How to diagnose parkinsonian central pain?

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Abstract

Among the different types of pain observed in Parkinson's disease, parkinsonian central pain (PCP) has the highest severity, and is poorly characterized and difficult to describe not only by patients but also by neurologists. Thus PCP remains not strictly defined and is difficult to distinguish from other types of pain on the basis of clinical description. Yet, standardizing PCP diagnosis is critical to improve the treatment of this debilitating pain subtype, but also to homogenize further studies investigating the pathophysiological mechanisms underlying this condition.

Accounting for the lack of reliable validated positive clinical criteria for PCP, and as the clinical features of PCP are difficult to specify, we suggest to consider so far the gold standard diagnosis of PCP mainly based on exclusion criteria. We propose a new algorithm aiming to disentangle PCP from other chronic pain subtypes in Parkinson's disease, by sequentially ruling out what PCP is not.

Introduction

Pain is one of the most invalidating non motor symptoms in Parkinson's disease (PD) and has a strong impact on patients quality of life, sometimes exceeding that of motor symptoms.[1] However pain in Parkinson's disease remains insufficiently diagnosed and treated. It has been reported in 40 to 85% of PD patients,[1–4] and different pain types may coexist in PD. The first recognized classification of pain in PD defined 5 subtypes: musculoskeletal, radicular/peripheral neuropathy, dystonic, central pain and akathisia.[3] Among the different types of pain observed in PD, parkinsonian central pain (PCP) has the highest severity,[5] and is poorly characterized and difficult to describe not only by patients but also by neurologists (e.g burning, tingling, bizarre, unexplained, ineffable sensation). Thus PCP remains not strictly defined and is difficult to disentangle from other types of pain on the basis of clinical description. Gold standard criteria for the diagnosis of PCP are still lacking.

Chronic pain subtypes in PD: prior classifications and scales

Before the classification proposed by Ford,[8] pain in PD was mainly categorized into different subtypes depending on its response to dopaminergic treatment, on the moment of its occurrence during the progression of the disease, and on its relation with motor fluctuations or dyskinesia.[6] Thereafter, it was also proposed to classify painful phenomena depending on their relationship with PD (i.e. "not related to PD" or "related to PD"), the last category being categorized into "directly related" or "not directly related" to PD.[4,7]

Increasing knowledge regarding the mechanisms of pain led to the emergence of more precise classifications,[2,8,9] with a pathophysiological approach defining nociceptive, neuropathic, and miscellaneous sources of chronic pain in PD.[9] Recently, the King's PD Pain Scale (KPPS) has been validated to assess pain specifically in PD.[10] This scale includes 14 items, allowing a rating of the severity and frequency of painful symptoms, covering 7 main domains. However these different domains are not specific, may be common to different subtypes of pain and do not allow a pathophysiological classification of pain. Thus, this scale is suggested, but not recommended, for syndromic classification of pain by the Movement disorders society (MDS).[11] Another study has proposed an original questionnaire for pain assessment in PD (Marburg - Sao - Paulo - Créteil Questionnaire for Pain in Parkinson's Disease) but does not include central pain.[12]

The prevalence rates of the different pain types in PD are heterogeneous among studies, in particular for PCP. For instance, musculoskeletal pain has been observed in 70% of PD Patients, while 40% described dystonic pain, 20% radicular-neuropathic and 10% central pain.[2] Yet in other studies, the prevalence of central pain was reported as 4.5%,[13] or 22%[14] and up to 27% in a recent UK study.[1] Moreover, PCP is probably underestimated because the diagnostic criteria are not well defined and overlap with those of other pain subtypes especially with the musculoskeletal one.

Difficulties to define PCP:

The definition of PCP in the classifications varies and fails to be precise: it is sometimes called “central or primary pain”[8] and described as a burning, tingling, formication, “neuropathic” sensation, often relentness and bizarre in quality, not confined to root or

nerve territory. It may have a dysautonomic character, with visceral sensations or dyspnea, and may vary in parallel with the medication cycle as a non-motor fluctuation. It is not explained by rigidity, dystonia, musculoskeletal or internal organs lesions.[8] PCP has also been defined as central neuropathic pain[2,9] (distinct from radicular neuropathic pain) and described as boring, constant, ineffable and poorly localized, not limited to a dermatome or specific neural distribution.[2] It has been reported to be intermittent or persistent, characterized as diffuse, aching, burning or cramping, to be bilateral or predominate on the side where motor symptoms first occurred, or to be situated outside the area of prominent motor symptoms such as in genital or oral areas.[9] In clinical studies, positive criteria for PCP are generally used but they are different depending on studies, and poorly defined.[2,8–10]

Based on a recent systematic review and recommendation by MDS,[11] among scales proposed for syndromic classification, which could potentially allow the identification of central pain in PD, (i.e. DN4 (douleur neuropathique en 4 questions), KPPS, LANSS (Leeds assessment of neuropathic symptoms and signs), and Pain Detect)), only one is recommended with caution (DN4) while the others are only suggested. To date, there is no validated scale for the specific diagnosis of PCP.

In the KPPS, there is no domain specifically referring to PCP, but several scattered items: item 1 of domain 2 “chronic pain”: “does the patient experience pain within the body? (generalized, constant, dull, aching pain-central pain)?”, item 6 of domain 3 “fluctuation related pain”: “does the patient experience generalised “off” period pain (in the whole body or areas distant to dystonia)?”, and Domain 5: “oro-facial pain”. Thus, in clinical practice, these classifications remains difficult to apply, mainly because of a semiological overlap between different subtypes of pain, and the identification of a specific pain such

as PCP is uneasy, probably leading to an insufficient or inaccurate diagnosis and treatment of central pain in PD.[5]

Pathophysiology of PCP

Most of the studies assessing the pathophysiology of pain in PD, do not distinguish central pain from other pain subtypes, and when doing so, the criteria for central pain may vary, putatively leading to heterogeneous populations and results. Therefore, the identification of PCP in PD is of major interest to allow a better understanding of the mechanisms sustaining this incapacitating type of pain, but also in order to target specific treatments for these subjects with PCP among "PD patients with various chronic pain".

Differences between pain subtypes in PD are attributable to varying peripheral mechanisms (peripheral neuropathic pain), to the role of motor symptoms causing or amplifying pain (nociceptive pain) and to the role of PD pathophysiology in pain processing (central pain).[9] Two main mechanisms have been proposed to account for the pathogenesis of central pain in PD: one is a diminished activity of the descending inhibitory control system,[15] the other is based on dopaminergic pathways involving the basal ganglia and the lateral (discriminatory dimension of pain) and medial (autonomic, affective and cognitive dimensions) pain pathways.[16]

Both spinal and cerebral components of pain perception could be affected in PD. Abnormal pain processing in PD is suggested by several lines of evidence. First, neuroanatomical findings reveal close connections between striatum and several structures of the pain matrix (both discriminative-sensory and motivational-affective pathways).[17] Second, reduced pain thresholds were shown in experimental animals model of PD.[18] In addition, PD patients also presented decreased pain thresholds to

various stimuli, improved under Levodopa and after deep brain stimulation of the subthalamic nuclei.[19–22.] Recently, two meta-analyses have confirmed the increase in pain perception in PD patients.[23,24] Third, studies have shown central mechanisms to abnormal pain processing such as abnormal pain induced cerebral activations in the two pathways of pain matrix using functional neuroimaging[20,25] and such as abnormal nociceptive withdrawal reflex[19] and laser evoked potentials.[26]

Regarding the specific subtype of PD patients with central pain, it was found using quantitative sensory testing that they exhibit lower heat pain and laser pinprick thresholds, higher Laser Evoked Potentials amplitudes compared to PD without pain or control subjects.[25,26] These abnormalities are attenuated by levodopa suggesting that the dysfunction occurs in dopamine-dependant pathways regulating inhibitory modulation of pain inputs. Using functional neuroimaging, when comparing PD patients with and without central pain, the medial affective pathway is reported to be preferentially recruited in those with central pain whereas a greater activation of the lateral discriminative pathways is observed in pain free PD patients suggesting an imbalance between the two pain systems in PCP.[25] Thus, the pathophysiology of PCP appears to be related to a dysfunction of the integrative processes of pain, resulting from central dopaminergic deficit. Yet, the lack of a clear definition of PCP is a limiting factor for pathophysiological studies aiming to improve our comprehension of this specific pain subtype.

Toward a better PCP identification

Very recently a new classification of chronic pain into nociceptive, neuropathic and nociplastic pain has been proposed in the general population.[27] These three types of

pain can be observed in PD and are considered either specific or unspecific to PD.[2–4,7,10,13]

In keeping with this recent classification, we propose to classify the different types of pain in Parkinson's disease according to their potential mechanisms (**Table 1**).

Pain unspecific to PD is defined as a manifestation related to other conditions. This includes musculoskeletal pain (characterized by pain in one or two joints maximum (including lumbar and/or cervical area), increased by physical activity or movement, possibly associated with local modifications of the joint (swelling, heat or redness)); radicular pain (pain in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment); and restless legs syndrome (uncomfortable and unpleasant sensations in the legs associated with an urge to move the legs).

These unspecific pain subtypes can be potentially worsened in PD due to central factors. First, central sensitization may contribute to many chronic pain conditions including musculoskeletal pain.[28] Neuroplastic changes at the central nervous system level may occur in patients with chronic pain, independently of PD, resulting in higher pain severity than what would be expected from musculoskeletal lesions. Second, even PD patients without pain have reduced pain thresolds,[19–21] suggesting enhanced pain perception.. Nevertheless, in PD patients with unspecific pain, these central mechanisms are not the core mechanism of pain and remain secondary as compared to PCP.

Conversely, pain specific to PD can be characterized by the presence of a chronological link (pain occurring at the onset of PD or influenced by motor condition, mainly during off period), a topographical link (pain located in the half of the body most severely affected by PD) and the lack of other evident painful condition (rheumatic, traumatic or orthopaedic disorders). Pain specific to PD includes two subtypes:[2,13] dystonic pain (twisting movement and posture, muscular contraction very forceful and painful)

corresponding to nociceptive process; and central–pain resulting from dysfunction of pain processing despite no evidence of actual or potential tissue damage nor lesion of the somatosensory system (i.e. “nociplastic”)

From this new proposed classification, we suggest an algorithm aiming to disentangle PCP from other chronic pain subtypes in PD by specifically and sequentially ruling out what is not PCP (e.g pains unspecific to PD and not related to dystonia) (**Figure 1**). Hereby, we currently propose to consider the diagnosis of PCP mainly with exclusion criteria that would so far constitute the gold standard. PCP may be defined as a chronic pain observed in PD that is not unspecific to PD (musculoskeletal, radicular or RLS), nor dystonic pain.

Nevertheless, our classification presents some limitations: first, it may lack specificity and complementary investigations (electrophysiology or imaging) may be judged necessary by clinicians for some patients to totally rule out the possibility of other pain subtypes in PD. Yet, we aim here to propose practical clinical algorithm that can be used in clinical routine to help distinguish different pain subtypes in PD, and better identify PCP

Also, it remains unclear whether parkinsonian rigidity itself without any dystonic component could lead to a nociceptive pain specific to PD. It could be argued that rigidity, cramp and dystonia could be a painful continuum. Yet, if rigidity is painful, then akinetorigid syndrome defining clinically PD would always be painful as a part of the definition, which is not the case. Furthermore there is no reported relation between the severity of rigidity and the severity of pain experienced by PD patients.

We voluntary chose not to include in our definition of PCP the response to dopaminergic treatment as it seems to be inconstant and cannot be used as a discriminatory criterion. Indeed, pain unspecific to PD can be partly improved by dopaminergic agents as they can be worsened by parkinsonism. Furthermore, pain specific to PD can be improved in a variable way (dystonia can be improved (off dystonia) but sometimes worsened (on dystonia) by dopatherapy. Finally, the effects of dopaminergic drugs have not yet been specifically evaluated in Parkinsonian central pain.

Conclusion

Hereby, accounting for the lack of reliable validated positive clinical criteria for PCP, and as the clinical features of PCP are difficult to specify, the better way to standardise PCP diagnosis so far remains a diagnosis of exclusion. Whether the diagnosis of PCP may also rely on positive criteria based on specific symptoms and signs remains to be determined with further studies.

TABLES AND FIGURE LEGENDS

Table 1**: **Classification of chronic pain in PD

***Figure 1**: **Proposed algorithm for subtypes identification and classification of chronic pain in Parkinson's disease (PD)**. Pain unspecific to PD: manifestation related to other conditions, but potentially worsened by PD; Pain specific to PD: can be characterized by the presence of a chronological link or a topographical link with PD, and the lack of other evident painful condition.*

AUTHORS' ROLES

AM and CBC contributed to conception and writing of the first draft of the viewpoint.
NA, DB, XM, NC, FD contributed to conception and review and critique of the viewpoint

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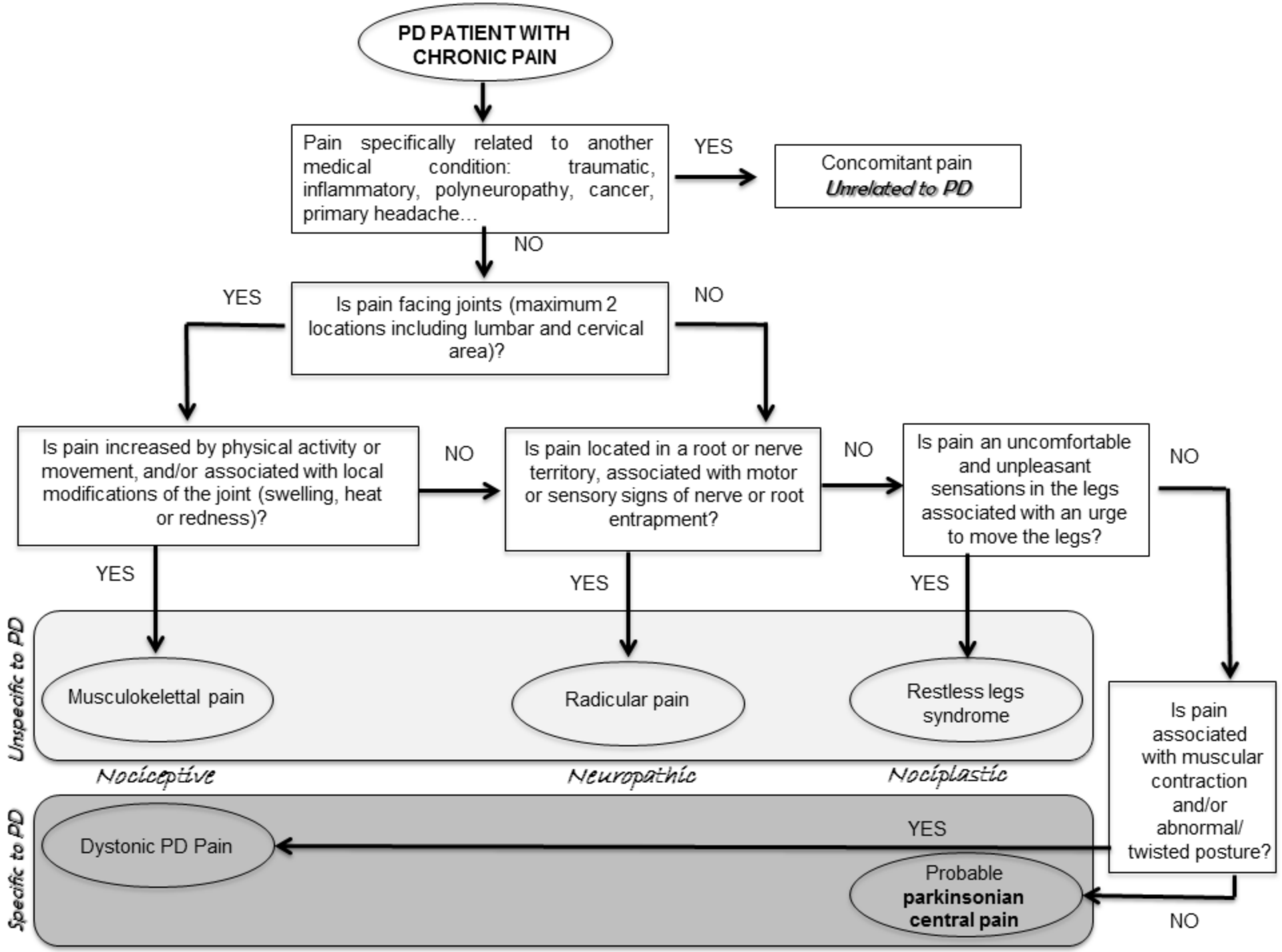
PD PATIENT WITH CHRONIC PAIN
Pain specifically related to another medical condition: traumatic, inflammatory, polyneuropathy, cancer, primary headache…
YES
Concomitant pain Unrelated to PD
NO
Is pain facing joints (maximum 2 locations including lumbar and cervical area)?
YES
NO
Is pain increased by physical activity or movement, and/or associated with local modifications of the joint (swelling, heat or redness)?
NO
Is pain located in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment?
NO
Is pain an uncomfortable and unpleasant sensations in the legs associated with an urge to move the legs?
NO
YES
YES
YES
Unspecific to PD
Musculokelettal pain
Radicular pain
Restless legs syndrome
Nociceptive
Neuropathic
Nociplastic
Is pain associated with muscular contraction and/or abnormal/ twisted posture?
YES
Specific to PD
Dystonic PD Pain
Probable parkinsonian central pain
NO

CHRONIC PAIN	Nociceptive	Neuropathic	Nociplastic
Unspecific to PD	**Musculoskeletal pain**	**Radicular pain**	**Restless leg syndrome**
Specific to PD	**Dystonic pain**	_	**Central pain**

***Table 1**: Classification of chronic pain in PD*