagnosis of PIDP may still be the best fit. Any links between PIDP and trauma are convoluted by studies examining 1458 patients who received 3rd molar extractions in a hospital setting revealed no cases of reported pain which could be attributed to PIDP¹⁵. This is further complicated as cases of PIDP following extraction or endodontic treatment will have likely been carried out when pain was already present. This makes it difficult to determine if the original pain has continued following the intervention or if

the intervention is responsible for the pain¹⁶. A final issue is that not all patients with PIDP present with a history of trauma or treatment associated with the onset of symptoms indicating that nerve injury is not the only factor affecting the establishment of PIDP.

Nerve trauma has previously been linked to PIDP/PTNP due to the potential for secondary injury following damage to peripheral nerves. This represents any damage, change of phenotype, altered gene transcription or modification of support cells which occurs in the period following the initial injury¹⁷. Release of local inflammatory chemical mediators, growth factors and increased afferent signalling follows nerve injury and may drive this secondary injury. These in turn may alter the transcription of proteins governing nociceptor excitability leading to persistent peripheral sensitisation and hyperalgesia¹⁸. Nerve growth factors may contribute via sprouting of nociceptive fibres to sympathetic fibres, causing nociceptors to fire when sympathetic fibres are triggered¹⁹. Increased afferent signalling in peripheral fibres may result in changes of second and third order neurons; termed 'central sensitisation' leading to membrane hyper-excitability and altered gene expression triggering allodynia, hyperalgesia and referred pain²⁰.

These changes may be compounded by a reduction in inhibitory mechanisms via the descending pain modulating pathway as a result of a decrease in the effectiveness of inhibitory opioid receptors and alterations to the GABA receptor response²¹. Finally, there is evidence to suggest that following peripheral injury sprouting of nerves may occur at central nerve terminals²¹ leading to increases in the number of connections possibly causing acute allodynia, referred pain and radiation of pain as seen in neuropathic conditions. It is therefore possible that trauma may still play a role in the aetiology of PIDP, but many of the changes may take place centrally rather than peripherally and so be difficult to attribute to the trauma or allow a diagnosis of PTNP.

Secondary injury may explain why 1 in 5 patients receiving endodontic treatment experience severe pain 1 week post-operatively, a phenomenon found to be independent of the specialist training of the operator²². However, it does not fully explain the aetiology of PIDP, as despite the frequency of immediate post-operative pain the reported incidence of PIDP is much lower. This difference may be accounted for by research linking the risk of persistent pain to the severity of pain at the outset²³ and the number of day's pain pre-operatively

Table 2 Detailing ICOP diagnostic criteria for persistent idiopathic dentoalveolar pain and two conditions for which PIDP may be confused; post-traumatic trigeminal neuropathic pain and Idiopathic trigeminal neuropathic pain

ICOP diagnostic criteria
<p><i>Persistent idiopathic dentoalveolar pain</i></p> <p><i>Previously used terms:</i> Atypical odontalgia, Primary PDAP, Phantom tooth pain</p> <p><i>Description</i></p> <p>Unilateral, or rarely multiple sites of intra-oral dentoalveolar pain with varying presentations but recurring daily for more than 2 h per day, over more than 3 months without close temporal preceding event.</p> <p><i>Diagnostic criteria</i></p> <p>A Unilateral, or rarely multiple sites of intra-oral dentoalveolar pain fulfilling criterion B and C</p> <p>B Recurring daily for >2 h per day for >3 months</p> <p>C Pain has both of the following characteristics:</p> <ol style="list-style-type: none"> 1. Localised to dentoalveolar site or sites (tooth or alveolar bone)¹ 2. Deep, dull, pressure-like quality² <p>D Clinical and radiographic examination are normal and no local cause may explain the pain³</p> <p>E Not better accounted for by another ICOP or ICHD-3 diagnosis.</p> <p><i>Notes</i></p> <ol style="list-style-type: none"> 1. Pain may be described as either deep or superficial. With time, it may spread to a wider area of the craniocervical region. 2. A wide variety of words are used to describe the character and the pain can have exacerbations, and be aggravated by stress. Adjunctive symptom description may also be used. <p><i>Post-traumatic trigeminal neuropathic pain</i></p> <p><i>Previously used terms:</i> Anaesthesia dolorosa, Painful post-traumatic trigeminal neuropathy</p> <p><i>Description</i></p> <p>Unilateral or bilateral facial or oral pain following and caused by trauma to the trigeminal nerve(s), with other symptoms and/or clinical signs of trigeminal nerve dysfunction. For the diagnosis of post-traumatic trigeminal neuropathic pain (PTNP), pain must persist or recur for ≥3 months and fulfil all criteria below.</p> <p><i>Diagnostic criteria</i></p> <p>A The pain is characterised by all of the following:</p> <ol style="list-style-type: none"> 1. History of a mechanical, thermal, radiation or chemical injury with possible peripheral trigeminal nerve involvement¹ 2. Pain onset in close temporal relation to the injury² 3. Pain distribution neuroanatomically plausible <p>B Pain is associated with somatosensory signs in the same neuroanatomically plausible distribution</p> <p>C Diagnostic test confirming the lesion of a peripheral trigeminal nerve (or nerves) explaining the pain</p> <p>D Not better accounted for by another ICOP or ICHD-3 diagnosis</p> <p><i>Notes</i></p> <ol style="list-style-type: none"> 1. The severity of nerve injuries may range from mild to severe. These include external trauma and iatrogenic injuries from dental treatments such as local anaesthetic injections, root canal therapies, extractions, oral surgery, dental implants, orthognathic surgery and other invasive procedures. 2. Pain appears no later than 6 months after nerve injury. <p><i>Idiopathic trigeminal neuropathic pain</i></p> <p><i>Description</i></p> <p>Unilateral or bilateral facial pain in the distribution(s) of one or more branches of the trigeminal nerve indicative of neural damage but of unknown etiology</p> <p><i>Diagnostic criteria</i></p> <p>For the diagnosis of idiopathic trigeminal neuropathic pain, pain must persist or recur for ≥3 months and fulfil all criteria below.</p> <p>A The pain is characterised by all of the following:</p> <ol style="list-style-type: none"> 1. No history of trauma or disorder with possible peripheral trigeminal nerve involvement 2. Pain distribution neuroanatomically plausible <p>B Pain is associated with somatosensory signs in the same neuroanatomically plausible distribution</p> <p>C Diagnostic test confirming the lesion of a peripheral trigeminal nerve (or nerves) explaining the pain</p> <p>D Not better accounted for by another ICOP or ICHD-3 diagnosis.</p>

to the risk of severe pain following endodontic treatment²². In these cases ongoing neurogenic inflammation and secondary injury may, therefore, be greater in pheno- and in geno-typically vulnerable individuals.

The argument behind phenotypic and genotypic factors playing a part in aetiology of PIDP is strengthened by reports that PIDP shows a preference for the maxilla over the mandible²⁴, and is more common in female patients²⁵. These indicate

that factors such as genetics and phenotype play a role in the establishment of the condition and could explain why PIDP is rare and estimated to occur in only 1.6% of patients who receive endodontic treatment⁴. However, if nerve injury does play a role in the establishment of PIDP, this 1.6% can still be a substantial number of patients when considering that roughly 3.5 million extractions and root canal treatments are carried out on the NHS in England each year²⁶, 15.5 million root canal treatments are carried out in the US each year²⁷ and that PIDP can be a lifelong condition.

An alternative theory behind the aetiology of PIDP is that the pain is psychological in origin. This theory is borne out of research showing that patients with PIDP have increased levels of psychological distress from conditions such as depression and anxiety²⁸. This association does not confirm causality, however, as there is a known association between chronic pain conditions with a significant impact upon QoL such as PIDP and the development of increased levels of psychological distress²⁹. This makes it difficult to determine if the psychological distress occurred as a result of the PIDP and the impact upon QoL or was present before this and so contributed to the establishment of the condition.

As an idiopathic condition there are many patients with PIDP for whom no obvious initial trigger and so cause can be found, highlighting the need for further research in this area. Whilst there are many theories of what could contribute to the condition practitioners should be cautious about attributing the origin of PIDP to just one factor as many elements may contribute and to do so is likely an oversimplification of the condition.

Management

Unfortunately, once established, PIDP is difficult to remedy, meaning many treatments focus upon managing the symptoms of condition rather than delivering a cure. The first and perhaps the most important step in the management of PIDP is to reassure the patient that the pain is real, but educate the patient that it is not dental in origin and as such is unlikely to benefit from surgical intervention³⁰. Discussing this with the patient in a sympathetic manner at an early stage will reduce the risk of unnecessary treatment borne from the somatic nature of pain and reduce the difficulty patients may have in accepting the diagnosis. It will also help when discussing medications such as antidepressants as these can have poor compliance due to their association with treatment for psychological conditions³¹.

To avoid situations which may cause secondary injury and exacerbate neuropathic pain, surgical interventions are often avoided in favour of reversible treatments such as medication. Unfortunately, there are very few medications formulated to specifically treat PIDP. As such, the first line medication for management of PIDP is a tricyclic antidepressant such as amitriptyline, which has been reported to successfully produce a 30% pain reduction in 65% of patients after 16 weeks³². SNRI (serotonin-norepinephrine reuptake inhibitors) such as milnacipran and duloxetine have also seen use. These have been reported to produce a significant reduction in VAS (visual analogue scale) pain scores for patients with burning mouth syndrome and PIDP following 12 weeks of treatment^{33–35}. Unfortunately none of these studies reported the separate response of just PIDP patients; likely due to the low patient numbers and SNRIs did not seem to produce this response for all patients³³. In spite of this, results indicate that SNRIs can be effective for some patients and that this response seems to be independent of plasma concentration³⁴.

Alternative systemic medications used in the treatment of PIDP include membrane stabilisers such as gabapentin and pregabalin. There are no RCTs investigating anticonvulsants in PIDP specifically, but a review of anticonvulsants in the orofacial pain conditions trigeminal neuralgia, myofascial pain and atypical facial pain concluded there was limited to moderate evidence to support their use³⁶. This is likely due to the small number of studies included, but single studies have reported benefits of a 30% reduction in pain in 51% of TMD patients taking gabapentin compared to 24% on a placebo³⁷. Despite the need for more data, antidepressants and anticonvulsants can provide relief to some patients and so should be considered. Unfortunately, as these medications are used systemically there are often significant side effects including sedation, dizziness and nausea³⁸, in turn affecting how well they are tolerated by patients. To combat this medications are often administered at low dosages and scaled up to try and improve patient tolerance, but issues can still occur.

Localised medication has the potential to reduce side effects by only targeting the areas of pain. A study examining the diagnostic potential of lidocaine injections with PIDP showed ~50% of patients reported a 50% reduction in VAS pain scores 30 min after administration³⁹. Unfortunately, this reduction only lasted 120 min and was not without side-effects as roughly 30% of patients reported adverse events subsequent to administration such as headaches and increased pain. This short therapeutic window means

that lidocaine injections are not routinely used. Localised botulinum toxin injections have been reported to produce significant reductions in pain and few side effects in patients suffering from PIDP^{40–42}. It must be noted that this therapy is new, so no RCTs or comparisons with placebos are currently available and papers on the topic comprise of case studies rather than trials with the largest study containing just 9 patients⁴¹. This means that more research is required and as such a consensus on dose and technique has yet to be reached⁴². Despite this botulinum injections remain promising treatment in PIDP as it has been reported the reduction in pain can last as long as 6 months⁴¹.

Topical application of medication has also been investigated in PIDP with EMLA cream producing a mean reduction in pain of 60% in 38 patients (range 0–100%) and 0.025% capsaicin ointment producing a mean reduction in pain of 50% in ~60% of patients at follow up at least 3 months later⁴³. Despite the length of pain reduction for EMLA cream not being recorded and neither treatment producing a reduction in all patients, it highlights the potential for treatment. Even though localised and topical treatments for PIDP require further work, the notion of treatments which not only reduce pain, but produce limited side effects make this a promising avenue of research.

Psychosocial therapy in the treatment of chronic pain conditions has advantages owing to non-invasive nature of intervention. These treatments do not aim to remove the pain, but rather improve a patient's management of the pain and attempt to reduce the resultant impact upon quality of life which follows⁴⁴. Unfortunately, there are no specific data on the efficacy of psychosocial management for PIDP and a Cochrane review on its use in orofacial pain supported its use, but concluded that the evidence was weak⁴⁵. Cognitive behavioural therapy (CBT) is one of the most commonly trialled therapies and coupled with conservative management has been reported to show a reduction in pain intensity of 50% in TMD patients 1 year after intervention compared to 30% in conservative management alone⁴⁶. This is promising as no invasive treatment is required, but it is dependent upon good patient compliance and research is required to see if psychosocial management proves as effective for PIDP.

Future directions

Despite the treatments listed, current evidence suggests that only approximately one third of patients

with PIDP perceive considerable improvement, and only 15% become pain free over a seven-year period⁴⁷. This was despite 83% of patients who reported no improvement receiving ongoing treatment and highlights the need for further research to improve these outcomes. Ideally development is required on targeted medications which are effective and can be applied locally with minimal side effects. Unfortunately, these efforts are hampered by our poor understanding of the aetiology behind PIDP which in turn has been slowed by the number of terms and changing definitions which have been applied over the years. The recent release of ICOP¹ created in consultation with several expert bodies and the definition of PDIP which it produced provides an opportunity for the research community to unite behind one terminology. This could assist future epidemiological studies which are required to determine the exact prevalence of the disease separate from PTNP and prospective research to investigate the incidence in the general dental population. Adoption of a universal term could also help with the creation of databases of patients which owing to the rarity of the condition could be used to provide further insight to triggers and symptoms associated.

Epidemiological work needs to go in hand with the creation of laboratory *in vitro* cell based and murine models which mimic the persistent pain seen in PIDP. These would allow a greater understanding of the cellular processes taking place at a local level and determine the role nerve and secondary injury may play in the condition. Without models the development of novel topical medications to treat and prevent the establishment of PIDP is all but impossible. The development and validation of such models will take time and the eventual use of any potential therapeutic targets will take longer. Immediate research would be best to focus upon RCTs to standardise methods and build an evidence behind current treatment, determine the most effective outcomes for PIDP specifically and to trial repurposing of current medications.

Ultimately extensive research into PIDP is required and future work must look to unify work from lab-based, clinical and epidemiological research to provide us with a more complete picture. Doing this will help with the translation of treatments to provide greater positive outcomes for patients clinically.

Conclusion

PIDP is an uncommon and poorly understood condition which has seen numerous definitions over the

years, making its diagnosis challenging and treatment even more so. Early diagnosis can reduce the risk of unnecessary surgical treatment highlighting the need for dental practitioners to consider the condition when screening for routine odontogenic disease. Whilst treatment is available, there is limited evidence to its efficacy and side effects can be present. Ultimately, more research is required in this area, first to understand the mechanisms behind PIDP and then to develop effective topical treatments to reduce and eliminate painful symptoms without side effects. Advances in research and clinician awareness of the PIDP will hopefully improve patient outcomes and reduce the associated burden to quality of life.

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