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Imaging of Neuropathic Pain

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Abstract

The International Association for the Study of Pain (IASP) defined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." The origin of neuropathic pain (NP) could be from the brain, spinal cord, or peripheral nerves. NP represents a major neurological problem, with a prevalence of 1%-2% of the total population. It is disabling, rendering an urgent need for non-addictive, effective new therapies, and is characterized by resistance to treatment and poor patient satisfaction. We aim to review the role of modern imaging in the diagnosis of NP and the potential advantages and limitations of each modality. (**International Journal of Biomedicine. 2022;12(1):19-23.**)

Key Words: neuropathic pain • peripheral nerves • imaging

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Abbreviations

MRI, magnetic resonance imaging; **NP**, neuropathic pain; **MI**, molecular imaging; **PET**, positron emission tomography

Pain is considered one of the most common reasons for patients to seek medical care. The attempt to understand pain represents one of the oldest challenges in the history of medicine.[1] Although research into the imaging of chronic neuropathic pain (NP) is promising, actual implementation remains a challenge. The International Association for the Study of Pain (IASP) defined neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[2,3] The origin of NP could be from the brain, spinal cord, or peripheral nerves.[4] NP represents a major neurological problem,[5,6] with a prevalence of 1%-2% of the total population.[7,8] NP is less common than nociceptive pain; however, it is usually more severe and accompanied by emotional reactions.[9] NP is disabling, rendering an urgent need for non-addictive, effective new therapies.[4,5] NP is characterized by resistance to treatment and poor patient satisfaction.[10,11] Patient collaboration is needed to establish a proper history and physical examination. Several factors influence patients' experience of pain; some of them are emotional, others are educational. Because of this, objective tools are now demanded. Management of NP is often challenging and requires a multifaceted approach. Over the last two decades, several studies have been devoted to NP. Identifying the anatomical location of the pain is a must for definitive diagnosis, which is something that current neurophysiological tools can do so.[12-24] Understanding the pathophysiological mechanisms responsible for translating sensory signs into NP can lead to an effective and treatment-based approach.[17] Sensitization of the nociceptive pathways includes adaptive structural changes, molecular signaling, and cell-cell interactions. The main classes of therapeutics include sodium channels, calcium channels, and descending modulatory inhibitory pathways.[18] Currently, NP is believed to be caused by a change in the sensitivity of central and peripheral nervous system signaling. The central mechanism includes processing and integration of information in brain centers like the brainstem, cerebellum, and cerebral cortex. These centers are related to chronic pain and associated signs and symptoms. Peripheral mechanisms include sensitization of nociceptors,

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changes in ion channel expression, sympathetic neurons related to dorsal root ganglia, pseudo synaptic conduction, and ectopic and spontaneous discharges.[9] The pain matrix in the brain includes somatosensory cortices, anterior cingulate cortex, and insula. These centers undergo maladaptive changes like microglial activation, synaptic plasticity, and central sensitization resulting in hyperalgesia.[1] Advanced studies of this pain matrix could help in understanding the pathophysiological basis of different symptoms of NP.[19]

Imaging

Recent advances in machine learning have improved the understanding of NP, utilizing a larger scale of data related to neuroimaging. In cases of NP, it is sometimes difficult to determine if the degenerative or inflammatory changes seen on imaging are part of the aging process or part of the disease process causing the patients' symptoms. Degenerative changes can be seen in more than 60% of asymptomatic patients. Some abnormalities can also be seen in asymptomatic volunteers. The frequency of these abnormalities increases with age and is somewhat irrelevant to the patients' clinical condition. The presence of multiple abnormalities at the same time makes it difficult to determine which of them is the source of pain. Since treatment decisions are guided by imaging, the low specificity of radiological diagnosis leads to ineffective, delayed, or even inappropriate treatment.[1] The radiological diagnosis of NP remains challenging since findings seen on conventional CT and MRI imaging, with their low specificity and sensitivity, don't always match the clinical picture.[25] Challenges for peripheral nerve imaging include the complex nature of human pain and the subjective component. Combining the high sensitivity and specificity of molecular imaging (MI) with high contrast resolution of MRI and CT would improve the diagnosis of NP and produce better outcomes of guided therapy.[1] For some time, NP has lacked a suitable imaging modality, which has limited concomitant research on the pathogenesis and considerably affected the treatment of NP.[26] In the past, the role of imaging was limited to identifying anatomical sites that could be responsible for pain generation. Methods related to ion channels could involve toxic effects.[25]

Molecular imaging

One of the imaging options for NP is MI. An important feature of MI is the ability to identify abnormal biological processes despite virtually normal anatomical appearance. It takes advantage of inflammatory mediators and receptors involved in the pathogenesis of pain. New innovations of MI could also help in the development of unique aspects of treatment options. Identifying a single molecular pathway is difficult because of the complex nature of the biochemical routes for NP. Several factors limit the use of MI. A single marker cannot be used for all types of pain. Another problem with MI is technical limitations like volume averaging and patient motion artifact.[1] ^{18}F-fluorodeoxyglucose could be used in PET imaging as a marker, but the background activity could overshadow the area of interest, which could be sought as the source of pain. This could be decreased by combining CT with PET. The use of PET/MRI could even yield better results with excellent soft-tissue contrast resolution. One of the problems related to pain imaging is the subjective nature of pain, which could differ from patient to patient. Whole-body imaging was suggested to study both the peripheral and central nervous systems. This could be accomplished by biomarkers, which could estimate areas of increased activity, including both systems. NP could be thought of as pain resulting from the interaction between the peripheral immune system, neurons, and different types of glial cells (e.g., astrocytes, microglia, satellite cells). A nociceptive nerve can be excited by different types of mediators; some of them are neuroimmune, others are inflammatory, in addition to interaction with macrophages and ion channel dysregulation. Inflammatory mediators like prostaglandin E2, bradykinin, and chemokines are released at the site of tissue damage, activating inflammatory cells and the ends of peripheral neurons. These mediators interact with cell receptors, ending with intracellular kinase activation, which phosphorylate target proteins, changing activation thresholds and producing increased synaptic transmission efficiency between afferent neurons and dorsal horn neurons, resulting in pain. The current imaging tools to study nociceptive activity include functional, cellular-based, and molecular approaches detecting metabolic and mediator-related changes related to abnormal physiologic activity in the nervous system and allowing targeted therapy.[1] Macrophages have been found to be intimately related to the sites of nerve injury and inflammation, enhancing pain. Knowing the location of macrophage activity is easy because these cells express translocator proteins in pathologic activity. Radioligands to translocator proteins can define areas of macrophage activity. The sigma-1receptor is a transmembrane protein concentrated in macrophages and Schwann cells, which are involved in neural damage as well as neural inflammation and repair. In the case of active nerve inflammation, there is increased density of sigma-1receptor, which can be detected by radiolabeled ligands and can identify the site of neural damage in different conditions like regional pain syndrome, and inflammatory and non-inflammatory causes of NP.[1]

Other tracers

Cyclooxygenase (COX)-2 is the dominant source of prostaglandins, which mediate pain and inflammation. COX-2 converts arachidonic acid into prostaglandin H2, the precursor of all prostanoids. The role of COX-2 in the inflammatory process was enhanced after the success of COX-2 inhibitors in treating chronic pain. Radiolabeled COX-2 inhibitors could be used to image chronic pain.[27] Sodium and calcium channels show increased flux across the membrane in cases of NP with a change in the action potential of the excitation threshold, leading to the persistent firing of nerves. Manganese physiologically follows calcium, and in exciting cells, the rate of efflux of both of them is slow, resulting in the accumulation of manganese in the cell. This could enhance imaging through manganese-enhanced MRI and could act as an alternative for estimating calcium fluxes in nerve cells using manganese as a T1-shortening contrast agent.[28] In chronic pain syndromes, neuron cells utilize a considerable amount of metabolic activity, which makes them glucose avid with the associated increase in the uptake of glucose. FDG mimics glucose and could be entrapped inside cells during the glycolytic cycle. The combination of 18F-FDG PET with MRI could help

imaging and localization of neural metabolism. It is proposed that identification of the sites of increased metabolic activity of the neural tissues on imaging could be a useful strategy for tracing NP generators.[1] MMP-12- targeted magnetic iron oxide nanoparticle (IONP) was introduced as a potential biomarker for the management and diagnosis. The use of IONP MRI enhances the spin-spin relaxation time of related water protons, thus decreasing the T2 signal. IONP detects enzyme activity when conjugated to peptide sequences; when this sequence is cleaved by the target enzyme, the released IONP is taken up by surrounding tissues. MMPs are responsible for extracellular matrix degradation; they are a member of the family of calcium-dependent zinc endopeptidase. They could be targets for IONP-based MRI.[24]

MRI

For more than 20 years, MRI was used as a noninvasive imaging tool to diagnose neural disease and injuries. MRI is considered a promising imaging diagnostic tool due to its multiplanar capability and high contrast resolution.[24] MR neurography was introduced in the 1990s to describe the use of fat-suppressed pulse sequences and diffusion-weighted imaging to discriminate peripheral nerves from the surrounding tissues.[29] Commonly, peripheral nerves cannot be distinguished from surrounding tissues in T2-weighted images. As T2 relaxation time is prolonged, injured nerves appear either isointense or slightly hyperintense (bright) on T2-W1. Although these changes are clear, however, they are nonspecific, as chronically degenerating nerves cannot be differentiated from regenerating ones. Contrast agents manganese, like gadolinium, proved to be nonspecific.[24] The diagnosis of the cause of NP depends on identifying the main pathology in addition to the anatomical location. MRI abnormalities are found in a high percentage of asymptomatic patients. Besides, the prevalence of anatomical abnormalities in symptomatic and asymptomatic patients is similar. Because of this, a demand for a more accurate imaging modality is raised. [13,14,30-32]

Functional MRI

In the last two decades, the perception and transmission of pain in the brain were studied by functional MRI (fMRI). This type of MRI can be divided into structural and functional imaging. Structural imaging studies the anatomy of the brain and fiber connection between brain regions. The main techniques are conventional imaging, voxel-based morphometry (VBM), and diffuse tensor imaging (DTI).[26] VBM provides regions of interest for changes in brain function. DTI can analyze functional connectivity on an anatomical basis. fMRI studies brain functional activities via monitoring alterations in cerebral blood flow. There are two main subcategories for fMRI. The first and most widely available is called the blood oxygenation level-dependent (BOLD) technique. It reflects variations in the deoxyhemoglobin content and changes in the local cerebral blood flow.[26] To obtain normal neuron function, a stable level of oxygen supplied by hemoglobin is needed. In the magnetic field, deoxyhemoglobin exhibits paramagnetism while oxyhemoglobin exhibits diamagnetism. The difference in susceptibility between both types can be obtained by BOLD fMRI.[33] Upon neuron excitation, oxygen consumption increases with a concomitant decrease in blood oxygen content. This will be associated with a downward initial tilt angle of the BOLD signal. When blood flow increases, there will be a compensatory-associated increase in the oxygen level, and this will let the BOLD signal go up again. When neuron excitation stops and the need for oxygen is decreased, a negative signal will be recorded on BOLD and will eventually return to normal. Two types of fMRI exist; the first is task-state fMRI, which is the traditional way to study the activation of brain regions in NP. Task-state fMRI is a suitable tool for studying allodynia, where non-noxious stimuli can cause pain, causing misreading of somatosensory information. In allodynia, task-state studies BOLD activation/deactivation in the functionally related areas of the brain and can reveal functional connectivity of different brain regions by comparing the states of the pain stimulation of the ipsilateral part of the body to the contralateral part.[34] The second type is resting-state fMRI, which emerged in the past ten years as an alternative way to recognize regions of neuronal activity by estimating the functional connectivity in the brain. This type collects data in the relaxing state, with the exclusion of external stimuli. The obtained information reflects the baseline activities of the central nervous system in the resting state, which could use more than fifty percent of the total energy of the cerebrum with a spatial pattern called the resting brain functional network, which is based on the functional integration of several brain areas. This pattern is influenced by NP, and advances in understanding its influence could improve the management of NP.[35] Berger et al.[36] showed that resting-state fMRI proved the association of the components of the limbic system—amygdala, striatum, hippocampus, medial prefrontal cortex—with NP. Functional connectivity is a good estimate of signal correlations of activation of brain voxels. Changes in the activation-resting state could reveal a specific pattern for NP.[26]

VBM

VBM analyzes MR images at the voxel level. VBM accurately displays morphological changes of the brain through quantitative calculation of the volume and density changes in local gray and white matter. In NP, there is variation in the density of gray matter and change in the plasticity of the brain cortex. VBM can help estimate the length of disease and pain intensity in NP.[37] For example, it was found that in patients with postherpetic neuralgia, there was increased volume in the gray matter of the temporal lobe and cerebellum. In contrast, the parietal lobe, frontal lobe, and occipital lobes showed a reduction in their volume. [38]

DTI

DTI is based on estimating the direction of water diffusion. This is achieved by considering that diffusion of water is more restricted across axonal membranes than the long axis. Significant anatomical changes have been detected with DTI in different brain regions in patients with NP.[32] There is a current solid scientific belief that the human brain is composed of a complex and efficient network.[26] The white matter fiber bundle is responsible for the connection of the nodes of the network for transforming information in the brain. Damage to these bundles will affect information

transmission and cause pain/disease manifestations. DTI is the ideal noninvasive imaging tool for tracking white matter fiber bundles, thus reflecting the dispersion characteristics of water in white matter fibers and revealing the connection state of the brain network.[26]

fMRI in NP types

Primary trigeminal neuralgia occurs as a result of neurovascular compression. This can be studied by DTI, 3D TOF-MRA, and 3D FIESTA sequences, which show the anatomical relationship between arteries, veins, and nerves.[39,40] Task-state fMRI helped in studying cortical remodeling found in patients with phantom pain after amputation.[41] In diabetic peripheral neuropathy, functional-weakened connections were found between the medial dorsal nucleus, ventral posterior nucleus, and cerebral cortex.[42] In fibromyalgia, a weakened connection was found between the insula and thalamus.[43] Also, in patients with postherpetic neuralgia, there is a change in the microstructure integrity of the white matter in several brain regions.[44] Thus, advanced fMRI with the help of machine learning techniques could be used as imaging markers to diagnose NP.

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