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Editor's comment: Non motor symptoms are increasingly recognized to be of clinical importance for Parkinson's disease (PD). Pain is a universal symptom associated with almost every medical condition. Pain in PD is complex as the symptom can be multifactorial in origin. In this article, Fil and colleagues conducted a detailed literature review of published literature on the possible mechanisms, classifications, evaluation and potential risk factors of pain in PD. In the review, the authors highlight the limitations of published studies and the difficulties in drawing guidelines and conclusions as there are significant methodological differences among published studies. This important review draws our attention to the need for a concerted effort to conduct a multicenter evaluation with similar standardized protocols so that possible mechanisms for pain in PD could be better understood, and risk factors could be identified early to enable more optimized management of this disabling problem.

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Review

Pain in Parkinson disease: A review of the literature *[Universally Available]*

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ABSTRACT

Parkinson's disease (PD) is a degenerative neurological disease presenting with motor and non-motor signs and symptoms. Approximately 30–50% of the patients experience pain. There is no consensus regarding the mechanisms and classification of pain in PD. This paper reviews current data on the possible mechanisms, classifications, evaluation and potential risk factors for pain in PD. Literature searches were performed to identify clinical trials and reviews covering patho-physiology, classification, type, evaluation and risk factors associated with pain in PD. Pain in PD could be related to pathologic changes in the anatomic structures involved in nociceptive mechanisms. Studies on pain mechanisms have been mostly conducted in animals. The mechanism of pain is complicated and influenced by different factors. There are several methodological differences between the studies trying to classify pain and to characterize its subtypes. Potential risk factors for pain in PD include: age, gender, and duration of the disease. Although pain is one of the non-motor symptoms most frequency experienced by patients, it is often under recognized and inadequately treated in contrast to motor symptoms Multicenter studies are needed that include a large cohort of subjects evaluated in multiple dimensions including pain in order to obtain more data and to allow improved management of pain in patients with PD.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by loss of nigrostriatal dopaminergic pathways [1]. Its prevalence in the general population is 0.1–0.3% [2], showing an increase in individuals aged ≥ 65 years [3]. Cardinal findings in PD are tremor, rigidity, akinesia (i.e., bradykinesia, hypokinesia) and postural instability. In addition to motor

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disturbances, non-motor signs and symptoms are also common in these patients. These symptoms are classified as autonomic, i.e., hyperhidrosis, orthostatic hypotension, sexual-urinary dysfunction, thermoregulation changes, cardiovascular disturbances, peripheral edema, dilated pupillae), sleep disturbances, neuropsychiatric problems, i.e., apathy, fatigue, anhedonia, depression, anxiety, panic attacks, dementia, psychosis, and sensory, i.e., internal tremor, restless leg syndrome, numbness, paresthesia, visual disturbances, and pain [4–7]. Among these sensory symptoms, pain is observed in approximately 30–50% of PD patients; however, the incidence can increase to 68–85% when all types of pain are taken into account [8]. Pain can appear at any time during the disease, and can be present before diagnosis [9]. There is no consensus on the classification and the mechanisms of pain in PD patients. The objective of this review is to review the available data on the possible mechanisms, classification, evaluation and potential risk factors for pain in individuals with PD.

2. Methods

2.1. Data sources

We performed computerized English language literature searches to identify clinical and controlled trials and reviews of pain in patients with PD making use of the following databases: PubMed (from 1975), Ovid MEDLINE (from 1975), Ovid EMBASE (from 1975), Cochrane Database of Systematic Reviews (CDSR), Cochrane Collaboration Trials Register (CCTR), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PEDro (Physiotherapy Evidence Database).

We used the following Medical Subject Headings (MeSH) and main key words for searches: classification, patho-physiology, assessment, risk factors, Parkinson disease or pain. The search was supervised by a librarian scientist who helped us during each stage of the search. When database facilities allowed search limits, searches were restricted to clinical or controlled trials. We also reviewed the reference lists of the papers that we identified during the searches. Two authors independently reviewed the selected articles. Published proceedings and abstracts were excluded.

2.2. Data-extraction

As with article selection, data from each study were extracted independently by 2 authors. A standardized data-extraction form containing questions on population, methodology, results, and outcome measures was used according to the Consolidated Standards of Reporting Trials (CONSORT) statement. For each selected article, the following data were recorded: inclusion–exclusion criteria, design, description of study subject attrition and subject/investigator blinding, outcome measures, and results. Finally, both authors had to achieve a consensus on each item on the data-extraction form. In case of no consensus, a third author helps in the decision.

3. Results

3.1. Patho-physiology of pain and Parkinson's disease

In 1986, pain was defined as a sensory and emotional experience associated with real or potential injuries or described in terms of such injuries, by the International Association for the Study of Pain (IASP) [10]. It is known that several anatomic structures are involved at the same time in nociception. The process leading to pain starts with the stimulation of nociceptors. The thinly myelinated Aδ nociceptors response to mechanical and thermal stimuli, while the un-myelinated C-fiber nociceptors (polymodal) usually respond to mechanical, thermal, or chemical stimulation. The stimuli from nociceptors arrive to the dorsal horn neurons of the spinal cord. The lamina II, also known as *substantia gelatinosa*, plays a major role in pain modulation at the spinal cord [10,11]. This area forms an intermediate system regulating the transmission to the t-cells on the lamina V, which in turn mediates the transmission of sensory stimuli to the brain. The *substantia gelatinosa* system acts as an inhibitory mechanism on the t-cells. Stimulation of the Aδ and C fibers inhibits the *substantia gelatinosa* cells, reducing the output and their inhibitory action on the t-cells. As a result, the t-cells increase their activity. The result is a reduction in the capacity of t-cells to receive the stimuli or react to them. This is, essentially, the gate-theory mechanism at the spinal level [12].

Two phylogenetically distinct systems, the medial and lateral pain systems, transmit pain to higher center brain neurons. The medial system is mainly constituted of paleospinothalamic, spinomesencephalic, spinoreticular, spinoparabrachial hypothalamic and spinothalamic tract fibers. These fibers travel in a caudal and rostral direction to higher centers by terminating in the parabrachial nucleus, the locus cæruleus (reticular formation), the periaqueductal gray substance (mesencephalon), intra-laminar and medial thalamic nuclei, thalamic ventral caudal parvocellular nucleus and ventral caudal portae, the insula, parietal operculum, the secondary somatosensory cortex, the amygdale and hippocampus (Fig. 1). The medial system is involved in the affective and cognitive-evaluative dimension of pain, pain memory, and autonomic responses. Similarly, the lateral system is formed by the neospinothalamic, the neotrigeminothalamic, and the cervical bundle and the beam of the dorsal horn. In the higher centers, these fibers terminate in the lateral thalamus, the primary and secondary somatosensory areas, the parietal operculum and the insula (Fig. 1). The lateral system is important for the sensory-discriminative component of pain since it provides information about pain localization and duration [10,11,13,14].

The descending pathways originating in the brain stem and cerebral structures also play an important role in the integration and modulation of nociceptive information in the dorsal horn. The serotonergic, noradrenergic and dopaminergic networks are the principal components of these descending pain mechanisms. The sensitivity of the dorsal horn neurons can be increased or decreased by these pathways [11].

PD, as a multifocal degenerative and progressive disease, could affect the pain process at multiple levels, from the transmission of the pain from peripheral structures to the higher centers, to its reception and interpretation as well as interfering with several anatomic structures involved in pain mechanism. In a study with PD patients, Nolano et al. showed that significant losses occur at the level of free nerve endings and encapsulated nerve endings (i.e., Meissner's corpuscles), independently of age or disease duration [15]. They indicated that these changes in receptor size and peripheral deafferentation could play a relevant role in the pathogenesis of the sensory dysfunction of PD [15]. Starting in early stage PD, degenerative changes can also occur in the spinal cord. Certain neuronal losses have been observed in Lamina I of the posterior spinal horn [16].

Braak et al. divided the disease into 6 periods [17,18]. The changes typical of the pre-motor period start in the olfactory bulb and progress toward the inferior brain stem area (including the medulla oblongata and pontine tegmentum) of Lewy neurites and Lewy bodies (period 1–2). In the following symptomatic periods, pathologic changes take place in the mid brain including the substantia nigra (period 3), the meso-cortex (period 4), and finally the neo-cortex (periods 5–6) [17,18]. Nociceptive information cannot be transmitted directly from the spinal cord to higher centers [19,20], since it is modulated by the descending pathways involving various brain stem nuclei. Some of these nuclei are affected early in PD [21]. As a result, this classification into 6 periods can be helpful for understanding those changes taking place in the anatomical structures of the pain related higher centers during the course of PD.

When examining the brain stem in PD, it is observed that rostromedial medulla, comprising the nucleus raphe magnus and gigantocellular reticular nucleus, starts to be affected in period 2 of PD. This area is important for its role in the descending regulation of pain since it is the last station of the descending anti-nociceptive