Psychiatria Danubina, 2019; Vol. 31, Suppl. 5, pp S724-S731
Medicina Academica Mostariensia, 2019; Vol. 7, No. 1-2, pp 2-9 *Review*

IDIOPATHIC TRIGEMINAL NEURALGIA (ITN): FACTS AND FICTION

Niko Zurak[1] & Darija Mahovic[1,2]

[1]School of Medicine, University of Zagreb, Zagreb, Croatia
[2]Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia

received: 22.10.2019; revised: 20.11.2019; accepted: 12.12.2019

SUMMARY

In this paper the authors present neuroanatomical and neurophysiological arguments against the microvascular compression in the root entry zone of trigeminal nerve nerve as an ethiopathogenetic factor of ITN. Clinical experience has proven that compression of mixed sensorymotor nerve (peripheral or central one), cannot provoke paroxysmal neuralgic pain.

The authors conclude that the well known fact that dental pulp has only pain sensory modality brings up the question what might be consequence of tooth extraction where neural fibers are broken in the innervation areas of maxillar and mandibular nerve. The answer could be only one. If exclusive algophoric deafferentation hypersensitivity after tooth extraction exceeds a certain threshold, patients will experience paroxysmal neuralgic pain. Broken neural fibers develop pathological ephaptic communication with other trigeminal sensory modalities through supraspinal central structures responsible for the transmision of dental pulp pain. This can explain trigger phenomena and latency between the touching of circumoral areas and onset of neuralgic paroxysm, which is a central epileptic phenomenon. In conclusion, the so-called idiopathic trigeminal neuralgia (ITN) is the expression of algophoric deafferentation hypersensitivity after tooth extraction.

Key words: *idiopathic trigeminal neuralgia - tooth extraction - algophoric deafferentation hypersensitivity - epileptic neuralgic phenomenon - ephaptic neural communication*

* * * * *

Introduction

Teeth are equipped with an abundant, sophisticated, protective sensory system that mediates the sensation of pain (Hildebrand et al. 1995). This system differs in many ways from nociceptive networks at other body sites. From a functional standpoint, it appears enigmatic why most or all stimuli that excite pulpal nerve fibers, either noxious cold or noxious heat to a fully intact tooth, or extremely light mechanical forces or subtle thermal, osmotic, or chemical changes to exposed dentin, result only in the sensation of pain, with no mechanism for discrimination (Fried & Gibbs 2014, Le Fur-Bonnabesse et al. 2017). To maintain an efficient afferent transduction system in highly mineralized teeth, there is a need for a low-threshold sensory apparatus that will be able to detect stimuli through a hard shell of calcified tissue (Hildebrand et al. 1995, Fried & Gibbs 2014, Le Fur-Bonnabesse et al. 2017) (Figure 1).

There are three main theories about pain mechanism of pulpal pain:

- *„The neural theory"* which stress that pulpal endings are directly activated by external stimuli and the transduction of nonspecific stimuli to an electrical nerve impulse is mediated by nociceptive receptors (Hildebrand et al. 1995, Fried & Gibbs 2014).
- *„The odontoblastic transduction theory"* states that the odontoblasts act as sensory transducers of noxious stimuli into electrical signals transmitted to neighbouring nerve endings (Hildebrand et al. 1995, Fried & Gibbs 2014).
- *„The hydrodynamic theory"* is the most widely accepted which involves dentin sensitivity on stimuli-induced fluid movements in the dentinal tubules and the consequent activation of nociceptors in the pulp/dentin border area (Hildebrand et al. 1995, Fried & Gibbs 2014).

Development of Dental Pulp

The ingrowth of trigeminal ganglion nerve fibers to the neural crest-derived condensed mesenchyme that will form the dental pulp occurs in comparatively late developmental stage. Only after the crown shape is set and mineralization of both enamel and dentin has commenced, around postnatal day 3-4 in the mouse and rat, do pioneer nerve fibers enter the apical region of the tooth germ. The dental papilla/pulp cells express neurite growth inhibitory factors at early stages, whose effects most likely dominate over the neurotrophic ones. Among several putative neurorepelling factors that could be active during ontogenesis, the semaphorin group of molecules has received the most attention (Fried & Gibbs 2014). As putative neurotrophic factors act probably growth factors as NGF, BDNF, NT3, NT4 and GDNF (Fried & Gibbs 2014, Fried et al. 2007, Lillesaar & Fried 2004, Nosrat et al. 1998). A shift in expression from neurorepulsive to neuroattractive dental/pulpal factors apparently takes place during odontogenesis (Fried & Gibbs 2014).

1. Crown; 2. Root; 3. Enamel; 4. Dentin; 5. Pulp;
6. Root channal; 7. Nerves/blood vessels

Figure 1. Dental pulp anatomy

The Structure of Pulpal Axons

Within the root pulp of permanent teeth in experimental animals and humans, ~70-90% of axons are unmyelinated, and most of the reminder seem to be Aδ fibers, in agreement since pain is only experience that can be evoked when pulpal nerves are excited. Some unmyelinated pulpal axons are „true“ C-fibers (Fried & Gibbs 2014, Yu & Abbott 2007).

Up to 90% of the myelinated axons lose their myelin within the short intradental course from the radicular to the coronal pulp.

A single intrapulpal axon might branch and innervate more than 100 dental tubules (Many, if not most dentinal afferents are not classical nociceptors, but rather low threshold mechanoreceptors (LTM) (Fried & Gibbs 2014).

Pulpal afferents terminate predominantly in the superficial laminae of subnucleus caudalis, but also in its deep laminae. Many dental fibers have their central endings more rostrally, especially in the trigeminal subnuclei interpolaris and oralis. Pulpal afferents are unique among painmediating neurons (Fried & Gibbs 2014, Yu & Abbott 2007). Since they have very different characteristics from classical nociceptors, Fried et al. proposed a novel definition, „algoneurons“. Consequently a majority of trigeminal pulpal afferents are low threshold mechanoalgoneurons (Fried & Gibbs 2014, Fried et al. 2011).

Pulpal nerve deterioration in senescence is paralleled by a reduced sensitivity to electrical pulp stimulation in human subjects (Fried & Gibbs 2014, Yu & Abbott 2007).

Studies support the existence of neuroplastic mechanisms that occur in response to deafferentation of the dental pulp and have the potential to contribute to persistent pain states subsequent to natural or iatrogenic dental pulp injury (Fried & Gibbs 2014, Fried 1987).

Autonomic Innervation

The autonomic nerves of dental pulp belong to the sympathetic division of the autonomic nervous system. The main sympathetic functional output in the pulp is related to blood vessel constriction (Fried & Gibbs 2014, Yu & Abbott 2007).

Neuroplasticity in the Peripheral and Central Nervous System Subsequent to Pulpal Injury

Significant anatomical and functional changes in activity are observed in the trigeminal nucleus subsequent to pulpal injury.The existence of neuroplastic mechanisms that occur in response to deafferentation of the dental pulp have the potential to contribute to persistent pain states subsequent to natural or iatrogenic dental pulp injury. Although persistent symptoms could be due to ongoing odontogenic causes (e.g. an undetected root fracture or recurrent infection), there are cases when pain persist despite the absence of obvious pathology. Historically such persistent pain was referred to as atypical odontalgia, or phantom tooth pain (PTP), or more currently, peristent dentoalveolar pain or peripheral painful traumatic trigeminal neuropathy (Fried et al. 2011, Fried 1987, Hughes et al. 2016, Jensen et al. 2014, Marbach & Raphael 2000). Usually PTP follows dental or surgical procedures such as root canal therapy, apicoectomy, or tooth extraction. Other facial traumas and surgical procedures may precede the onset of PTP. PTP is characterized primarily by persistent pain. Neither repeated endodontic treatment, apicoectomy, nor more tooth extraction render the affected area free of pain. On the contrary , procedures and other surgical intervention, such as trigeminal rhizotomy and microvascular decompression, frequently exacerbate pain severity and, in addition may increase the distribution of pain in the trigeminal nerve area (Hughes et al. 2016, Jensen et al. 2014, Marbach & Raphael 2000).

ITN has paroxysmal, sharp, sudden, electrical-like stabbing recurrent pain and is unlike the dull uninterrupted pain of PTP (Marbach & Raphael 2000, Fromm et al. 1984, Derbyshire 2008, Gadient & Smith 2014, Katusic et al. 1990, Love & Coakham 2001, Manzoni & Torelli 2005, Montano et al. 2015, Mumenthaler 2004, Rojas-Ramirez et al. 2016, Rozen et al. 2008, Varela-Lema et al. 2015, Zdila et al. 2016, Zurak et al. 1981, 1989, Zurak 1990, Kubo et al. 2008, Sessle 2011).

Diagnostic criteria for Phantom tooth pain/PTP

(Marbach & Raphael 2000)

- Pain is located in the face or described as a toothache.
- The pain is described as a constant dull, deep ache (Sharp pain is not essential for PTP).
- A brief (seconds to minutes) pain-free period is reported upon awakening from sleep. There are no other refractory periods.

- Pain develops (or continous) within one month following endodontic treatment or tooth extraction, or other trauma or surgical procedure related to the face.
- Overlying the area of dental (or other) treatment (usually on the surface of the face but occasionally intraorally) is a location with a much lowered pain threshold (hyperalgesia), often surrounded by a larger area with less severe hyperalgesia.
- Sleep is undisturbed by pain or other phantom sensations.
- No radiographic or laboratory test suggest other sources of pain (Zurak et al. 1981).

Note: Prevalence does not differ by sex (Fromm et al. 1984, Feller et al. 2017). The loss of deciduous teeth does not result in PTP (Marbach & Raphael 2000).

Spinal and Supraspinal Pathways of Pulpal Pain and Cortical Representation areas of Human Dental Pulp (Figure 2)

In the thalamus, tooth pulp-driven neurons have been identified in ventral posteromedial (VPM) and mediodorsal (MD) nuclei. Functional magnetic resonance imaging (fMRI) has demonstrated that painful electrical tooth pulp stimulation leads to bilateral activation of S1, S2 and the insular region of the cerebral cortex, cingulate gyrus, as well as motor and frontal areas including the orbital frontal cortex (Fried & Gibbs 2014, Yu & Abbott 2007, Ianetti & Mouraux 2010).

Melzack's opinion that mentioned supraspinal structures are pain specific projections sites is not convincing. However, cortical columns responding preferentially to nociceptive stimuli have never been described. Indeed, somatosensory cortical columns containing neurons responding to nociceptive stimulation also contain neurons responding to non-nociceptive stimulation. Conclusively, at cortical level, nociception may not be represented as a distinct sensory modality or even as distinct submodality of somatosensation (Kubo et al. 2008).

Human electroencephalographic studies demonstrated cortical potentials in response to painful electrical stimulation of dental pulp with a first-peak latency of 84 ms, suggesting activation of the secondary somatosensory cortex by intradental A-delta neurons (Fried & Gibbs 2014, Le Fur-Bonnabesse et al. 2017, Yu & Abbott 2007, Ianetti & Mouraux 2010).

Aging of Pulpal Nerves

With increasing age odontoblasts shrink. However, secondary dentin formation continues at a slow rate during the life of the tooth causing a gradual reduction of the pulpal space. Concomitant with this, a protracted phase of age-related axonal alterations and axon loss occurs. Pulpal nerve deterioration in senescence is paralleled by a reduced sensitivity to electrical pulp stimulation in human subjects (Fried & Gibbs 2014, Fried 1987).

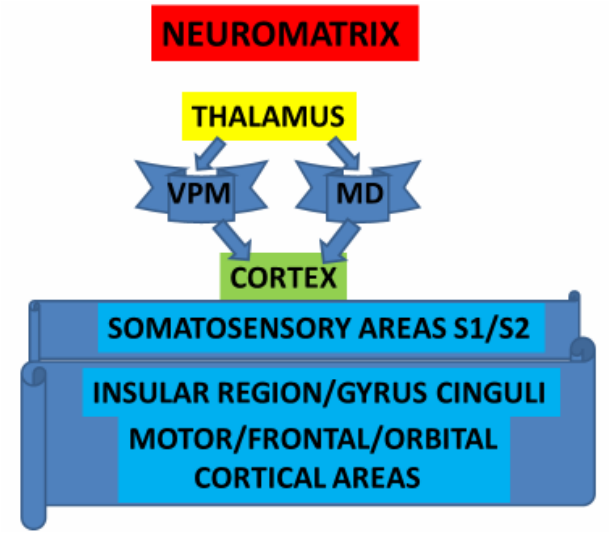


Figure 2. Central projections areas of dental pulp pain

Phantom Pain

Phantom Limb Pain (PLP) and Phantom Limb Sensations (PLS)

The mechanism responsible for PLP and PLS is still debatable, however a lot of theories had been given (Ehde & Czerniecki 2000, Finn et al. 2017, Neil 2016, Privitera et al. 2017, Schley et al. 2008, Soares et al. 2018, Sicuteri & Nicolodi 1987, Hanakawa 2012). Following amputation, there may be formation of neuroma showing abnormal spontaneous activity, and on mechanical and chemical stimulation (Sessle 2011, Feller et al. 2017, Ianetti & Mouraux 2010, Neil 2016). Other factors though to have an influence on the PLP are decreased threshold for PLP, increased c-fiber activity, inverse relationship between pressure pain threshold and phantom limb pain intensity, abnormal activity of dorsal root ganglion, and so on (Sessle 2011, Ianetti & Mouraux 2010, Neil 2016). Sympathetic nervous system also plays a role in maintainig PLP. Further, there is spinal plasticity, i.e., increase in the excitability of spinal neurons, more accessibility of Aδ- and c-fibers to other pathways. N-methyl-D-aspartate receptor systems are also believed to have a role in „wind-up“ phenomenon seen in PLP. Spinal and cerebral reorganization occurs and there is a relationship between degree of reorganization and pain (Sessle 2011, Feller et al. 2017, Ianetti & Mouraux 2010, Ehde & Czerniecki 2000, Neil 2016).

After limb amputation we have dissection of all sensorymotor fibers of a mixed peripheral nerve. Phantom manifestations should be both motor and sensorial phenomena. After dissection of pure sensorial peripheral nerve, patients might have phenomena in all modalities of epicritic and protopathic sensation (Nosrat et al. 1998, Fromm et al. 1984, Neil 2016).

Deafferentation pain

Deafferentation pain can follow spinal cord injuries, peripheral nerve injuries, brachial plexus avulsions,

and limb amputations. Damage to the thalamus causes similar symptom (Nosrat et al. 1998, Gadient & Smith 2014, Sessle 2011).

The pathophysiology of deafferentation pain remains to be elucidated. Progress in neuroimaging and brain stimulation techniques has begun to cast light on the neural mechanisms underlying neuroplastic changes after limb amputation. It must to say, that in the cases of limb amputation we have denervation hypersensitivity, which is caused from dissection of mixed, sensorymotor peripheral nerve. Exclusive deafferentation pain and other sensitive phantom phenomena should be expected in the cases of the total damage of sensorial neural pathways. Most of neuroscientific researchers explain denervation and deafferentation hypersensitivity phenomena via neuroplasticity mechanisms in the supraspinal neural structures (Nosrat et al. 1998, Gadient & Smith 2014, Sessle 2011, Ianetti & Mouraux 2010, Neil 2016).

Algophoric Deafferentation Pain (ADP)

As it is implicated from the title, in the case of algophoric deafferentation, only the pain sensation is lost. Subsequently only possible phantom phenomenon must be the pain. (Zdila et al. 2016, Zurak et al. 1981, Zurak et al. 1989).

Dental Pulp Exclusive

As we have stressed before, the dental pulp is unique example in human and mammalian organisms , in which the stimulation of any kind can provokes only pain and nothing else. (Hildebrand et al. 1995, Fried & Gibbs 2014, Yu & Abbott 2007).

ITN as Consequence of ADP

Theories attempting to explain mechanism of pain in ITN have to take into account the unique features of this condition, including the paroxysmal nature of the pain, its abrupt onset and cessation, short duration, agonizing severity, triggering by innocuous stimuli, change of periods with pain and without pain, exclusive localization of the pain in the innervation area of maxillar and mandibular branchs of trigeminal nerve, and first of all, absence of any other sign of neurologic affection of mixed sensorymotor trigeminal nerve as fifth cranial nerve is (Fried & Gibbs 2014, Marbach & Raphael 2000, Fromm et al. 1984, Rojas-Ramirez et al. 2016, Zdila et al. 2016, Zurak et al. 1981, Zurak et al. 1989, Kubo et al. 2008). There is agreement that the single paroxysm in ITN is an epileptic phenomenon with central pathogenesis (Gadient & Smith 2014, Love & Coakham 2001, Manzoni & Torelli 2005, Rojas-Ramirez et al. 2016, Zdila et al. 2016, Zurak et al. 1981, Zurak et al. 1989, Jiruska et al. 2010, Ahmed et al. 2017).

Dental pulp pain can't be localized, because the dental branches of maxillar and mandibular nerves are exclusive algophoric one (Fried & Gibbs 2014, Yu & Abbott 2007, Varela-Lema et al. 2015, Zurak et al. 1981). There are no receptors for a touch and pressure in the dental pulp. Touch and pressure sensory modalities are essential for the topographic identification of sensorial information (Fried & Gibbs 2014, Yu & Abbott 2007). Because of that, pain in the ITN spreads in the neigbouring teeth and other part of the head (Fried & Gibbs 2014, Yu & Abbott 2007, Varela-Lema et al. 2015, Zurak et al. 1981).

The absence of teeth has always implied an obstacle to the acceptance of dental and alveolar disease as a cause of ITN. In our opinion, the absence of teeth is the real essence of the problem (Varela-Lema et al. 2015, Zurak et al. 1981).

Discussion

If we accept the possibility that ITN is caused by organic deafferentation and especially algophoric one, there is no other candidates for paroxysmal kind of denervation hypersensitivity than the cells concerned with dental pulp sensitivity (Varela-Lema et al. 2015, Zurak et al. 1981).

The main criticism directed to our theory, in letters and personal communications, was the fact that tooth extraction is so frequent while ITN relatively rare. However, ITN is a much more frequent condition than phantom tooth phenomenon. The main reason is first and foremost of quantitative nature, because of the well-known small number of the dental tooth fibers in comparison with the number of the algophoric fibers in the skin for example (Fried & Gibbs 2014, Varela-Lema et al. 2015, Zurak et al. 1981). Sicuteri and Nicolodi stressed the importance of the number of the broken fibers in the development of denervation hypersensitivity (Black 1974).

We think that an important role could be played by possible mechanism which prevents the development of algophoric deafferentation hypersensibility after the shedding od deciduous teeth. It is known fact that there are no cases of ITN in the. This mechanism is probably the strong activation of the inhibitory antinociceptive neural system (ANS). The deciduous teeth maintain neural contact, up to the moment of their loss, by way of pulpal and periodontal tissue (Fried & Gibbs 2014, Yu & Abbott 2007). It is possible that some anatomical and functional imperfections of these physiological processes could make antinociceptive system (ANS) vulnerable and unstable. These persons in their later life might become algophoric deafferentation hypersensitivity prone, and after tooth extraction in older adult and older age they could develop ITN.

Our theory can explain the clinical fact of absence of any clinical sign of trigeminal nerve affection (neither sensorial nor motor) (Varela-Lema et al. 2015, Zurak et al. 1981). This clinical fact is the main objection against all the theories dealing with compressive mechanisms, including today so popular microvascular compression theory.

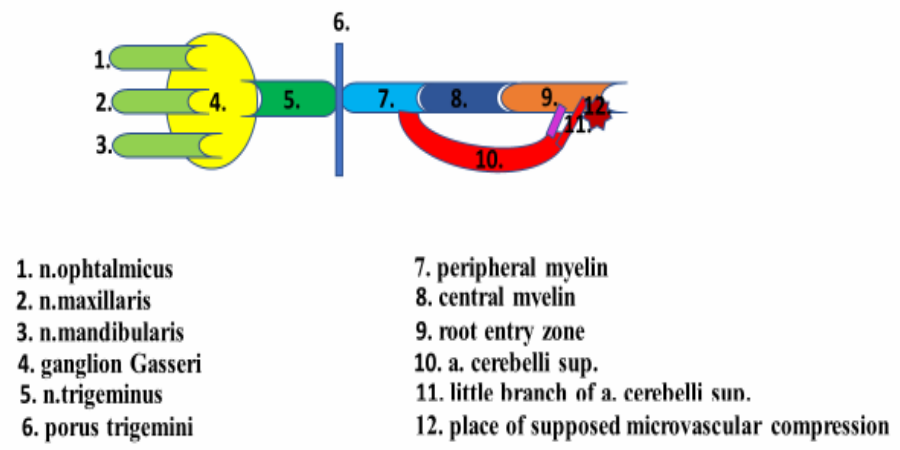
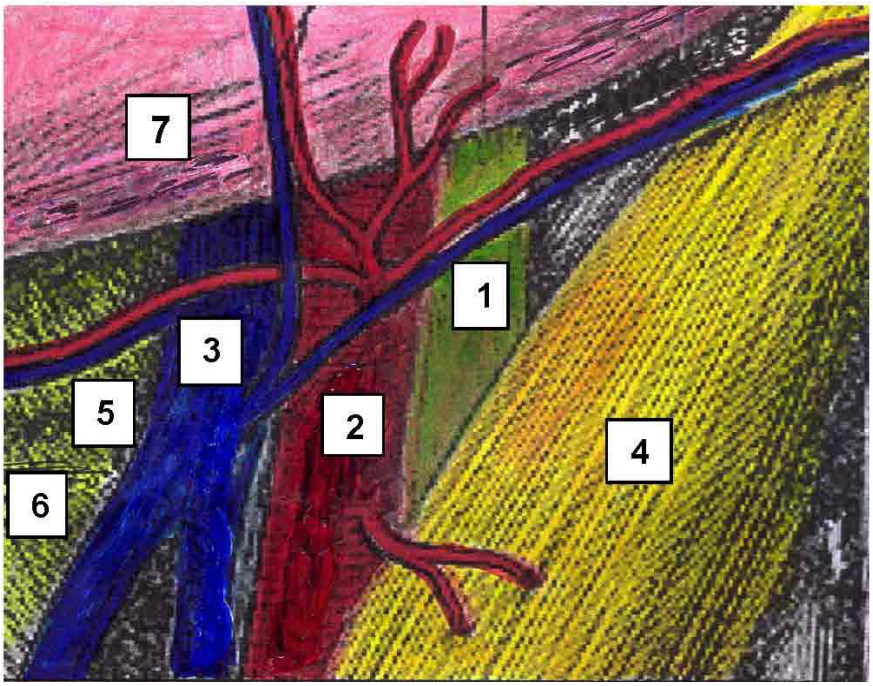


Figure 3. Nervus trigeminus and its root entry zone (REZ) in the pons



1. n. femoralis; 2. a. femoralis; 3. v. femoralis; 4. m. sartorius; 5. m. pectineus;
6. m. adductor longus; 7. ligamentum inguinale Pouparti

Figure 4. Trigonum scarpe

Compression of trigeminal nerve with venule or aberant artery and mostly of the small branch of superior cerebellar artery can't explain clinical picture of the ITN (Fromm et al. 1984, Derbyshire 2008, Gadient & Smith 2014, Love & Coakham 2001, Varela-Lema et al. 2015, Zurak et al. 1981) (Figure 3).

Wartenberg has already, arguing against the compressive genesis of the disease, pointed out that the clinical picture caused by the compressive mechanism is characterized by gradual progression, increasing number of symptoms, their gradual worsening, and finally, by the occurence of the complete stop of the nerve conduction (Fromm et al. 1984). It is well known that the most sensitive on the compression are large myelinizated beta fibers and motor fibres of the nerve (Fromm et al. 1984, Zdila et al. 2016, Zurak et al. 1981, Zurak et al. 1989).

In the femoral triangle in upper part of the hip (Scarpa's triangle) exists tight contact between one of the largest artery (arteria femoralis) and femoral nerve. However, there is no one case of femoral neuralgia or other signs of its damage caused by compression of femoral artery (Figure 4).

The general sensation when keeping legs crossed for a long period in the knee joint reveals to us more than any theoretical discussion on clinical symptomatology of mixed nerve compression. This position causes compression of the tibial and fibular (peroneal) nerves in the fossa poplitea. The compression affects exclusively thick, myelinated fibers. This can explain the sensorial clinical damage with touch and proprioceptive insensitivity of the foot. At the same time subjects feel paresthesias (often as formication) and

inability to correctly locate their foot and foot muscles. These phenomena are expression of denervation hypersensitivity. At the same time compression with complete blockage of motor neural transmission causes foot paresis. Because of this it is not possible to take footsteps. However, soon after ceasing popliteal compression, all of these phenomena disappear and all nerve functions are restored. During compression of mixed nerve in the fossa poplitea there is no painful sensation.

After the failure of medicament therapy many patients have been underwent to surgical microvascular decompression procedure (Marbach & Raphael 2000, Derbyshire 2008, Love & Coakham 2001, Zurak et al. 1989, Zurak 1990, Neil 2016, Jiruska 2010, Ahmed et al. 2017, Black 1974).

Such intervention often results in longer remission or even complete cessation of pain attacks (Marbach & Raphael 2000, Derbyshire 2008).

We think that is no effect of microvascular decompression, but of general anesthesia. It is well known that general anaesthesia should be therapeutic ultima ratio in medicament intractable epileptic seizures (Varela-Lema et al. 2015, Zdila et al. 2016, Zurak et al. 1981).

Single paroxysm of ITN is epileptic phenomenon as a such of central, supraspinal pathogenesis (Derbyshire 2008, Rojas-Ramirez 2016, Varela-Lema et al. 2015, Black 1974, Burkholder et al. 2017, Stacey et al. 2015, Froelich et al. 2018). It is impossible that peripheral nerve compression might cause an epileptic phenomenon (Varela-Lema 2015, Zurak et al. 1981, Stacey et al. 2015, Froelich et al. 2018).

With experiments on cats, many years ago Black found, that after tooth extraction occur the development of epileptiform deafferentation hypersensitivity in central neural structure connected with dental pulp nerves (Burkholder et al. 2017).

For central pathogenesis speak among others, painful tics and trigger zone which pointed out for existence of an ephaptic cross-talk communication with clear latency between stimulation and pain manifestation (Zdila et al. 2016, Zurak et al. 1989, Sicuteri & Nicolodi 1987, Jiruska et al. 2010, Froelich et al. 2018). The latency speak for a slow propagation through nonphysiologic ephaptic contact, essentially different from electrotonic epileptic transmission.

One of our 31 patients with ITN, 45 year old female with myomatosis uteri has been underwent to hysterectomy. In that time she suffered from rare ITN attacks. After the operation she was permanently pain-free.

Patients with ITN who have experienced phasic dental pulp pain before beginning of ITN attacks, as a rule describe their pain as a equal as tooth pain. Often they insisted on the revision of the postextraction wund beleiving that „small piece of nerve has been remained“.

Neuroplasticity process is responsible for clinical manifestations of phantom sensations and their gradual transformation until their complete cessation. At very beginning, for example, after transtibial amputation, patients felt phantom sensation in the projection site of the lost foot. Beside the pain, patients feel different kind of sensations (paraesthesisas, sense of moving etc). It is very interesting appearance of so-called telescopy. Patients gradually experience phantom more and more near to knee, and finally in the stump (Kubo et al. 2008, Sessle 2011, Finn et al. 2017).

ITN patients might have periods of remissions and periods of relapses. Usually pain attacks stop after different duration period.

Inference

- The fact that ITN is a unique clinical picture among human pain conditions, implies the existence of certain anatomical specificities of the sensorial input in maxillar and mandibular branches of trigeminal nerve. This specificity is the exclusive algophoric afferention from the dental pulp. The shedding of deciduous teeth is an unique case of the physiologic organic algophoric deafferentation.
- Any kind of organic deafferentation can provoke clinical manifestations of denervation hypersensitivity in the sensory modalities which an organ was supplied before.
- Clinical manifestation of organic deafferentation hypersensitivity after tooth extraction, can be only the pain. Because of that, there are no clinical signs of trigeminal nerve disfunction at all.
- Because of reactive neuroplasticity of supraspinal neural structures, emerges an ephaptic, cross-talk communication between epicritic, protopathic and pain sensorial pathways, which are responsible for the existence of so-called trigger zones. Thalamus is the main candidate for development of such cross-talk, ephaptic communication.
- It is the common sense that single pain paroxysm in ITN is epileptic phenomenon, i.e. taking rise in the supraspinal neural structures. Because of that, anti-epileptic drugs are the medication of the first choice.

Conclusion

Psychological scotoma connected with the ITN pathogenesis enigma is caused by the fact, that the problem we encountered is situated in the territory between dentistry and neurology. This situation is, in the certain sense alike, well-known HC Andersen's fairy tale Emperor's new clothes. Similar scotoma we can find in the case of syncope (Zurak & Bilic 2004, Zurak 2018).

In both cases we assume the role of little child in Andersen fairy tale, when cries out “But he isn't wearing anything at all“ (Andersen 2004).

Acknowledgements: None.

Conflict of interest : None to declare.

Contribution of individual authors:

Nko Zurak: idea, concept and design of the article, literature searches, writing manuscript, approval of the final version.

Darija Mahovic: concept and design of the article, literature searches, writing manuscript, approval of the final version.

References

1. *Ahmed A, Bhatnagar S, Mishra S, Khurana D, Joshi S, Ahmad SM: Prevalence of Phantom Limb Pain, Stump Pain, and Phantom Limb Sensation among the Amputated Cancer Patients in India: A Prospective, Observational Study. Indian J Palliat Care 2017; 23:24-35*
2. *Andersen HC: The Emperor's New Clothes. Hougaton Mifflin Harcourt, 2004, pp. 39-44*
3. *Black RG: A laboratory model for trigeminal neuralgia. In: Bonica JJ (ed) Advances in Neurology. New York: Raven Press 1974; 4:651-658*
4. *Burkholder DG, Koehler PJ, Boes CJ: Trigeminal Neuralgia and Multiple Sclerosis: A Historical Perspective. Can J Neurol Sci 2017; 44:589-593*
5. *Derbyshire SW: Gender, pain and the brain. Pain Clin Updates 2008; 16:1-4*
6. *Ehde DM, Czerniecki JM: Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation. Arch Phys Med Rehabil 2000; 81:1039-1044*
7. *Feller L, Khammissa RAG, Fourie J, Bouckaert M, Lemmer J: Postherpetic Neuralgia and Trigeminal Neuralgia. Pain Res Treat 2017; 2017:1681765*
8. *Finn SB, Perry BN, Clasing JE, Walters LS, Jarzombek SL, Curran S et al.: A Randomized Controlled Trial of Mirror Therapy for Upper Limb Extremity Phantom Limb Pain in Male Amputees. Front Neurol 2017; 8:267-274*
9. *Fried K, Gibbs JL: Dental Pulp Innervation In: Goldberg M. (ed.) Dental Pulp Berlin Heidelberg: Springer-Verlag, 2014, pp 75-95*
10. *Fried K, Lillesaar C, Sime W, Kaukua N, Patarroyo M: Target finding of nerve fibers: neural growth mechanisms in the tooth pulp. Physiol Behav 2007; 92:40-45*
11. *Fried K, Sessle BJ, Devor M: The paradox of pain from tooth pulp: low threshold „algoneurons"? Pain 2011; 152:2685-9*
12. *Fried K: Changes in innervation of dentin and pulp with age. Front Oral Physiol 1987; 6:63-84*
13. *Froehlich K, Winder K, Linker RA, Engelhorn T, Dörfler A, Lee DH et al.: Supratentorial Lesions Contribute to Trigeminal Neuralgia in Multiple Sclerosis. Cephalalgia 2018; 38:1326-1334*
14. *Fromm GH, Terrence CF, Maroon JC: Trigeminal Neuralgia: Current Concepts Regarding Etiology and Pathogenesis. Arch Neurol 1984; 41:1204-1207*
15. *Gadient PM, Smith JH: The Neuralgias: Diagnosis and Treatment. Curr Neurol Neurosci Reports 2014; 14:459-467*
16. *Hanakawa T: Neural Mechanisms Underlying Deafferentation Pain: A Hypothesis from Neuroimaging Perspective. J Orthop Sci 2012; 17:331-335*
17. *Hildebrand C, Fried K, Tuisku F, Johansson CS: Teeth and tooth nerves. Prog Neurobiol 1995; 45:165-222*
18. *Hughes MA, Frederickson AM, Branstetter BF, Zhu X, Sekula RF Jr.: MRI of the Trigeminal Nerve in Patients with Trigeminal Neuralgia Secondary to Vascular Compression. AJR Am J Roentgenol 2016; 206:595-600*
19. *Ianetti GD, Mouraux A: From the neuromatrix to the pain matrix (and back). Exp Brain Res 2010; 205:1-12*
20. *Jensen Troels S, Finnerup Nanna B: Allodynia and hyperalgesia in neuropathic pain: Clinical manifestations and mechanisms. Lancet Neurol 2014; 13:924-35*
21. *Jiruska P, Powell AD, Chang WC, Jefferys JG: Electrographic high-frequency activity and epilepsy. Epilepsy Res 2010; 89:60-65*
22. *Katusic S, Beard CM, Bergstrahl E, Kurland LT: Incidence and clinical features of trigeminal neuralgia. Rochester, Minnesota, 1945-1984. Ann Neurol 1990; 27:89-95*
23. *Kubo K, Shibukawa Y, Shintani M, Suzuki T, Ichinohe T, Kaneko Y: Cortical Representation Area of Human Dental Pulp. J Dent Res 2008; 87:358-362*
24. *Le Fur-Bonnabesse A, Bodere C, Helou C, Chevalier V, Goulet JP: Dental pan induced by an ambient thermal differential: pathophysiological hypothesis. J of Pain Res 2017; 10:2845-2851*
25. *Lillesaar C, Fried K: Neurites from trigeminal explant grown in vitro are repelled or attracted by tooth-related tissues depending on development stage. Neuroscience 2004; 125:149-161*
26. *Love S, Coakham HB: Trigeminal Neuralgia: Pathology and Pathogenesis. Brain 2001; 124:2347-2360*
27. *Manzoni GC, Torelli P: Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci 2005; 26(Suppl 2):s65-s67*
28. *Marbach JJ, Raphael KG: Phantom Tooth Pain: A New Look at an old Dilemma? Pain Med 2000; 1:68-77*
29. *Montano N, Conforti G, di Bonaventura R, Meglio M, Fernandez E, Papacci F: Advances in Diagnosis and Treatment of Trigeminal Neuralgia. Ther Clin Risk Manag 2015; 11:289-299*
30. *Mumenthaler M: Neurology. Georg Thieme Verlag Stuttgart- New York, 2004*
31. *Neil MJE: Pain After Amputation. BJA Education 2016; 16:107-122*
32. *Nosrat CA, Fried K, Ebendal T, Olson L: NGF, BDNF, NT3, NT4 and GDNF in tooth development. Eur J Oral Sci 1998; 106(Suppl 1):94-9*
33. *Privitera R, Birch R, Sinisi N, Mihaylov IR, Leech R, Anand P: Capsaicin 8% Patch Treatment for Amputation Stump and Phantom Limb Pain: A Clinical and Functional MRI study. J Pain Res 2017; 10:1623-1634*
34. *Rojas-Ramirez MV, Bertoli M, Smith JH: Short-lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing Secondary to Head and Neck Trauma. J Oral Facial Pain Headache 2016; 30:68-72*
35. *Rozen TD, Capobianco DJ, Dalessio DJ: Cranial neuralgias and other causes of faciala pain. In: Silberstein SD, Lipton RB, Dodick DW (eds) Wolff's Headache and other pain. New York: Oxford University Press, 2008, pp. 633-650*
36. *Schley MT, Wilms P, Toepfner S, Schaller HP, Schmelz M, Konrad CJ et al.: Painful and nonpainful phantom and*

stump sensations in acute traumatic amputees. J Trauma 2008; 65:858-864

37. *Sessle BJ: Peripheral and central mechanisms of orofacial inflammatory pain. Int Rev Neurobiol 2011; 152:2685-2689*
38. *Sicuteri F, Nicolodi M: Redundant pain transmission from functional deafferentation, In: Clifford Rose F (ed.) Advances in Headache Research. London, Paris: J. Libbey, 1987, pp 11-18*
39. *Soares CD, Panungati PK, Shrivastava A, Aroor S, Keinath KM, Bromagen MC et al.: Experimental Pain Assesment in Patients with Poststroke Aphasia. Neurology 2018; 91:e793-e799*
40. *Stacey RG, Hilbert L, Quail T: Computational Study of Synchrony in Fields and Microclusters of Ephaptically Coupled Neurons. J Neurophysiol 2015; 113:3329-3341*
41. *Varela-Lema L, Lopez-Garcia M, Maceira-Rozas M, Munoz-Garzon V: Linear Accelerator Stereotactic Radiosurgery for Trigeminal Neuralgia. Pain Physician 2015; 18:15-27*
42. *Yu C, Abbott PV: An overview of dental pulp: its function and response to injury. Australian Dental Journal Endodontic 2007; 52(Suppl 1):S4-S16*
43. *Zdila MJ, Hatfield SA, Mangus KR: Angular Relationship Between the Foramen Ovale and Trigeminal Impression: Percutaneous Cannulation Trajectories for Trigeminal Neuralgia. J Craniofac Surg 2016; 27:2177-80*
44. *Zurak N, Bozicevic D, Brnobic M: Idiopathic trigeminal neuralgia-a phantom pain phenomenon? The biorhythms neogenesis theory. Neurologija 1981; 31:91-106*
45. *Zurak N, Randic B, Poljakovic Z, Voglein S: Intravenous Chlormethiazole in the Management of Primary Trigeminal Neuralgia Resistant to Conventional Therapy. J Int Med Res 1989; 17:87-92*
46. *Zurak N: Primary Trigeminal Neuralgia. Algophoric deafferentation hypersensitivity syndrome. Neurologija 1990; 39:75-90*
47. *Zurak N, Bilic E: Syncope: Facts and Fiction. Medical Hypotheses 2004; 63:394-401*
48. *Zurak N: Metaneurobiology of death. Zagreb: Medicinska naklada, 2018, pp. 77-83*

Correspondence:

Prof. Darija Mahovic, MD, PhD
Department of Neurology, University Hospital Centre Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: darija.mahovic@zg.t-com.hr