CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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The Role of Sensory Fiber Demography in Trigeminal and Postherpetic Neuralgias

ABSTRACT

In this study, we systematically investigated fiber demography, based on function and distribution, from the periphery to their destinations in the various central (sub) nuclei in the trigeminal brainstem nuclear sensory complex. Conventional and novel compelling information is provided, demonstrating that the ratio and somatotopy of types *A* and *C* sensory fibers at the site of a lesion can elucidate important puzzles in TNP disorders. For instance, we explain how of a major shift in the fibers' direction and ratio at the level of the trigeminal root entry zone (REZ) influences the pathophysiology of pre- and typical trigeminal neuralgia. As a result, there is a high *A/C* ratio of oral and peri-oral fibers in the supero-medial region of the REZ, which is mostly susceptible to vascular compression. However, this *A/C* ratio varies considerably at lower proportions in other areas along the peripheral trigeminal pathway, where an injury (viral, vessel compression, or trauma) can lead to a broader spectrum of fiber involvement and, consequently, pain outcome. In summary, we explain how fiber demography can influence pain quality, location, temporal features, progress, and treatment prognosis of TNP in those patients who develop it.

KEY WORDS: pain, orofacial pain/TMD, oral medicine, nervous system, trigeminal neuralgia, pre-trigeminal neuralgia.

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INTRODUCTION

Trigeminal neuropathic pain (TNP) disorders, as typical, atypical, and post-herpetic trigeminal neuralgias, are commonly incapacitating conditions with pain that is either spontaneous or can be evoked by harmless but crucial activities, such as eating and talking, or by light touch to the facial skin. The puzzling and overly simplistic current view of the TNP disorders is mainly due to our limited understanding of their pathophysiology. Hitherto, TNP animal models noticeably do not duplicate all of the behavioral signs seen in the clinic. In addition, there are no objective tests available for patients. Therefore, except for imaging studies to detect possible lesions along the trigeminal sensory pathway, dentists and other health professionals depend almost entirely on clinical criteria for their diagnosis.

Here we discuss each of the most common TNP disorders based on fiber demography, including ratio and somatotopic distribution of myelinated and non-myelinated fibers affected by different types of injuries in the trigeminal system, whether viral (post-herpetic neuralgia), traumatic, tumors, or vessel compressions (atypical and typical-TN). Although peripheral injuries to the trigeminal system induce TNP in only a minority of patients—demonstrating the participation of pain modulation from multiple mechanisms, many outside of the scope of this paper—we present substantial data attesting to the fact that nuances in the quantitative and spatial organization of afferent fibers at the location of injury will mostly determine various unique features of TNP symptomatology. Even considering the effects of several peripheral and central mechanisms (*e.g.*, inflammation, central sensitization), each type of afferent sensory fiber will supposedly respond to an insult in a different way, triggering a selected cascade of neurologic events and, consequently, pain outcomes. Nonetheless, the injuries commonly do not affect a single type of afferent fiber, but a wide-ranging combination of them. Hence, the study of fiber demography is a more tangible and physiologic way to understand their role in the final clinical presentation of TNP disorders.

For additional information regarding trigeminal sensory fibers, trigeminal neuropathic pain from dental origin, and the effects of different modalities of treatment on the function of sensory fibers, please refer to the Appendix.

TYPICAL TRIGEMINAL NEURALGIA (TYPICAL-TN)

Typical-TN is described as a disorder with an incidence of 3 to 5 cases *per* 100,000 persons, affecting, on average, elderly people. The pain is characterized as sharp and shooting. Severe brief paroxysmal pain is spontaneous or elicited when the trigger-point, usually located in the oral or peri-oral region,

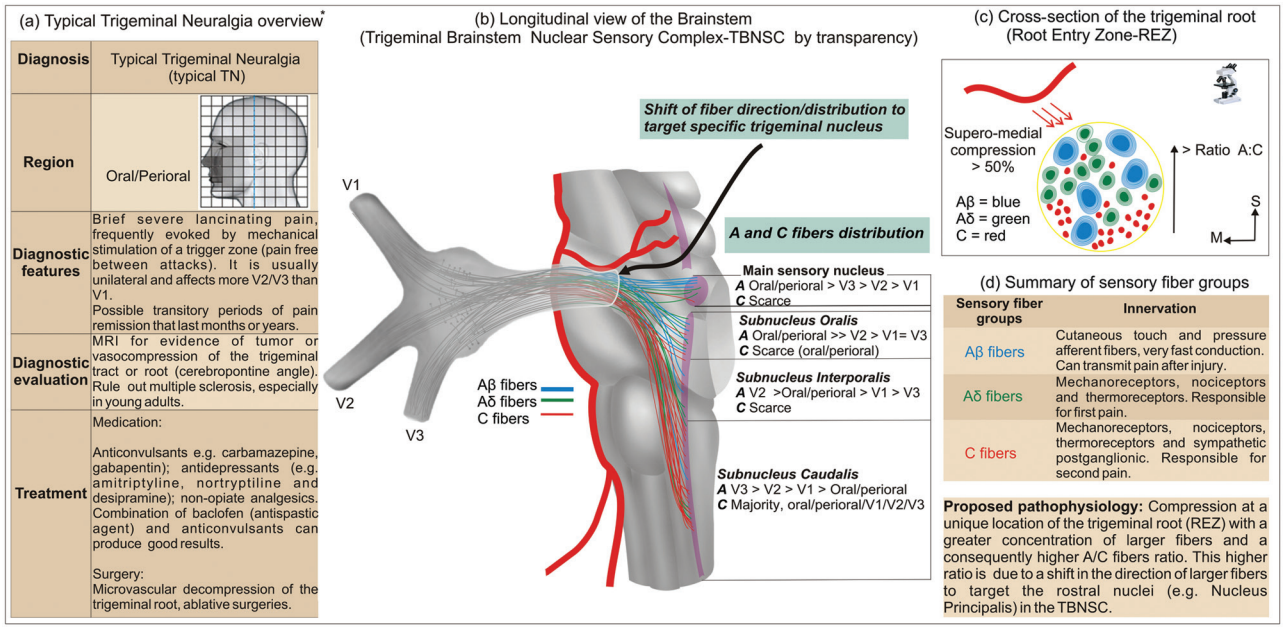

Figure 1. Clinical characteristics and pathophysiology associated with typical trigeminal neuralgia (typical-TN). *All images are original, with the exception of the left table (**a**), which was reprinted, with small adaptations, from DaSilva and Acquadro (2005), with permission from SNELL Medical Communication Inc. **The A- and C-fiber distribution in the trigeminal brainstem nuclear sensory complex, located in the center table, is based on available animal studies.

is stimulated by light touch. It is postulated that typical-TN is caused by compression of the trigeminal root by a blood vessel or tumors at the level of the root entry zone (REZ).

The Unique Ratio and Somatotopic Distribution of Rostral Fibers in the Trigeminal Root Entry Zone: Why Is It a Key Region for Typical-TN Pathophysiology?

The majority of nociceptive impulses from the orofacial region are mainly (but not exclusively) mediated by the trigeminal nerve. The action potentials are transmitted from its peripheral branches, ophthalmic (V1), maxillary (V2), and mandibular (V3), by pseudo-unipolar neurons with the cell bodies located in the trigeminal (gasserian or semilunar) ganglion. From the trigeminal ganglion, the central processes of these cells follow the trigeminal sensory root and enter the lateral portion of the pons in a region frequently referred to as the trigeminal root entry zone (REZ) (Shankland, 2000).

Although a somatotopic organization has been demonstrated in the trigeminal ganglion (Borsook *et al*., 2003), a functional segregation of fibers in the trigeminal root proposed by some authors is extremely controversial, having elicited many scientific debates in the past (Samii and Jannetta, 1981; Hussein *et al*., 1982). However, analysis of anatomical and clinical data supports our concept that at the level of the brainstem, when leaving the trigeminal root, specifically at the REZ, the sensory fibers change their direction to target their proper nuclei in the trigeminal brainstem nuclear sensory complex (TBNSC) (Crissman *et al*., 1996; Pajot *et al*., 2000; Devor *et al*., 2002b; Sindou *et al*., 2002, 2006; Miller *et al*., 2009). Consequently, many of the *A*β fibers transmitting tactile information from the orofacial region leave the trigeminal root rostrally in their trajectory to the main sensory nucleus, located at the level of the midpons (Samii and Jannetta, 1981; Sessle, 2000) (Fig. 1). Similar rostral convergence occurs with *A*δ, in fact both A-fibers, when targeting other rostral nuclei in the TBNSC such as the subnucleus oralis and interporalis (Pajot *et al*., 2000). Conversely, only scarce C-fibers coming directly from the trigeminal root have terminals in the main sensory nucleus, oralis, and interporalis (Tashiro *et al*., 1984; Sugimoto *et al*., 1997; Woda, 2003). The majority of the C-fibers travel with a lower number of A-fibers (than in the rostral subnuclei) to the subnucleus caudalis (Samii and Jannetta, 1981; Tashiro *et al*., 1984; Pajot *et al*., 2000; Sessle, 2000), which is located inferiorly, extending from the level of the obex for approximately 15 mm to the C2 level, where it becomes continuous with the dorsal horn in the human spinal cord (Paxinos and Huang, 1995; Paxinos and Mai, 2004). Such C-fibers in the subnucleus caudalis terminate mainly in the superficial layers, and they can also modulate the activity of convergent neurons in the subnucleus oralis *via* interneurons (Dallel *et al*., 1998, 2003; Woda *et al*., 2001; Woda, 2003).

This peculiar anatomical distribution of sensory fibers based on their function and TBNSC targets translates into a unique higher A/C fiber ratio in the most superior regions of the trigeminal root in the REZ. In contrast, this A/C fiber ratio decreases in more caudal parts of the REZ, due to the higher numbers of C-fibers going to the subnucleus caudalis. In fact, a recent study demonstrated that the ratio of myelinated to unmyelinated fibers is about 4:1 in the region adjacent to the trigeminal root compression in biopsy specimens taken from patients with trigeminal neuralgia (Marinkovic *et al*., 2009). Typical studies have described a reduced A/C fiber ratio in the spinal dorsal roots (up to 80% of unmyelinated fibers), when compared with the trigeminal sensory roots (40-50% of unmyelinated

fibers), which could represent a greater proportion of C-fibers in lower segments of the body (Windle, 1926; Young and King, 1973; Samii and Jannetta, 1981).

In typical-TN, compressive injury occurs especially at the superior area of the REZ (actually supero-medial in more than 50% of cases) (Sindou *et al*., 2002), where the average diameter of myelinated fibers is larger compared with that in other regions of the trigeminal root (Crissman *et al*., 1996) (Fig. 1). Histological analysis from typical-TN patients showed that compressed trigeminal root specimens had axonopathies and axonal loss that could induce ectopic after-discharge and cross-excitation of neighboring fibers (Devor *et al*., 2002a,b). Those axonopathies are also evidenced by recent studies with diffusion tensor imaging (DTI) that demonstrated microstructural changes in the trigeminal roots of patients with trigeminal neuralgia (Fujiwara *et al*., 2010; Lutz *et al*., 2011). Furthermore, focal demyelination was demonstrated exactly at the REZ in cases of trigeminal neuralgia due to multiple sclerosis (Love *et al*., 2001). The main reason for the unique symptomatic features in typical-TN, with spontaneous but mostly evoked pain from tactile stimulation of the trigger zone, might be a high ratio of A-fibers in the root entry zone (REZ) area, as discussed above, given that they are critical for pain triggered by tactile stimulation (Devor, 2009). Although *A*β fibers are usually associated with innocuous sensations and respond to brush-touch stimuli, they can mediate pain after peripheral nerve injury. Some mechanisms have been proposed to explain this fact, including central sensitization, disinhibition, and central afferent sprouting. Furthermore, changes in the properties ("phenotype") of low-threshold *A*β fibers, named "phenotypic switching", have been recently suggested (Woolf and Mannion, 1999; Maihofner *et al*., 2003; Costigan *et al*., 2009; Devor, 2009). Notwithstanding, in addition to the *A*β fibers' dysfunction, the impairment of *A*δ fibers probably also contributes to the phenomenon of trigger zones in typical-TN (Cruccu *et al*., 2001; Obermann *et al*., 2007). Moreover, such massive activation of A-fibers is associated with another patent clinical phenomenon in typical-TN: the refractory period that follows the TN attacks, where immediate re-stimulation of the trigger zone will not elicit another bout of pain, at least for a few seconds or minutes. This is partially explained by the suppressive effect, at least in non-pathological states, of A-fiber stimulation (*e.g*., tactile, vibrotactile, pin-prick) on C-fiber responses (*e.g*., heat), and *vice versa*, *via* central inhibitory mechanisms (Watanabe *et al*., 1999; Hoshiyama and Kakigi, 2000; Nahra and Plaghki, 2003; Tran *et al*., 2008).

Why Is There a Higher Incidence of Trigger Zones in Maxillary and Mandibular Trigeminal Branches in Typical-TN Patients?

Another interesting characteristic concerning typical-TN is the main localization of the trigger zones in the oral and peri-oral regions (The International Classification of Headache Disorders, 2004; Truini *et al*., 2005), commonly affecting the maxillary (V2) and mandibular (V3) branches and sparing the ophthalmic branch (V1) (Wall *et al*., 2006). This fact is explained by the large oral/peri-oral somatotopic fiber distribution (Pajot *et al*., 2000; Truini *et al*., 2005) along with its high concentration of larger fibers (*A*β and *A*δ fibers) when compared with the lateral zones of the face (Sugimoto *et al*., 1986, 1988). The same *A*β and *A*δ fibers are located in a more superior position in the REZ and, consequently, are more vulnerable to compression, mostly by the superior cerebellar artery (SCA) (Sindou *et al*., 2002). Such fibers from oral and peri-oral structures are mainly projected to the higher regions of the TBNSC as a whole (Azerad *et al*., 1982; Broton and Rosenfeld, 1982; Dallel *et al*., 1987, 1988, 1990; Duale *et al*., 1996; Luccarini *et al*., 1998; Bae *et al*., 2004), and also in a pattern similar to each one of its subnuclei (Shigenaga *et al*., 1986a,b; Toratani *et al*., 2008). Conversely, fibers from the peripheral regions of the face, including V1, are primarily projected to the lower portions of the TBNSC (Azerad *et al*., 1982), especially the lower levels of the subnucleus caudalis, which constitutes the typical onionskin representation of the face at the TBNSC (DaSilva *et al*., 2002) (Fig. 1).

What Is Pre-trigeminal Neuralgia, and Why Do the Pain Quality and Location Differ from Those of Typical-TN?

Some individuals with typical trigeminal neuralgia have reported a prodromal pain termed 'pre-trigeminal neuralgia' (Symonds, 1949; Mitchell, 1980; Fromm *et al*., 1990; Evans *et al*., 2005).

As discussed above, although the majority of C-fibers project to lamina II and lamina I of the subnucleus caudalis (Kobayashi and Matsumura, 1996), there are reports of few and isolated nociceptive C-fibers arriving in the dorsal part of the main sensory nucleus, the medial edge of the interporalis, and the dorsal half of the oralis (Sugimoto *et al*., 1997). Those scarce C-fibers are almost exclusively from the oral region, especially the pulp (Azerad *et a*l., 1982; Takemura *et al*., 1991; Kwan *et al*., 1993; Sessle, 2000). Interestingly, most pre-trigeminal neuralgia patients experience a toothache-like pain with continuous, aching, or burning quality resembling atypical-TN pain, which are symptoms associated with C-fiber input. Nonetheless, pre-TN is certainly not an exclusive contribution of unmyelinated fibers, since some patients also describe the pre-TN pain as sharp, and it is treated with the same array of medications used for typical-TN (Mitchell, 1980; Fromm *et al*., 1990; Evans *et al*., 2005). Hence, it is possible that the infrequent occurrence of pre-TN may, in some cases, represent the early stages of the REZ compression, where those few intra-oral C-fibers in the root targeting rostral nuclei are mostly affected initially. Later, with increased accommodation of the vessel on the superior portion of the root where A-fibers are in the majority, the symptoms shift to a more typical-TN scenario, with paroxysmal attacks.

ATYPICAL TRIGEMINAL NEURALGIA (ATYPICAL-TN)

Atypical-TN affects a larger number of patients and is described in a wider variety of pain descriptors, including burning and throbbing. Nonetheless, patients have also reported, to a lesser degree, sharp pain as typical-TN (Eller *et al*., 2005). For those patients, the mild to severe pain is usually constant, with a characteristic after-sensation. This condition is caused by damage to the trigeminal system, usually peripheral, and is associated with tumors (Vassilakis *et al*., 1988; Nomura *et al*., 1994; Shankland,

2009), trauma (Shankland, 2009), or surgeries (Grigoryan Yu *et al*., 1994). Its classification is rather confusing and lacks agreement among different institutions; hence, in this article for the purpose of differentiation from typical-TN, and not taxonomy, we will use the term 'atypical-TN'.

How Does the Local Ratio of Sensory Fibers Influence the Symptoms in Atypical-TN?

Orofacial Region

The ratio of sensory fibers at the location of injury is crucial to determine the clinical characteristics of atypical-TNP (*e.g*., more sharp or burning pain). For example, traumas to the oral/peri-oral areas of the face affect branches that contain a high A/C fiber ratio, albeit not as high as the superior portion of the REZ, and will translate into a more episodic and sharp pain, with some C-like descriptors of pain (*e.g*., burning). In contrast, superficial lesions to more lateral regions of the face, where the proportion of C-fibers is higher (Sugimoto *et al*., 1986, 1988), result in constant and burning pain, with a minor component of sharp pain.

Trigeminal Ganglion and Root

Following the same principle, the clinical characteristics of pain due to lesions at the level of the trigeminal ganglion or root will be influenced by the local A/C fiber ratio. For example, lesions in the trigeminal root closer to the ganglion will lead to more atypical descriptors, due to the sorted concentrations of A- and C-fibers, and lesions close to the root entry zone (REZ) from above will lead to more typical-TN symptomatology (Cusick, 1981; Tancioni *et al*., 1995; Turp and Gobetti, 1996) (Fig. 2). Likewise, the type of vessel compression and the extension of its area of contact along the trigeminal root can also influence symptoms. While arterial compressions, especially at the REZ, are strongly associated with typical-TN, venous compressions usually extend for a larger area and are firmly attached to the trigeminal root (Dandy, 1934); consequently, the latter do not spare any particular group of fibers, and the symptoms are more associated with atypical-TN than with typical-TN (Roski *et al*., 1982; Sekula *et al*., 2009). Similar principles apply to the clinical outcome of surgical treatments available for TNP, based on their selective or non-selective harmful effects upon the local groups of trigeminal fibers, sensory and motor.

Regarding pain location, if there is a lesion in the trigeminal ganglion, the pain will be restricted to the peripheral trigeminal somatotopy. Hence, injuries at the medial and anterior parts of the ganglion mostly lead to pain in V1, caudal and lateral injuries produce pain at V3, and intermediate injuries pain in V2 (Cusick, 1981; Bullitt *et al*., 1986; Nomura *et al*., 1994; Borsook *et al*., 2003; Eller *et al*., 2005). Conversely, lesions closer to and beyond the REZ will obey central pain somatotopy, which resembles the onionskin pattern. As a consequence, the trigeminal root area between the trigeminal ganglion and the REZ will serve as a transition zone between peripheral and central systems, which will translate into a less-defined arrangement of sensory fibers (Fig. 2). In fact, the different somatotopic dispositions of sensory fibers along the trigeminal somatosensory system may be a potential clinical tool to suggest whether a particular pain location and irradiation are associated with a peripheral or central lesion.

POST-HERPETIC NEURALGIA (PHN)

Post-herpetic neuralgia (PHN) is one of the most common conditions of neuropathic pain disorders that affect the elderly population. PHN is often acquired after the reactivation of a latent varicella zoster virus (VZV) associated with an earlier infection during chickenpox (varicella) occurrence (Fig. 3). The later reactivation of varicella causes a clinical condition known as herpes zoster. Most patients recover completely from herpes zoster after some months. However, in some, the pain persists after the rash heals (Watson and Oaklander, 2002, 2006; Dworkin *et al*., 2008; Delaney *et al*., 2009).

Why Is There a Predilection for the Trigeminal Ophthalmic Branch in PHN?

Despite the involvement of most of the body regions during a chickenpox event, a viral overload is reported in specific dermatomal areas (*e.g*., ophthalmic, mid and lower thoracic, and upper lumbar) (Kennedy and Steiner, 1994). Subsequent to the resolution of the primary varicella infection, residual provirus segments migrate through sensory nerve endings to sensory fibers. After colonization of the dorsal root or cranial ganglia (usually the trigeminal ganglia), VZV settles in neuronal or satellite cell nuclei, where it is protected from antibodies present in the circulation in response to the primary infection (Weinberg, 2007). As a consequence, the virus will be latent in great proportions in the cell bodies of sensory fibers associated with those overloaded regions (Kennedy and Steiner, 1994), notably at the ophthalmic division of the trigeminal nerve, which accounts for more than 75% of herpes zoster cases localized in the cranial region (de Leeuw, 2008). As previously mentioned, this region (V1) has a large concentration of unmyelinated fibers and consequently, a lower A/C fiber ratio when compared with V2 and V3 (Sugimoto *et al*., 1986, 1988). This ratio of fibers is strongly related to the symptoms described by patients with PHN affecting the ophthalmic region.

It has been well-established that VZV recurrence is usually a single event that occurs only after the immunological system is compromised. One speculation for this is the VZV DNA and RNA tissue amounts present in the peripheral sensory ganglia (PSG) during latent infection. Therefore, VZV is much less capable of reactivation than HSV-1, and only the most affected dermatomes (such as the ophthalmic) are able to supply the PSG with a heavy load of viral particles. This explains the high incidence of herpes zoster as well as PHN for the ophthalmic division at the trigeminal nerve (Hope-Simpson, 1965; Kennedy and Steiner, 1994).

How Do the Virus Spread and Ratio of Affected Sensory Fibers Influence the Symptomatic Progression in Acute Herpes Zoster (AHZ) and Post-herpetic Neuralgia (PHN)?

Following its reactivation, the VZV spreads by a neuronal/non-neuronal (*i.e*., satellite cells) pathway (Kennedy and Steiner, 1994; Arvin and Gershon, 2000). As a consequence, active

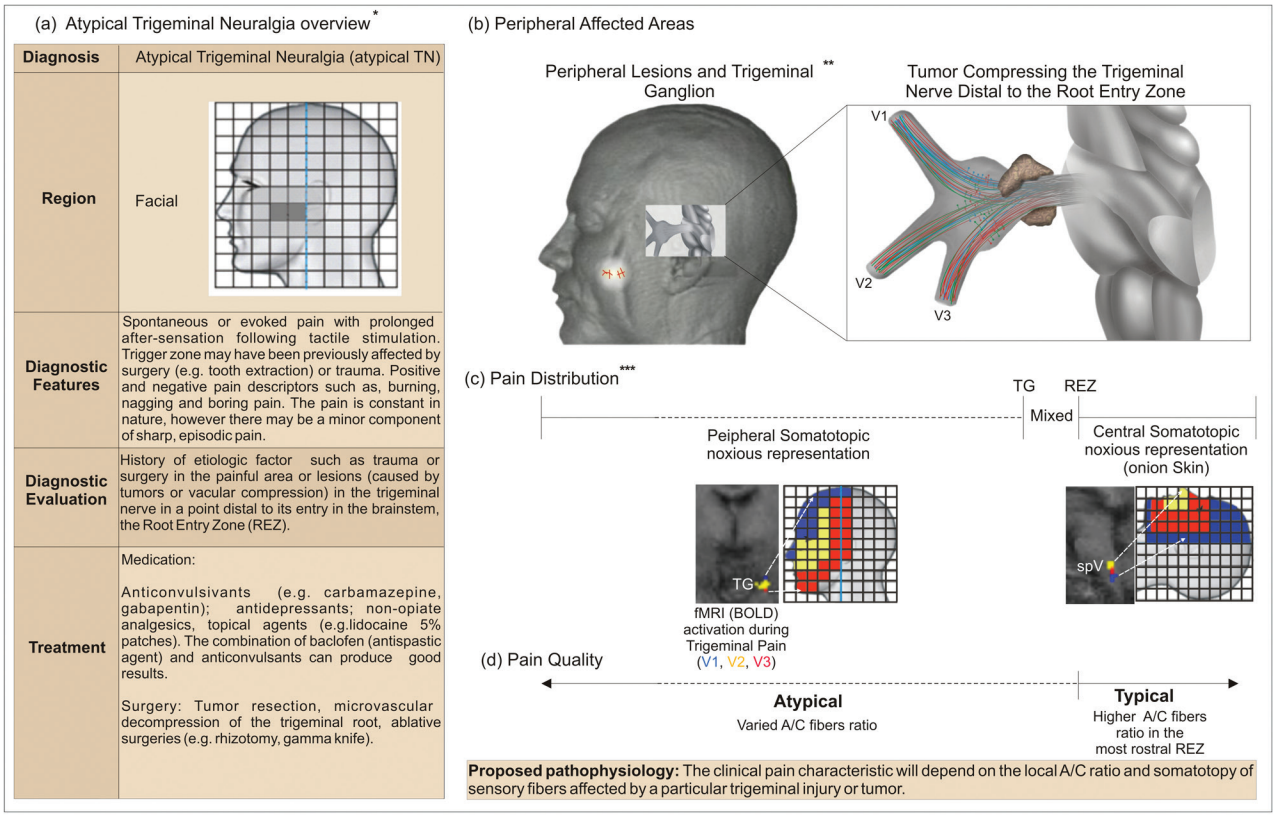

Figure 2. Clinical characteristics and pathophysiology associated with atypical trigeminal neuralgia (atypical-TN). *The left table (**a**) was reprinted, with small adaptations, from DaSilva and Acquadro (2005), with permission from SNELL Medical Communication Inc. **3-D image modified from DaSilva (2002). ***fMRI images reprinted from DaSilva *et al.* (2002), with permission from the *Journal of Neuroscience*, and from Borsook *et al.* (2003), also with permission from the *Journal of Neuroscience*.

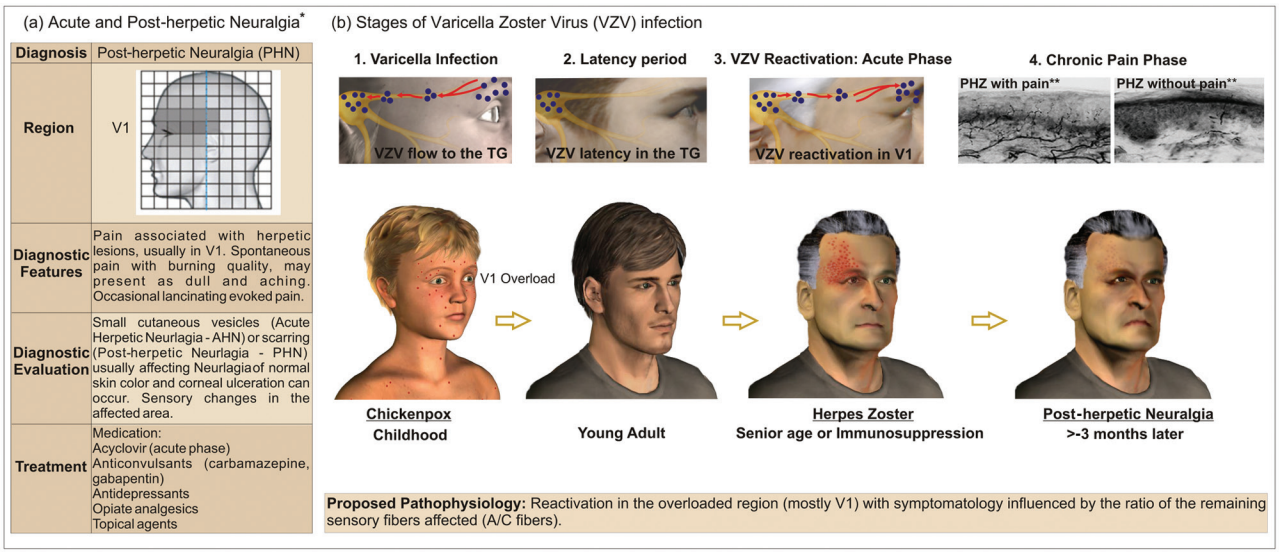

Figure 3. Clinical characteristics and stages of varicella zoster virus (VZV) infection related to the pathophysiology of post-herpetic neuralgia (PHN). All images are original with the exception of: *the left table (**a**), which was reprinted, with small adaptations, from DaSilva and Acquadro (2005), with permission from SNELL Medical Communication Inc.; and **the top images in illustration 4 (chronic pain phase), which were reprinted, with minimal adaptations, from Oaklander (2008), with permission from Elsevier, with special credit to Oaklander (2001), also reprinted with permission from Elsevier.

replication will release infectious particles that will extend to most of the branch in a cell-to-cell manner, infecting many neurons and glial cells, culminating in a peripheral disease within the distribution of the nerve affected. This fact will result in a destruction of many neurons and surrounding satellite cells, affecting an extensive region and producing a transient or permanent sensory loss. Actually, the permanent neurological damage, such as post-herpetic neuralgia, that occurs following herpes zoster may be due to extensive neuronal destruction.

There is scientific evidence indicating that the varicella zoster virus (VZV) migrates from the dorsal root or trigeminal ganglia to the periphery mostly *via* myelinated fibers. This concept is based on the initial spread of the VZV to the skin *via* the isthmus of hair follicles, the same place where myelinated fibers predominantly end (Kennedy and Steiner, 1994; Muraki *et al*., 1996; Iwasaki *et al*., 2001; Walsh *et al*., 2005). This means of peripheral transportation used by VZV might determine symptoms during the acute phase of herpes zoster (AHZ). Patients at this initial phase appear to report sharp, stabbing, as well as lancinating pain (Dworkin *et al*., 2008; Oaklander, 2008), generally related to damage to A-fibers. Following infection of the follicular and sebaceous epithelium, the virus spreads to the neighboring epidermis (Boer *et al*., 2006). During a subsequent phase, burning pain is more often reported, which is a common characteristic of post-herpetic neuralgia (PHN) (Filadora *et al*., 1999; Dworkin *et al*., 2008; Oaklander, 2008). This later symptom could partly reflect the damage by VZV to smaller diameter sensory fibers such as the C-type in the adjacent epidermis. Ultimately, most patients with PHN describe multiple types of pain, such as constant, deep, burning, paroxysmal, and lancinating. However, it is important to mention the possible contributions of C-low-threshold mechanoreceptors for tactile allodynia, reported in a recent publication (Seal *et al*., 2009). In addition, other sensory disturbances frequently associated with PHN are paresthesia, dysesthesia, hyperalgesia, and itching (Dworkin *et al*., 2008; Truini *et al*., 2008). Many hypotheses have been proposed to explain this diversity in symptomatology during PHN. Initially, it was proposed that there was a preferential destruction of larger myelinated fibers (Aβ fibers), leaving an excess of the small myelinated (Aδ) and unmyelinated (C) fibers interpreted as the cause of sensory dysfunction in PHN (Noordenbos, 1959; Watson *et al*., 1988). Recent studies have stated that all sets of sensory fibers may be affected in this condition (Truini *et al*., 2008; Delaney *et al*., 2009), and data from neurophysiological-clinical correlations suggest a relationship between constant pain and loss of Aδ and C fibers and between paroxysmal pain and Aβ fiber demyelinization (Truini *et al*., 2008). Furthermore, the density of epidermal innervation has been associated with the occurrence of PHN, since samples from skin biopsies, when immunolabeled with PGP 9.5 (an axonal marker), have shown a greater amount of neuritis/mm^2 in individuals without PHN than in those with PHN (Oaklander, 2001). By the same technique, an inverse correlation was demonstrated between the loss of cutaneous innervation and allodynia in patients with PHN (Rowbotham *et al*., 1996). According to this scenario, it is possible to establish that the progression of the disease and the remaining A/C ratio of injured fibers in the peripheral skin following herpes zoster determine the symptoms frequently reported by PHN patients. In addition, it explains the great variety of pain descriptors (Dworkin *et al*., 2008) usually related to PHN.

CONCLUSIONS

Pain research advanced dramatically with the novel neuroimaging tools that became largely available in the past decade, providing non-invasive access to human brain function and dysfunction. This opportunity has opened new frontiers in the study of central neuropathic pain mechanisms, complementing findings associated with other crucial sectors in animal pain models and genetics. Nonetheless, the field has recently refocused its attention on the peripheral nervous system in TNP, with a more ample description of the molecular, anatomical, and functional properties of afferent sensory fibers and their subclasses. Independent of the intermingled contributions of other, also important, central and even peripheral mechanisms, sensory fibers are the first gateway in the neuronal system for inputs that will later lead to pain perception. The role of the ratio and somatotopic distribution of injured sensory fibers in trigeminal neuropathic pain is a notable component of its pathophysiology and can immensely influence clinical pain characteristics, including its quality descriptors, location and irradiation, temporal features, progress, and treatment prognosis.

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