Introduction

The non-motor manifestations of Parkinson's disease have been known since the description of the disease by James Parkinson in 1817. In his "Essay of the Shaking Palsy", he clearly stated "*sleep becomes much disturbed . . . the bowels, which had been all along torpid, in most cases demand stimulating medicines of very considerable power . . . sometimes the expulsion of feces requiring mechanical aid*" [1]. However, for years the emphasis has been on the motor features which define the disease, largely by the availability of dopaminergic and other agents which alleviate the bradykinesia and rigidity, and partly also the tremor. In fact, these drugs added new non-motor manifestations.

As seen in this book, the spectrum of non-motor features is extremely large and spans practically all body organs and functions [2]. Awareness of these can help in their prevention or treatment. In this volume we have included chapters dedicated to all of them.

It should be recognized that non-motor features of Parkinson's disease occur in all stages of the disease, may precede the appearance of the classical motor symptoms [3] and thus are challenging the diagnosis of the cause of these phenomena. Some, such as hyposmia or anosmia, may in fact serve as biomarkers, alerting the clinician to the evolving disease and allowing early initiation of neuroprotective therapy [4].

Once diagnosed with Parkinson's disease, it may become clear why patients have reported constipation, pains, loss of smell sense, erectile difficulties, depression, and sleep problems, particularly REM sleep behavior disorder (RSBD) for several years [5], in many preceding the onset of the motor symptoms. These manifestations are important for several reasons. They indicate that the neuropathology of Parkinson's disease is not limited to the nigrostriatal system or dopamine itself, and emphasize the need to develop specific therapies. For example, although depression is very common in Parkinson's disease, and in many cases affective manifestations may precede by several years the motor symptoms, we do not know what the underlying pathophysiology is and it is unclear whether there should be a specific treatment in these cases [6].

The existence of these pre-motor manifestations shows the heterogeneous phenotypic expression of the disease, which will continue in the more advanced stages. In addition, they may help in the early diagnosis of the disease. We still do not know the exact sensitivities and specificities for each of them, however RSBD and hyposmia have proven to have a stronger correlation as predictors of the disease than others [7]. As such, there are increasing attempts to develop and validate clinical biomarkers which can diagnose Parkinson's disease at an early stage. This will be particularly relevant once a disease-modifying therapy is developed, as ideally these should be used early for a diagnosis, if we are to change the natural history of the disease.

A special case is cognitive impairment. As the frequency of dementia increases gradually over the years in patients with Parkinson's disease, many will become demented, placing a huge burden on the patients themselves, caregivers and healthcare services. The cognitive decline may begin at any time in the neurodegenerative process, before or after the onset of motor symptoms. Patients in whom the onset of the cognitive impairment begins prior to the motor symptoms have been termed Dementia with Lewy bodies, but there is nothing known about the underlying mechanisms that cause the early α-synucleinopathy deposition in the cortex and particularly in the limbic system [8].

Thus there is still a long way to go in deciphering the underlying mechanisms of Parkinson's disease and finding interventions to alleviate the associated suffering. We hope that this volume will help in addressing these issues.

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