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The Clinical Definition of Parkinson's Disease —Time for a Change?

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Ever since the seminal description by James Parkinson almost 200 years ago the clinical definition of Parkinson's Disease (PD) is anchored on the presence of motor symptoms. The internationally most widely used UK Brain Bank Criteria require the presence of bradykinesia plus at least one additional feature of tremor, rigidity or deficient postural reflexes for a clinical diagnosis of PD. On the other hand it is now widely acknowledged that a variety of non-motor symptoms form an integral part of the clinical spectrum of this disorder and that their first occurrence may antedate the manifestation of classical motor signs. This has been particularly well studied for REM sleep behavior disorder (RBD), but many patients also report on the presence of hyposmia, constipation as well as panic attacks and depression well before the appearance of any motor disability. Consistent with this, several epidemiological studies have shown an increased risk to develop PD in healthy subjects with hyposmia, constipation or depression.

In addition, healthy subjects with hyposmia or RBD also have an increased prevalence of subclinical abnormalities in imaging signals commonly observed in PD, including decreased striatal DAT-SPECT binding or myocardial signal loss on MIBG-SPECT as well as hyperechogenicity of the SN midbrain region upon transcranial ultrasound.

Taken together these observations not only suggest that the pathology of Parkinson's Disease starts years before the appearance of first clinical motor symptoms and likely affects extranigral structures before producing supra-threshold nigrostriatal dopaminergic dysfunction, but they also pose new challenges regarding the definition of Parkinson's Disease. A new definition of PD might eventually be able to differentiate three distinct phases of disease, where phase 1 would correspond to preclinical PD, where PD specific pathology is indicated by molecular, imaging or other markers in subjects free of any clinical symptoms. Phase 2 would correspond to "pre-motor" Parkinson's Disease where early non-motor signs are present due to supra-threshold extranigral PD pathology but classical motor signs have not yet developed, while motor PD as currently defined would mark the third phase of the evolution of PD. Such a definition would open new opportunities for defining at-risk cohorts and the earliest phases of disease and might lead to new target populations for disease-modification trials.

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