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VOL XXII • NO 4 • NOVEMBER 2014

## Painful Traumatic Trigeminal Neuropathy

**T**he patient profile in orofacial pain clinics points to an increasing prevalence of painful traumatic neuropathies

affecting the trigeminal nerve. This rise in prevalence may be partly due to the increasingly invasive character

phantom pain, which makes meta-analyses and data comparison impossible.

### Classification

The issue of classification of neuropathic pain remains contentious. Scientists have taken different approaches,



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of dentistry, improvements in clinicians' awareness and diagnosis of such conditions, and possibly today's greater risk of vehicular accidents and violent altercations. Indications that traumatic trigeminal neuropathy is particularly resistant to standard pharmacological treatment<sup>1</sup> suggest a need for further research, which in turn will demand a clear definition of the clinical phenotype and its adoption by researchers. In the past, authors have used a number of terms with slightly different criteria, including anaesthesia dolorosa, atypical facial pain, atypical odontalgia, and

with some favoring mechanism-based and others ontologically driven approaches. The following represents the thinking of one such group.

Work by two groups<sup>2,3</sup> has led to a more precise characterization of the clinical phenotype of what has come to be described as "painful traumatic trigeminal neuropathy" (PTTN).<sup>2</sup> The criteria suggested for PTTN<sup>2</sup> are based on accepted classification approaches to neuropathic pain.<sup>4</sup> In 2013, the International Headache Society (IHS) adopted the proposed terminology and criteria,<sup>2</sup> dropping the historical term "anaesthesia dolorosa."<sup>5</sup> The classification of PTTN has not yet gained universal acceptance, and it is expected

that as discussion continues changes may be incorporated.

Additionally, the IHS classification is in its beta phase, awaiting data collection. Specifically, the classification currently refers only to pain following injury to the peripheral branch of the nerve. There will be a need to address pain following injury to the soma in the trigeminal ganglion (ganglionopathy) and the central branch (trigeminal nerve root). Notwithstanding, this classification lays the groundwork for consistent research and the future pooling of data.

A key characteristic of PTTN is that its initiating factor is a continuous burning and/or shooting pain in an area that has a clear history of trauma. In addition, neurophysiological, psychophysical, and imaging modalities should support damage to the somatosensory system. Clinically, there

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may be positive and/or negative neurological signs and symptoms, which are the hallmark of PTTN.<sup>2</sup> Similar to other peripheral painful neuropathies, a local anesthetic block to the painful area gives ambiguous results and is not completely effective at eliminating the pain.

The quantitative sensory profile in PTTN patients is a mix of sensory gain and loss.<sup>6,7</sup> There are usually no differences between PTTN patients and controls for warm and heat-detection thresholds,<sup>6</sup> and a comprehensive study in PTTN patients found no differences in warm detection threshold and heat-pain detection thresholds.<sup>7</sup> Studies of brainstem reflexes in PTTN consistently show abnormal blink reflexes,<sup>8</sup> suggesting a dysfunction of the incoming afferents or a dampening effect at the brainstem level.

## Initiating Events

It is interesting to note that routine dental practice frequently involves damage to small sensory afferents. Every dental extraction, along with all root canal therapies and surgical procedures, can induce neuronal damage. The use of local analgesic agents is almost universal, and neuropathy subsequent to direct needle or local anesthetic injury, although uncommon, has been reported.

the risk of trauma to adjacent nerves. Common neuronal complications following implant insertion and damage to adjacent nerves include sensory neuropathy and neuropathic pain.<sup>9</sup> The incidence of neuropathy ranges from 0.6% to 36%,<sup>10</sup> but the incidence of PTTN remains unclear. Given that implants are placed into cancellous bone, which is sparsely innervated, the question arises as to where exactly the neuropathic pain originates. However, evidence suggests extensive peri-implant innervation,<sup>11</sup> so theoretically, neuropathic pain may originate there. Additionally, perineural inflammation, in the absence of direct injury, may induce secondary nerve injury from pressure build-up, leading to neuropathy. This possibility is particularly relevant in the closed spaces around the trigeminal nerve, and indirect evidence of this type of inflammation-induced trigeminal injury can be obtained from animal experiments.<sup>12</sup>

Extraction of mandibular third molars carries the risk of damage to the inferior alveolar nerve, which runs close to the root tips and to the lingual nerve that runs medial to the third molar. Post-extraction neuropathy may remain in these nerves for varying periods and has been found in 0.3% to 1% of cases.<sup>13</sup> The incidence of PTTN is unclear, but the condition seems rare;

**Dental implants, which have become increasingly popular, carry the risk of trauma to adjacent nerves. Common neuronal complications following implant insertion and damage to adjacent nerves include sensory neuropathy and neuropathic pain.**

Dental interventions probably underlie the majority of events leading to PTTN. Dental implants, which have become increasingly popular, carry

follow-up of more than 1,900 patients failed to identify any neuropathic pain cases.<sup>14</sup> Nonpainful neuropathy is rarer in the lingual nerve than in

the inferior alveolar nerve,<sup>15</sup> but with extraction techniques involving nerve retraction, the incidence may reach 4%.<sup>16</sup> However, dysesthesia of the tongue may remain in a small group of patients (0.5%).<sup>16,17</sup> Among patients seeking treatment for extraction-related trigeminal neuropathy, about 70% had comorbid pain.<sup>18</sup> While it is clear that extraction-related painful neuropathy of the inferior alveolar and lingual nerves does occur, such cases are extremely rare.

Root canal or endodontic therapy involves the removal of tissue within the tooth that is richly innervated. It induces axotomy at the level of the root apex. This is probably the most standardized model of iatrogenic nerve injury, and persistent pain after successful endodontic treatment occurs in 3% to 13% of patients.<sup>19</sup> One result of pulp removal and canal obturation is the formation of a disorganized group of sprouting and branching axons that have some features in common with neuromas,<sup>20</sup> and this process may be the origin of neuropathic pain.

Following considerable injury to trigeminal nerve branches, such as crush injury from facial bone fractures, chronic pain develops in about 3% to 5% of patients.<sup>21,22</sup>

## Risk Factors

Factors significantly associated with PTTN following root canal therapy include a history of painful treatment in the orofacial region and female gender.<sup>23</sup> Additionally, significant predictors of PTTN include long duration of preoperative pain, preoperative symptoms in the tooth requiring a root canal, and previous chronic pain problems. The preoperative parameters suggest that some form of sensitization may have occurred to

increase the likelihood of chronic pain, while the presence of comorbid pain suggests a predisposition of the patient to develop chronic pain. The effects of ongoing pain on the nervous system may increase the tendency to develop further pain syndromes.

The exact reasons why some patients develop persistent pain following such mild nerve injury remain unclear. One candidate is a faulty endogenous pain modulatory system. Pain modulation is different in patients with various chronic pain conditions,<sup>24,25</sup> and some experts suggest that the pain modulatory system can affect chronic pain susceptibility.<sup>26,27</sup> Using the experimental paradigm of conditioned pain modulation (CPM) to examine the efficacy of pain inhibition, studies from our laboratory (unpublished data) demonstrate that patients with PTTN following root canal treatment exhibit reduced CPM compared with healthy controls. These studies suggest that measuring CPM preoperatively might help identify patients “at risk” of developing chronic post-traumatic pain.

Indeed, patients undergoing thoro-

racotomy who present preoperatively with altered pain modulation are more prone to develop chronic post-surgical pain.<sup>28</sup> Moreover, drugs that enhance descending inhibition may

a number of single-nucleotide polymorphisms (SNPs). Pain modulation in healthy (pain-free) controls showed a clear association with haplotypes at both the *GCH1* and *COMT* genes known as “low pain sensitivity” (or “protective”) haplotypes (unpublished data). Taken together, these results indicate a relationship between the genotype that is probably involved in the clinical phenotype consisting of impaired CPM and an increased risk for developing PTTN.

In summary, the incidence of PTTN of the trigeminal nerve is low, around 3% to 5%, and does not seem directly related to the severity of nerve damage. However, indications from animal studies suggest that the nature of the injury may significantly affect the incidence of PTTN,<sup>30</sup> but verification would require clinical studies. This low incidence compares with about 5% to 17% in other body regions,<sup>31</sup> which suggests that the trigeminal nerve may react differently to injury relative to spinal nerves.

## Is the Trigeminal Nerve Different?

The trigeminal nerve seems to display some unique pain syndromes unknown in other anatomical sites. These syndromes include trigeminal neuralgia, migraines, and the trigeminal

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be particularly useful in patients with reduced CPM, and indeed, less efficient CPM in patients with painful diabetic neuropathy is associated with greater benefit from duloxetine treatment.<sup>29</sup>

We also found that development of PTTN in this group of at-risk patients was significantly associated with

autonomic cephalgias. This nerve also seems to react differently to trauma (with less electrophysiological activity at the level of the neuroma),<sup>32</sup> displays a lower incidence of neuropathic pain,<sup>21</sup> and shows no sympathetic-sensory relationships at the level of the dorsal root ganglion, unlike those seen in the

sciatic nerve.<sup>33,34</sup> Additionally, there is a significantly lower incidence of other painful syndromes such as complex regional pain syndrome and painful diabetic neuropathy.

Factors that may be involved may include the rich blood supply in the head and neck. Additionally, the trigeminal nerve is the only nerve that “deafferents” itself spontaneously; this deafferentation occurs at the site of every deciduous tooth that is shed in preparation for the erupting permanent tooth with its new source of innervation.

### Imaging

In neuropathic pain, imaging has enabled the identification of brain areas involved in sensory, emotional, cognitive, and modulatory processes.<sup>35</sup> Neuropathic pain originating from nerve injury may result in a decrease in contralateral thalamic gray matter volume<sup>36</sup> as well as cortical reorganization.<sup>37</sup> Thalamic gray matter changes were positively correlated with the length of time after the injury and implicate the thalamus in PTTN.

In a patient with PTTN,<sup>38</sup> light mechanical and thermal (45°C) stimulation activated the trigeminal spinal tract nucleus and thalamus. Mechanical stimulation resulted in a more rostral

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activation of the trigeminal spinal tract nucleus than did thermal stimuli. This interesting finding points to the differential control of neuropathic pain characteristics and is in accordance with other studies.<sup>39</sup>

Changes in cortical thickness in patients with trigeminal neuropathic pain frequently co-localize and correlate with functional activations induced by experimental allodynia. The changes in cortical thickness suggest a dynamic, functionally driven plasticity of the brain.<sup>40</sup> The structural changes correlate with pain duration, age at onset, pain intensity, and cortical activity. Sensory processing in patients with trigeminal neuropathic pain is associated with distinct activation patterns consistent with sensitization within and outside of the primary sensory pathway,<sup>41</sup> and both sensory and emotional circuits display changes. The data point to the possibility that a diagnostic pattern may be identified for neuropathic pain.<sup>40,41</sup> Additionally, these data and findings of differential control of pain characteristics may elucidate specific targets for therapeutic interventions.

### Treatment of PTTN

Pharmacological management of PTTN relies on standard pharmacological protocols recommended for other neuropathic pain syndromes such as postherpetic neuralgia (PHN) and painful diabetic neuropathy (PDN).<sup>42</sup> These protocols rely heavily on tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and the newer antiepileptics gabapentin and pregabalin. The response rates to these drugs for PHN, PDN, and painful spinal traumatic neuropathies are in the range of 20% to 40%,<sup>43</sup> but they are lower for PTTN, around 10%.<sup>1</sup> It is unclear why the response rate in PTTN should be lower, but it may be related to the traumatic origin versus a “disease-based” origin, as in PDN and PHN. Certainly, these figures stress the need for newer, better drugs for neuropathic pain. Additionally, multimodal treatment may offer better outcomes, although a meta-analysis did not show a significant effect of cognitive-behavioral therapy on pain intensity and quality-of-life measures in chronic neuropathic pain.<sup>44</sup>

International Classification of Headache Disorders (ICHD) Painful Post-Traumatic Trigeminal Neuropathy		
Criteria		Comments
A	Unilateral facial and/or oral pain fulfilling criterion C	
B	History of an identifiable traumatic event to the trigeminal nerve, with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypoesthesia, hypoalgesia) signs of trigeminal nerve dysfunction	Traumatic event may be mechanical, chemical, thermal or caused by ionizing radiation.
C	Evidence of causation demonstrated by both of the following: 1. Pain is located in the distribution of the same trigeminal nerve 2. Pain has developed within 3–6 months of the traumatic event	Pain duration ranges widely from paroxysmal to constant, and may be mixed. Following radiation-induced nerve injury, neuropathy may appear after more than 3 months.
D	Not better accounted for by another ICHD-3 diagnosis	Note that most nerve injuries do not result in neuropathic pain.

## Conclusions

With the establishment of a clearer clinical phenotype and advanced

neurophysiological, imaging, and genotyping capabilities, we are now in a position to reliably study the risk and

perpetuating factors involved in PTTN and ultimately provide improved preventive and management options.

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