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Non motor subtypes and Parkinson's disease

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ABSTRACT

Non motor symptoms (NMS) represent a significant burden in Parkinson's disease (PD) with numerous studies highlighting the importance of NMS both in "pre-motor" phase of PD as well as throughout the course of disease. In part this has led the international Parkinson and Movement Disorder Society (IPMDS) task force to attempt a re-definition of PD incorporating NMS and not base the diagnosis solely on motor symptoms. While motor subtypes within PD have been recognized and researched, recent clinical and neurobiological research suggests the existence of discrete non motor subtypes in PD, particularly in untreated (drug naïve) and early PD patients. Several independent observers have reported specific "clusters of NMS dominant PD" using a data driven approach in early and untreated PD patients while others have reported on the burden of NMS in untreated PD and specific NMS dominant phenotypes in untreated or treated PD using observational case series based data. In this review we report on specific NMS dominant phenotypes of PD as described in the literature using clinical observational studies and address pathophysiological concepts. A proposal for several NMS subtypes are reported combining clinical reports with, where possible, evidence base supporting probable biomarkers.

1. Introduction

1.1. Why non motor subtypes?

Motor symptoms of Parkinson's disease (PD) such as tremor, bradykinesia and rigidity are the hallmark based on which diagnosis and treatment are started and are now known to be preceded by the "pre-motor" phase of PD largely dominated by a range of different non motor symptoms (NMS) [1–3].

Virtually every PD patient has NMS, which are now widely recognized as an important unmet need in PD [3] and a major determinant of health related quality of life (HrQoL) of patients with PD and their carers [4]. In a survey by Parkinson's UK, patients listed NMS such as pain, sleep disorders and anxiety ahead of motor problems in clinical importance, and two further studies have outlined the key impact of NMS as declared by patients themselves [3,32].

Despite this importance, little has been done to establish NMS clinical phenotypes in the context of the multi-morbid PD patient even though several workers have reported clinical phenotypes driven by specific NMS such as pain, cognitive problems, apathy and sleep dysfunction. Additionally, cluster analysis from several large early and untreated PD cohorts have all suggested specific NMS dominant or only NMS driven clustering [12–14]. This review aims to highlight these phenotypic variants that have been described within the rubric of Parkinson's disease.

1.2. Pathophysiological basis of nonmotor subtypes in Parkinson's disease

NMS based subtyping of PD is plausible from a clinical point of view that in some PD patients, but not all, specific NMS are predominantly expressed, while in others NMS may not be evident or are less relevant. The clinical expression of a range of NMS highlights the fact that the phenotype of PD results from varying rates of Lewy body deposition and neurodegeneration in PD and represents the effects of widespread brain and peripheral Lewy body pathology instead of a single neural structure affected or the loss of the monoamine neurotransmitter such as dopamine [3,5]. This convergence of deficits in multiple transmitter systems and

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pathways, including the cholinergic, noradrenergic, and serotonergic systems, may all be associated with clinical expression of NMS. In addition, glial pathology, neuroimmune responses, and proinflammatory cytokines may also play a key pathogenic role adding to the heterogeneity of PD [5,6]. Furthermore, non-dopaminergic areas in the brainstem may be affected and involved ahead of dopaminergic involvement as recently reviewed by Todorova et al. [3,5–7]. Jellinger has suggested that neuropathological spread of the neurodegenerative process may be initiated via the olfactory bulb and thereafter through the limbic or brainstem areas while spread via the enteric nervous system via the nervus vagus has also been suggested [5–8]. A limbic, brainstem and cortical dominant pathophysiological process as proposed by Braak et al. [11], Jellinger et al. [5], Beach et al. [9] or Halliday et al. [7] is the basis of our proposal as shown in Fig. 1. All of these processes would lead to dominant expression of NMS over motor symptoms as also underpinned by the Braak hypothesis of α-synuclein accumulation starting in the lower brainstem and the olfactory bundle well before there is significant involvement of substantia nigra [11].

NMS subtyping is thus based on the evidence that early and substantial neuronal loss occurs in many non-dopaminergic nuclei in the limbic and brainstem areas, either before or concomitantly with involvement of dopaminergic projections [5,9,10]. The dorsal motor nucleus of the vagus (DMV) is a key area for control of autonomic signaling responsible for symptoms such as constipation. Neuronal loss in the DMV could be as profound as that in the substantia nigra (SN), and large (43–57% loss) cholinergic and substance P expressing neurons are preferentially lost while tyrosine hydroxylase neurons may be relatively spared in PD [5,10].

A further contributor in the pathophysiology of non motor subtypes within PD is the age of onset of PD. Preferential Lewy body deposition in the brainstem in young onset PD versus a cortical dominant pathology in late onset PD has been described, the latter being associated with Alzheimer's disease type pathology [7,11].

It is likely therefore, in these subjects patterns of NMS, dependent on relevant neuropathological involvement of non-dopaminergic areas, will underpin the clinical expression of specific NMS such as sleep problems, apathy, pain, depression/anxiety, ahead of and dominating the typical motor deficit of PD.

1.3. Evidence from studies in untreated PD

Untreated PD patients represent a suitable model to study the expression of NMS in comparison to motor symptoms. Erro et al. have conducted a cluster analysis coupled with validated cognitive, motor and nonmotor assessments in a untreated PD cohort and found 4 discrete clusters within the cohort termed benign pure motor, benign mixed motor-non-motor, nonmotor dominant and motor dominant [12]. The non motor dominant cluster reported higher urinary dysfuction and a rapid progression rate compared to the benign mixed motor, nonmotor cluster.

In the recently reported ONSET-PD study, the authors highlighted specific non motor clusters of PD ranging from cognitive and mood clusters to sensory, RBD dominant and autonomic dysfunction related cluster further supporting our attempt of NM subtying of PD [13]. Studies have also identified specific clinical phenotypes in untreated PD underpinned by NMS such as sleep dysfunction, cognitive and neurosychiatric disturbances (depression, apathy), fatigue, dysautonomia, pain and olfaction recently reviewed by Zis et al. [14]. These observations fit well with the neuropathological studies, which have suggested a differential rate of neuronal degeneration and Lewy body deposition in the non-dopaminergic brainstem and limbic areas in PD, with consequent expression of a variety of related NMS.

2. The literature descriptions of specific NMS dominant subtypes of PD

A proposal of at least six different NMS dominant clinical phenotypes within PD mainly in early and untreated phase has been proposed based on clinical observation and in this review we discuss the patterns that have been reported and published so far [15].

2.1. Park cognitive

The Park cognitive subtype predominantly presents with cognitive impairment even at an early stage.

Neuropathologically, this subgroup may represent the late onset pattern of Lewy body deposition [7]. The patients are likely to present with mild cognitive impairment (MCI), which may progress to frank dementia (Fig. 1). The condition overlaps clinically with dementia with Lewy bodies (particularly when there is fluctuating cognitive state however, Park cognitive shows sustained levodopa responsiveness) and Alzheimer's disease. The use of thioflavin ligand based positron emission tomography (PET) scans, amyloid scans, cholinergic imaging or cortical thinning (functional MRI) may help to further refine the clinical classification [16].

Early dementia – probably reflecting a high cortical Lewy body load, occurs but importantly the patients retain levodopa responsiveness in part. Clinical studies by Williams-Grey et al. suggest that in this cohort (Park cognitive) impaired semantic fluency (less than 20 words in 90 s) and inability to copy an intersecting pentagons figure are predictive of dementia [17].

Clinical differences between amnestic and non-amnestic subtypes within the PD-MCI have been reported and microtubule-associated protein tau (MAPT) H1/H1 genotype may be a molecular biomarker [17,18] (Table 1a).

2.2. Park apathy

Clinically the Park apathy subtype scores high on apathy scales, and a specific apathy dominant phenotype in untreated PD has been described (excluding the possibility of dopamine agonist withdrawal syndrome as a confounder) [19] (Table 1b). There are also high rates of cognitive impairment as well as anhedonia in these cases. Current perception suggests apathy in PD may be a dopamine responsive NMS. Clinically, some patient might present with severe apathy but mild Parkinsonism and need treatment in spite of their mild motor impairment.

2.3. Park depression/anxiety

The Park depression/anxiety phenotype might occur in late and early onset PD with both depression and anxiety and it is important to consider these symptoms in the context of motor fluctuations. This description is based on the clinical analysis of cases as reported in the Prospective Study of Mood States in Parkinson's Disease (PROMS-PD) study [20,21]. Brainstem as well as limbic involvement could be responsible (Fig. 1). The clinical protocol for the PROMS-PD study specifically addressed fluctuation related changes in depression and anxiety states to account for non motor fluctuations as well as exclusion of confounders such as generalized anxiety states or comorbid illnesses.

Three different subtypes namely anxious depressed, depressed and anxious have been described (Table 1c) and there is a correlation with cognitive impairment and an overlap with the Park cognitive phenotype.

Reduced catecholaminergic (^{11}C-RTI-32) binding has been reported in depressed versus non-depressed PD patients and reduced

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