Concept of acute neuropathic pain. The role of *nervi nervorum* in the distinction between acute nociceptive and neuropathic pain

Conceito de dor neuropática aguda. O papel do nervi nervorum na distinção entre dores agudas nociceptiva e neuropática

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DOI 10.5935/1806-0013.20160038

ABSTRACT

BACKGROUND AND OBJECTIVES: Several pathophysiological mechanisms are involved in the genesis of neuropathic pain. However, available justifications for its onset are unsatisfying and do not explain the participation of *nervi nervorum* and *nervi vasorum* abnormalities on functional aberrations which characterize pain generated by injuries to the peripheral nervous system. There are evidences that *nervi nervorum* contribute to the development and justify many clinical findings and prophylactic, therapeutic and rehabilitation alternatives related to neuropathic pain. This study aimed at presenting a review of anatomic and functional studies and theories about their objectives and at giving examples of conditions in which *nervi nervorum* have markedly participated in neuropathic pain generation and maintenance.

CONTENTS: *Nervi nervorum* are a set of unmyelinated or poorly myelinated fibers located in peripheral nerves sheaths which, among other functions, seem to participate in the transmission of evoked sensory information and in the environmental regulation of peripheral nervous system structures.

CONCLUSION: *Nervi nervorum* structural and functional abnormalities may contribute to the onset, maintenance and worsening of neuropathic pain and "demodulatory" painful syndromes. Further studies, especially with the application of more specific and sensitive histological, biochemical and electrophysiological methods are necessary to clarify the realities of their biologies.

Keywords: Nervi nervorum, Neuropathic pain, Nociceptive pain, Pathophysiology, Peripheral nerves.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Diversos mecanismos fisiopatológicos estão envolvidos na gênese das dores neuropáticas. Entretanto as justificativas disponíveis para sua ocorrência são insatisfatórias e em nada esclarecem a ocorrência das assim chamadas dores desmodulatórias. Há crescente interesse em se compreender a participação das anormalidades dos *nervi nervorum* e *nervi vasorum* nas aberrações funcionais que caracterizam as dores geradas pelas lesões que acometem o sistema nervoso periférico. Há evidências de que os *nervi nervorum* contribuem para desenvolvimento e justificam muitos dos achados clínicos e as alternativas profiláticas, terapêuticas e reabilitacionais relacionadas às dores neuropáticas. O objetivo deste estudo foi apresentar uma revisão sobre os estudos anatômicos e funcionais e as teorias sobre suas finalidades e exemplificar condições em que os ner*vi nervorum* participam de modo marcante na sua geração e manutenção da dor neuropática.

CONTEÚDO: Os *nervi nervorum* são um conjunto de fibras amielínicas ou pouco mielinizadas localizadas nas bainhas dos nervos periféricos que, dentre outras funções, parecem participar da veiculação de informações sensitivas evocadas assim como da regulação do meio ambiente nas estruturas do sistema nervoso periférico.

CONCLUSÃO: As anormalidades estruturais ou funcionais dos *nervi nervorum* podem contribuir para a ocorrência, manutenção e agravamento das dores neuropáticas e das síndromes dolorosas "desmodulatórias". Mais estudos, em especial com a aplicação de métodos histológicos, bioquímicos e eletrofisiológicos mais específicos e sensíveis são necessários para esclarecer as realidades de suas biologias.

Descritores: Dor neuropática, Dor nociceptiva, Fisiopatologia, *nervi nervorum*, Nervos periféricos.

INTRODUCTION

According to the International Association for the Study of Pain (IASP) definition, pain is "an unpleasant sensory and emotional experience related to tissue injury or described in such terms"[1]. The precise definition of the origin of pain is involved by imponderable meanings in the developmental, anatomic, etiopathogenic, physiopathogenic, epidemiologic, clinical, evaluative, therapeutic, prognostic, rehabilitation and reinsertion contexts[2].

Based on some of its aspects and on consensus meetings, pains were classified in five major groups, namely: nociceptive pains; neuropathic pains, dysfunctional pains, psychogenic pains, and mixed pains[3].

According to IASP consensus, nociceptive pain is that "manifested as consequence of actual injury or which is about to be installed in a non-neural tissue and is induced by the activation of nociceptors"[4]. According to Teixeira[5], it was after 1906 that Dejerine and Roussy have described the first cases of thalamic syndrome and progressively a larger number of studies were published about "neuropathic pain". Riddoch[6] has defined central pain as "spontaneous pain or excessive reaction to objective stimulation, including dysesthesias and unpleasant sensations resulting from injuries confined to the central nervous system (CNS). According to Tasker, Organ and Hawrylyshyn[7], pain by deafferentation is that resulting from injuries in nervous structures. According to IASP consensus, neuropathic pain (NP) is "pain triggered or caused by primary injury or dysfunction located in the CNS or in the peripheral nervous system (PNS)"[8]. According to Hansson, Lacerenza and Marchettini[9], NP is "pain caused by primary CNS or PNS injury". Recently, a IASP consensus has redefined NP as "pain directly induced by injury or disease affecting the somatosensory system"[10]. This means that there might be direct relationship between an injury or disease affecting the sensory nervous system and the installation of pain, regardless of the onset of symptoms being immediate or late.

The inclusion of the term dysfunction in the first IASP NP definition made it imprecise because included among neuropathic pains, nociceptive or psychogenic pains, since neurobiological reactions faced to neuropathies, especially the adoption of compensatory attitudes, especially musculoskeletal, generate a wide range of abnormalities implied in worsening previous sensitization of CNS and PNS constituent elements[11,12].

According to Teixeira[12], pain may also be a consequence of injuries or even dysfunctions located in PNS or CNS which are expressed morphologically or biochemically in such a mild way that several subcellular abnormalities generated by them still cannot be identified with currently available methods which have sensitivity and specificity far away from meeting diagnostic realities of demodulatory pain[7]. Baron[13] has proposed an NP classification based on symptoms and pathophysiology of sensitivities. It has to be stressed however that classifications based on pain-generating mechanisms have not yet been validated, although they might be applied to some cases of neurogenic pain[14]. Regardless of its concept, NP is debilitating, significantly impairs quality of life and in general is resistant to treatment including the use of opioids[15,16].

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Conflict of interests: none – Sponsoring sources: none.

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ORGANIZATION OF PERIPHERAL NOCICEPTIVE NERVOUS SYSTEM

Peripheral nerves are made up of several hundreds of nervous fibers surrounded by connective tissue layers and organized in fascicles juxtaposed to each other and supported by connective tissue frames. Fibers have bimodal distribution. Sensory fibers have diameter of 4 and 10 mm while motor fibers have diameters of 2 and 6mm. The number of myelinated fibers in sensory nerves varies from 5000 to 9000, with considerable variability among individuals. Unmyelinated fibers are three to six times more numerous than myelinated fibers; diameters vary from 0.5 to 3.0mm, with unimodal peak of 1.5mm.

In most nerves, motor and sensory fibers are intermingled in peripheral nerves. In general, nerves have four to 10 or more fascicles. Individual fascicles are not continuous because they suffer fusion and ramification along their pathway, so that fibers of one fascicle move by means of connective tissue layers to other fascicles. There are three envelopes structurally supporting and regionally nourishing peripheral nerves.

The epineurium is the most external layer which continues with the surrounding connective tissue involving fascicles of nervous trunks; it tends to be disposed longitudinally along the nervous trunk and provides its resistance and elongation. Perineurium is the intermediate layer, made up of a sheath with several layers of flat cells surrounded by a baseline membrane, disposed circumferentially to continuously and individually cover nervous roots fascicles at terminal ends of peripheral nerves; cells arrangement and their metabolic activity suggest that they act as a blood-nerve barrier, regulating endoneuronal environment.

Endoneurium is the most inner layer, made up of connective tissue individually surrounding intrafascicular nervous fibers and fine fluid and fibrilar material[17]. Schwann cells are long and flat and involve the axon with a spiral form made up of compact layers of membranes with few cytoplasms between myelin and have their nuclei in a region external to the packaging region. Each Schwann cell covers 300 to 2000mm of the axon length, being longer in larger axons.

Myelin package thickness increases with axonal diameter and is uniform in the internodal region, but is decreased in the perinodal region. There is a space of approximately 1mm between two adjacent Schwann cells, called Ranvier's node. The axon has uniform diameter in the internodal region, but becomes frilled in the paranodal region and has its diameter decreased 50% in the Ranvier's node.

A baseline membrane covers Schwann cells and Ranvier's nodes and is a tube guiding axonal regeneration. Groups of one to six unmyelinated fibers are weakly involved by individual Schwann cells, forming a bundle of Remake fibers. Schwann cells cover 300 to 500mm of the surface along the axons. Schwann cells extremities are interdigitized not leaving exposed axonal segments. Unmyelinated fibers also cross from a Remake package to the other. Thick and thin myelinated and unmyelinated fibers tend to group inside the fascicles. Cell body (sensory ganglion or cellular body of motoneurons present in spinal cord ventral gray matter) is responsible for the maintenance of axonal metabolic process[18].

Peripheral nervous trunks fibers have elasticity and corrugated pathway in a way that they may be elongated for up to 50% of their length before tension is directly transmitted to nervous tissue. Nervous roots have less connective tissue and more individual nervous fibers which are less corrugated, which makes them more vulnerable to mechanical distortion[19].

Peripheral sensory nervous system is made of afferent nervous fibers and sensory ganglia which transfer tissue information and molecules to the CNS and regulate vasoactivity, trophism and composition of tissue environments where they are located. PNS myelin is produced by Schwann cells and the distance between Ranvier nodes determines action potentials conduction velocity. The endoneurium shelters blood capillaries which supply nervous fibers and their envelopes with nutrients and oxygen. PNS sensory fibers contain a sensory ganglion made up of a conglomerate of neuron bodies and satellite cells.

Sensory ganglia neurons are pseudounipolar and originate after common pathway of central and peripheral projections to CNS and peripheral tissues, respectively. Nervous axons vary in diameter. Larger axons (2 to 22mm diameter) are individually involved by a linear layer of Schwann cells (myelinated fibers), while groups of smaller axons are involved by Schwann cells (unmyelinated fibers).

Nervous trunks are perfused by blood vessels originated from collaterals of branches of arteries adjacent to them. Blood supply is made up of an extrinsic and intrinsic system. The extrinsic system includes arterioles, capillaries and epineurium and perineurium venules; intrinsic vessels perforate the perineurium and constitute an intrinsic system made up of wide anastomotic chain of longitudinal microvessels inside the fascicular endoneurium, the *vasa nervorum*, which in turn are made up of arterioles, capillaries, post-capillary venules and venules[20].

Endothelial cells of these latter vessels are juxtaposed to each other by narrow connections and have the baseline membrane organized which constitutes the blood-nerve barrier which selectively regulates the transfer of circulating substances to inside the endoneural nervous case[21]. Nervous fibers may perform anaerobic metabolism, but anastomoses between internal and external vascular systems maintain blood flow even in conditions of extreme ischemia. However, there might be microvascular ischemia in case of vasculitis, condition where there might be localized nervous injury.

Nervous trunks are mechano-sensitive because their connective tissue has afferents normally participating in mechano-reception[22,23]. Peripheral nerves are innervated by neurovegetative fibers, the *nervi vasorum*, and by intrinsic nerves, the *nervi nervorum*, made up of unmyelinated or thin myelinated fibers composing a thin plexus layer of free nervous terminations in the epineurium, perineurium and endoneurium and some encapsulated Pacini terminations in the endoneurium[16,22-26]. In late 19th century, John Marshall, mentioned by Powell[27], and neurosurgeon Victor Horsley, mentioned by Sugar[28], both English citizens, have evaluated histological features of peripheral nerves and have observed nervous ramifications in the epineurium coming from the nerve itself, the *nervi nervorum*.

In the publications "Nerve stretching for the relief of pain", Marshall has inferred that *nervi nervorum* would participate in pain generation mechanism observed in cases of peripheral nerves compression[27]. Together with Horsley[28] he has shown that *nervi nervorum* were sensitive to pain, especially to pressure[29]. Hromada[22] has observed that *nervi nervorum* originated from *vasa vasorum* nervous plexus or from nervous trunks themselves where they reached their targets following blood vessels.

He has evidenced four distinct regions of peri and non perivascular innervations in nervous trunks: perivascular innervation of extraneural arteries and veins; perivascular innervation of intraneural blood vessels (vasa nervorum); non-perivascular fibers (nervi nervorum) originated from the nervous trunk and perivascular plexus and distributed by epi, peri and endoneural connective tissues; and intrafascicular fibers with major adrenergic component, particularly in the sciatic nerve. Adrenergic *nervi nervorum* and *vasa vasorum* innervation is modified in a non uniform way in nerves of experimental diabetes mellitus models[30].

Pia-arachnoid of cranial nerves and ventral roots have structure similar to the perineurium[31] and innervation patterns similar to *nervi nervorum*[22,32,33]. Unmyelinated axons[23] associated to specific glycoconjugated[34-36] with terminations distribution patterns different from sensory peptidergic axons innervate blood vessels[37-39]. There is great probability that unmyelinated fibers of *nervi nervorum* containing CGRP are nociceptive[38,40].

PERIPHERAL NEUROPATHIC PAIN PATHOPHYSIOLOGY

NP physiopathogenesis is not well understood. Although cellular and subcellular structural, electrophysiological and biochemical abnormalities have been evidenced in the nervous system, there is still uncertainty about mechanisms of pain induced by PNS injuries, especially acute NP, referred NP and pain attributed to "demodulation"[5].

Sensory neurons transfer tissue information to the CNS involving high level of regional specialization. Nervous terminations are specialized in coding sensory information and originating generation and action potentials in peripheral nerves reaching spinal cord gray matter dorsal horn (SCDH) without marked qualitative and quantitative changes[5]. So, functional properties of axons and central neuronal units should be kept intact for sensory information to be adequately transmitted and processed[13].

If there are changes in function or anatomy of terminations or peripheral nervous trunks or of neuronal units or conduction pathways and of central sensory information processing, there might be spontaneous pain or pain generated by non-nociceptive stimuli due to the installation of action potentials ectopic focuses in peripheral nervous fibers, sensory roots ganglia and central neural units, ephatic currents, abnormal activity of processing units of peripheral and central sensory afferences, sensitization of nociceptors by

algiogenic substances produced in tissues or released in them by sympathetic neurovegetative nervous system (SNVNS) or peripheral terminations of nociceptive neurons, development of synapses by CDME aberrations, hypoactivity of pain suppressing modulating system and physical, psychic, neuroendocrine and neurovegetative reactions associated to pain and incapacity[5].

The organization of a neuroma after nervous injury is normal and important cause of NP[41]. It is admitted that many acquired neuropathies especially affect cell body function or axonal transportation, causing early changes in peripheral nerves distal regions. Many neuropathies are characterized as abnormalities which, together, have common pathologic features, including dying-back neuropathy and distal axonopathty. Pathologic changes of dying-back neuropathy are similar to those of distal Wallerian degeneration manifested after axonal injury, except for the fact that they are slower and coexist with regenerative changes.

In case of PNS injury, larger and more distal myelinated fibers are the first to be affected. There is initially a buildup of abnormal mytochondrias, organelles and disorganization of microtubules and neurofilaments. The myelin sheath becomes edematous in paranodal regions and suffers secondary changes such as the formation of rows of myelin ovoids which increase in size becoming digestion chambers. Injured region is invaded by macrophages with remnants of myelin and Schwann cell nuclei divide and proliferate. In acute axonopathy models, axonal regeneration occurs after degeneration, while in chronic axonal neuropathies regeneration often occurs in parallel with degeneration.

Several growth cones sprout from a single axon and become remyelinated. Regeneration fibers have decreased diameter and are myelinated. Several thin myelinated axons sprout within the space previously occupied by larger axons. Schwann cells division shortens intermodal lengths. There may be diffuse axonal loss inside a fascicle in localized areas. Endoneural fibrosis and hypercellularity (fibroblasts) are installed inside the fascicle. In case of primary segmental unmyelinization abnormalities initially affect myelin sheath, but the pathological process may secondarily damage axons.

Onionskin-like bulbs, that is interlinked Schwann cells processes involving axons separated by collagen tissue, reflect underlying pathological unmyelinization and remyelinization processes. Secondary unmyelinization refers to Schwann cells degeneration as a consequence of primary axonal degeneration. Initially there is Schwann cell auto-phagocytosis with subsequent removal of myelin debris by macrophages. There are often nonspecific perivascular infiltrates of non-vasculitic mononuclear cells. Nonspecific inflammatory cells can be seen in the perineurium as well as endoneural edema, resulting in increased interstitial or subperineal space filled with amorphous substance with mucopolysaccharides or osmotic fluids.

Localized ischemia results from incomplete axons loss; larger axons are more often affected. There is also lumen narrowing, thrombosis, sclerosis, wall disorganization, medium layer injury, internal elastic layer rupture, localized calcification, hemosiderin deposit and reperfusion and proliferation of capillaries in vessels. There might be mild or severe decrease in the number of axons with no relation with the level of vascular failure. There are also frequent evidences of axonal regeneration.

When there is peripheral nervous fibers section or partial injury, proximal stumps of sectioned or injured axons are sealed and adjacent myelin sheath, in addition to proximal and distal stumps axons suffer Wallerian degeneration in the extension of some millimeters. Simultaneously, there is widespread degeneration with different magnitudes along the whole extension of peripheral nervous fibers[41]. Wallerian degeneration starts with axoplasm and axolemma degradation induced by activation of axonal proteases and calcium inflow. When there is partial injury, continuous baseline lamina supplies orientation for axonal regeneration of proximal stumps toward their targets.

Nervous fibers as from the proximal stump elongate in growth cones by means of the distal segment and target tissues and, eventually, reinnervate non afferent tissues. After axonal injury, peripheral nervous fibers regenerate as from the proximal stump. Axonal regrowth velocity is from 3 to 4mm/day after nerve crushing and of 2.5mm/day after its section. Regenerating axons grow preferentially inside endoneural tubes of Schwann cells. Schwann cells depletion does not influence axonal elongation when the baseline lamina remains in continuity, because extracellular matrix proteins are essential for axonal regeneration. Molecules promoting neuritis growth in the distal stump are positively regulated.

After initial extrusion of myelin sheaths, Schwann cells are divided reaching their maximum value in three days and align inside the baseline lamina tube to form Büngner's bands, which orient nervous fibers regeneration. Hematogenic macrophages penetrate the distal stump and migrate to ovoids as from the second day, reaching maximum concentration in four to seven days, and in two weeks they completely remove myelin residues. Schwann cells may degrade short-segment myelin without the assistance of macrophages.

Within two days, Schwann cells scavenge myelin residues and fragment their own myelin sheaths into ovoids. Schwann cells fagocyte myelin debris to a certain extent and form lipid droplets before invasion of nerves degeneration by macrophages, which happens in the fourth day. Neutrophyls are transiently present during the first hours after peripheral nervous injury. Genes MAG, MBP and PMP22 specific for myelin synthesis, suffer upregulation in Schwann cells during the myelinization period, while gene NCAM-1 and RhoAS-GTPase, suffer downregulation.

Hours after axonal injury, mRNA concentrations for nervous growth factor (NGF) increase and suffer a second expression peak within two to three days after injury, simultaneously with slow and continuous increase of ARNm of brain-derived neurotrophic factor (BDNF) and reach maximum values three to four weeks after. Schwann cells produce NGF, BDNF and insulin-like growth factor I (IGF-1). After the seventh day, macrophages infiltrate and become the predominant source of IGF-1 in the distal stump. Protein concentrations for pro and anti-inflammatory cytokines suffer upregulation in the absence of T cells.

Twenty-four hours after nervous crushing, concentrations of IL1B-mRNA increase and remain high during the first week; IL-1 induces NGF synthesis in Schwann cells. There are also increased concentrations of nRNA pairs IL-6 and IL-10 after nervous crushing. Within some days, there is ARNm induction for pro-inflammatory cytokines IFNg and IL-12. Myelin-derived lipids are reused for regeneration and remyelinization. As from the fourth day, Schwann cells express cell surface molecules from L1 and N-CAM. Laminine B mRNA is decreased and then it gradually increases when regeneration reaches distal segments and the contact axon-Schwann cell is reestablished[42,43]. Macrophages infiltrated in Wallerian degeneration express immunoreactivity for TNF-alpha.

In pericarium there is cromatolysis and upregulation of the jun transcription factor, which persist until regeneration of peripheral nerve is complete in association to upregulation of protein GAP=43/B50 and to intermediate peripherin filament protein which is installed in the first day after axonal injury as well as the three genes of neurofilament NF-L, NF-M, NF-H and mRNAs for b-tubulin class II and III.

The mRNA for IL6 appears one day after sciatic nerve section on large and medium ganglia and has maximum expression in two to four days. TNFa and IL1B ARNm suffer upregulation. LIF, galanin and nitric oxide suffer upregulation.

When axons emerge from terminal bulbs under adequate conditions and alignment and coherence of motor and sensory fascicles, there is regeneration and functional recovery because proximal nervous fibers sprout guided by neurotrophic factors in the distal growth cone and reach nervous terminations in target tissues.

When nervous growth of proximal stump of a transversally sectioned nerve is blocked, distal Schwann cells do not proliferate and proximal axons sprout intensively forming an extremely sensitive bulb, or terminal bulbs, made up of chaotic and disorganized groups of myelinated nervous fibers with randomly oriented organelles and surrounded by connective tissue which constitutes approximately 80% of its cutoff face and myofibroblasts[41]. When the injury is partial and regeneration is interrupted at different intervals, spindle microneuromas appear disseminated along partially intact fibers[3].

After losing axonal contact, Schwann cells suffer downregulation of mRNA of myelin components of the basic myelin protein (MBP), of myelin associated to glycoprotein (MAG), of zero protein (P0), of protein-22 of peripheral myelin (PMP22) and of periaxin. Initially, Schwann cells are not differentiated and acquire the phenotype of the pre/non myelinating phase with the expression of receptors p75 with low affinity of NGF-r, glial fibrilar acid protein (GFAP), factor B of glial maturation, neural cell adhesion molecule L1 and neural cell adhesion cell (NCAM). Transcription factors Pax3, SCIP, cJun and Krox-20 are involved in regulation and re-differentiation of Schwann cells.

Bulbs become apparent six to ten weeks after trauma and become well evident one to 12 months after injury and increase in volume during the first two to three years. Neuromas or bulbs result from the regeneration of thin axons, many of them unmyelinated and without growth direction. Unsatis-

factory regeneration of distal fascicles or the presence of unexpected abnormalities on nervous terminations generate functional deficit and in many cases hyperalgesia in the distribution of the injured nerve and formation of painful neuroma in addition to deficits[41]. Neuromas may cause spontaneous continuous pain, intermittent spontaneous pain or pain evoked by mechanical stimuli, scar tissue which enclose them or not, or thermal or chemical stimuli[42]. However, not all neuromas are painful[43]. The level of maturity of regenerated nervous fibers in the neuroma plays important role in neuroma's development[42].

There are action potentials in injured nerve proximal stump which, in turn, are retrogradely transferred to the cell body located in sensory ganglia where there is peptide synthesis and are produced factors which stimulate axonal regeneration, including neurotransmitters and their precursors which, in turn, are ortho and anterogradelly transported.

NP is expression of plasticity abnormality of the nociceptive system in the context of different abnormalities manifested in neuronal diseases which contribute for the generation of complex painful phenotypes[44].

Several pathophysiological simultaneous or sequential mechanisms seem to relate to the installation and maintenance of neuropathic pain, including phenomena related to distal and proximal degeneration and regeneration of neuronal units, to repercussions of the installation of ephatic currents between nervous fibers, the modification of reactivity of cells which structure, nourish, protect and reorganize the nervous system, to changes in density, nature and distribution of receptors and ion channels of nervous cells or cells responsible for their support, to peripheral tissue concentrations and in the nervous system of enzymes, coenzymes, enzymatic systems cofactors, neurotransmitters, trophic and inflammatory factors and other substances generated by diseases or disorders of the nervous system itself, generated by injuries or as consequence of mismatching caused by them and implied in the generation of suppression of stimuli, nutrition, sensitization and immune-modulation of the nervous or glial system, peripheral NP is in general associated to negative and positive signs and symptoms[45].

Positive symptoms of neuropathies include in addition to pain, paresthesias and spasms, and negative symptoms include anesthesia and other sensory, neurovegetative and motor deficits etc.[44]

NP may be spontaneous or induced by stimulation of nociceptive receptors or not. Three types of pain may manifest when a peripheral nerve is damaged: pain at nervous trunk injury site, described as stabbing or tenderness and attributed to increased activity of abnormal nociceptors chemically or mechanically sensitized; disestesic and piercing pain, described as burning, smarting, tingling or electricity and paroxysms described as sensations of shock, stabbing or jumping and allodynia localized in the distribution of a sensory or mixed nerve in areas where sensory deficits are identified together with allodynia[45] and attributed to nociceptive afferent axons injury[46,47]; and referred pain of nervous trunks, attributed to hyperactivity of mechanically and chemically sensitized nociceptors of *nervi nervorum* present inside nervous sheaths, with convergent projections and centrally projected in CDME and described as deep, following nervous trunk course and worsened with movement, stretching or nervous palpation[46]. Healthy nervous trunk pain is more difficult to be evoked with regard to pain evoked on unhealthy nervous trunks[48].

It is said that disestesic pain is consequence of regeneration of nociceptors neurits which become abnormaly excitable, from primary hyperexcitable afferents injury and from repercussions of CNS sensitization and deafferentation[44,46], such as during search for Tinel and Spurling sign or the abnormal activation of nociceptive afferents present in *nervi nervorum*[46,48,49]. However, in general both pains coexist[46].

Normal peripheral nervous trunks and nervous roots are painless to non-noxious mechanical stimulation. However, there is mechanical allodynia during nervous trunk palpation of compression or tension applied along the length of nervous trunks when *nervi nervorum* become sensitized. The possibility that pain from PNS injury may be neurogenic is not recent[28,29]. *Nervi nervorum* actively participate in the presence of pain in cases of PNS injury[48]. Evoked pain when peripheral nerves are manipulated may result from the stimulation of intact nerves present in surrounding connective tissue. Painful stimuli which activate nociceptors around nerves include inflammation and injury of tumor or trauma tissues. Anatomic particularities of *nervi nervorum* and of epineural blood vessels make them vulnerable to certain situations, such as when there is nervous tissue stretching[50,51]. When there is peripheral roots or nerves injury, there might be abnormal tissue regeneration, characterized by sprouting of nervous terminations[52], endoneural fibrosis sodium channels upregulation[53,54], sympathetic hyperactivity etc.[55]

According to Bove and Light[56], several inflammatory, traumatic or compressive affections may injure *nervi nervorum* and, as a consequence, their nervous sprouting and development of adjacent neuromas, resulting in neuronal hyper-reactivity, which is worsened by friction movements, release of algiogenic inflammatory substances and regional edema, which together act as a vicious circle. They have also inferred that many musculoskeletal pains are a consequence of such phenomenon. *Nervi nervorum* fibers have substance P, peptide related to calcitonin gene (PGRC) and other peptides linked to nociceptive transmission and vasodilation and to plasma leakage, localized and characteristic of neurogenic inflammation[57].

These substances sensitize and are able to generate action potentials in their peptidergic afferents where there is nervous tissue injury and where localized NP is located[58]. There is major possibility that unmyelinated *nervi nervorum* fibers are nociceptive. These statements were confirmed by studies showing immunoreactivity by means of immune-histochemistry technique for PGRC and periphery of these nervous fibers related to intrinsic innervations of sciatic nerve sheath regardless of fibers innervating neural vasculature. These results suggest that, at least one subset of *nervi nervorum*, regardless of *nervi vasorum* may have nociceptive functions.

The activation of *nervi nervorum* nervous terminations was implied in peripheral nervous trunk referred pain[25,46,57,58]. Bove and Light[59] have observed that *nervi nervourm* fibers were arranged in the neural space to respond to induced stimuli during nervous injury such as mechanical compression and tension and are positioned to react to changes of the medium were nervous damages occur, such as those caused by increased subperineural pressure and environmental concentrations of histamine and bradikinin[60,61]. *Nervi nervorum* and *nervi vasorum* are vulnerable to nervous tissue injuries resulting from friction and chronic compressive syndromes[56].

According to some clinical trials, in normal circumstances nervous trunks are insensitive to non-noxious mechanical deformation[62,63]. In case of nervous injury, it is possible to have isolated disestesic pain and nervous trunk pain. Peripheral nervous tissue may be source of localized, irradiated or referred pain. Localized pain and pain evoked by mechanical stimuli may result from inflammatory processes, tissue injury, tumor or trauma of *nervi nervorum* present in connective tissue around nervous fibers[44].

If there is peripheral nervous injury, *nervi nervorum* release PGRC, substance P, peripherin and nitric oxide inside the nervous tissue. These substances trigger vasodilation and increase *vasa nervorum* and neighbor blood vessels patency[25], cause neurogenic inflammation[25,56,57] and markedly participate in the onset and maintenance of pain induced by PNS injury[21,22].

According to Bove and Light[56], localized nervous information is mediated by *nervi nervorum*, especially when there is intrafascicular axonal injury. According to some electrophysiological studies[64] at least some *nervi nervorum* have nociceptive function in face of mechanical, chemical and thermal stimulation. Most *nervi nervorum* evaluated by Bove and Light were sensitive to excessive or localized longitudinal stretching and to localized compression, but were not activated during stretching with normal movement limits.

Due to *nervi nervorum* sensitization and activation it is common to have proximal referred pain in patients suffering median nerve compression, expansion of regional hypersensitivity area in patients with nervous entrapment (carpal tunnel, tarsal or Guyon channel syndrome) or fibrosis installed after surgeries aiming at treating them[48] and referred pain and lumbar paravertebral muscle spasm as a consequence of sensitization of primary recurrent branches of lumbosacral sensory roots[65]. Maneuvers evoking nociception as from nervous trunks, such as brachial plexus[66] or upper limb[67] tension test also suggest the participation of nervous tissue innervations themselves as source of referred NP.

It is said that propagation of mechanosensitivity along the nervous trunk distant from the nervous injury site is mediated by neurogenic inflammation generated by *nervi nervorum*[68].

Along time, the whole nervous trunk behaves as a sensitized nociceptor and generates evoked potentials in face of low magnitude mechanical stimulation[43] and causes mechanical allodynia in normal nervous trunks where the injury is proximal and many times in the nervous root[69]. When there is nervous root compression or trauma in the intervertebral foramen due to spinal discontrose, there are root symptoms and neurological deficits[70]; the whole sciatic nerve extension is sensitized when a lumbosacral root related to it is traumatized[69]; the same is true for cervical radiculopathy[63,71].

When *nervi nervorum* become sensitized, pain may be evoked with tension applied along the length of the nerve and with direct compression of nervous trunk which in normal conditions is painless to non-noxious mechanical stimulation[62,63,69]. *Nervi nervorum* sensitization propagation is attributed to neurogenic inflammation[68]. There might also be even severe radicular pain in cases where nervous conduction is normal, when the nervous trunk becomes mechanically sensitized by the action of chemical or inflammatory stimuli[72]; radicular pain in the absence of nervous root inflammatory abnormalities is presumably due to chronic compression of nervous root axons[73].

Bove and Light[56] admit that exaggerated painful sensitivity to mechanical neural tissue stimulation in cases of radiculopathy is caused by *nervi nervorum* activation and sensitization. *Nervi nervorum* sensitization justifies the finding that pain and paresthesia observed in cases of cervical or lumbar radiculopathies are not precisely located in regions of distribution of affected nervous roots in almost 50% of cases[74,75].

According to Omarket and Myers research[76], intervertebral disk puncture in rats followed by pulpous nucleus herniation, however without root compression or just chronic compression of root L4 and its sensory ganglion without exposure to disk material, has not generated changes in behavioral patterns, while root compression combined with disk material exposure, possibly for causing inflammatory phenomenon, has induced hypernociception as from the second day after procedure.

Patients with labor-related musculoskeletal disorders (RSI/DORT) or pain in upper limb caused by whiplash effect injury are positive to brachial plexus and upper limb peripheral nerves test, translated as painful reactions and hyperalgesia to digital mechanical compression applied to plexus and peripheral nervous trunks[68,77]. *Nervi nervorum* sensitization also generates nervous tissue mechanosensitivity observed in pain evoking tests, such as Lazeg test[78].

It has been shown that nerves, even when suffering mild injuries or inflammation, generate neuropathic symptoms. Nervous trunk inflammatory process in animals induces increased action potentials to pressure and to stretching in the physiologic band of the nervous tissue[79,80], findings which justify nervous trunks hyperalgesia and the relevance of neuromechanosensitivity with regard to simple nervous tissue compression in the generation of symptoms in peripheral nervous compressive affection. These, among other mechanisms, justify painful reactions in patients with symptoms suggestive of neuropathy in the absence of obvious signs of their presence, even when longitudinal nervous excursion is normal, such as observed in cases of localized nonspecific pain in limbs, RSI/DORT, carpal tunnel syndrome or whiplash effect injury[77].

Nervi nervorum sensitization and activation and intraneuronal release of PGRC, substance P and nitric oxide may be additional mechanisms generating pain in patients with post-herpetic neuralgia[58]. Pain around the ear which precedes or is simultaneously developed with Bell's palsy, in general is located beyond the sensory innervation territory of facial nerve. Cranial nerves are also innervated by *nervi nervorum* so that their stimulation may be transmitted from the facial nerve to trigeminocervical complex nuclei and originate segmental referred pain in craniofacial region[81]. It is possible that pain related to optic neuritis in multiple sclerosis patients is nociceptive and caused by optic nerve trunk inflammation which activates intraneural nociceptors innervated by *nervi nervorum*[82].

However, very often peripheral nerves compression does not generate pain[83]. According to Sorkin, Wagner and Myers[84], the hypothesis of Bove and Light[56] has not yet been shown due to the difficulty in isolating and stimulating perineural fibers because in general electric stimuli are spread to axons located in their proximity. According to such authors, one major pain generating element in models of chronic nervous compression and constriction is ischemic injury of endoneural nervous fibers which results in TNF factor release.

Willis[85] has confirmed Bove and Light theory with a report of good results observed with peripheral blocks to treat pain at nervous injury site in animals and the occurrence of neural sprouting and neuroma formation in models of sciatic nerve constriction. Nervous sheath inflammation without significant axonal degeneration, that is, when axonal and *nervi nervorum* continuity is maintained, may create conditions where afferent C fibers become mechanically sensitive and spontaneously activated.

Another possibility of PNS intrinsic nerve abnormalities causing pain is abnormality of nervous perfusion manifested in many neuropathies. Blood flow reduction in peripheral nerves plays important role in diabetic neuropathy pathogenesis[86]. These abnormalities may include localized involvement of microcirculation by microangiopathy[87,88] or deficiency of blood flow control mechanisms by *vasa vasorum*[89]. Self-regulation of peripheral nerves is still poorly understood[89,90]. Nervous, peptidergic, noradrenergic and serotoninergic fibers participate in *vasa nervorum* and provide neurogenic control mechanism[91,92].

Variation on *vasa nervorum* noradrenergic fibers activity plays important role in nervous trunks blood flow regulation[93]. There is adrenergic fibers increase in perivascular, tibial and sciatic nerves, higher levels of norepinephrine in vagus nerve of diabetic animals[30], but adrenergic innervations density is equal or lower than that of non-diabetics[94] and norepinephrine density is decreased in the sciatic nerve of diabetic rats[95]. These changes may contribute to microvascular abnormalities of peripheral nerves in cases of diabetic neuropathy and impair nervous trunks blood flow regulation.

Van Buren et al.[96] have concluded that pre-synaptic deficit of *nervi vasorum* sympathetic fibers impairs sciatic nerve *vasa nervorum* blood flow in diabetic rats so that adrenergic neurovegetative abnormalities of *vasa nervorum* have minor action on decreasing baseline blood flow in diabetic rats. Blood flow neurovegetative control of peripheral and cranial nervous trunks due to *vasa nervorum* injury in animals with STZ-induced diabetes may cause ischemia, change localized axonal reflexes and contribute to disease pathogenesis.

Miller et al.[97] have observed in rats that eight weeks after diabetes induction with streptozotocin, there have been changes in neuropeptide concentrations in epineural and perineural sheaths of peripheral spinal and cranial nerves, but not in intrafascicula nervous fibers structure. Innervations in such conditions are changed, especially in *vasa vasorum* and *nervi nervorum*. There is increased NPY immunoreactivity for the optic nerve and increased in the sciatic nerve of CGRP and substance D concentrations together with NPY-IR deficit.

CONCLUSION

Peripheral nerves are essential for transduction and transmission of painful impulses. Their complex structural organization allows bidirectional communication between CNS and different body regions, when sending sensory superficial and deep information, transmitting motor and neurosecretory impulses. Peripheral nerves have their own vascularization system, called *vasa nervorum*, regulated by *vasa nervorum* and own nervous fibers and terminations located in the periphery of nerves, the *nervi nervorum.*

Nervi nervorum participate in the pathophysiology of PNS injuries in situations such as nervous tissue compression, trauma, stretching and inflammation. Several infectious, inflammatory, compressive or traumatic diseases may injure *nervi nervorum* and promote their abnormal sprouting and as a consequence induce functional changes such as algiogenic substances release, edema and neuronal hyper-reactivity, which contribute to installation, worsening and maintenance of different neuropathic pain presentations. It is worth stressing that in spite of structural injuries being necessary, they are not enough to generate NP; genetic polymorphisms, epigenetics, ethnics, gender and age influence the risk to develop persistent pain.

So, there is the need for further clinical and laboratory studies to clarify the real meaning of each structural component of peripheral nerves to justify symptoms and clinical findings and to establish adequate prophylactic, therapeutic and rehabilitation measures for NP patients.

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