The changing concept of Parkinson’s disease

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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), where up to 60% of affected individuals may convert to clinical PD within 10 years or more. Likewise, healthy subjects with hyposmia, constipation of depression have been found to carry a two- to four-fold risk for Parkinson’s disease in population-based studies. Together with pathological observations of a stagewise progression of PD-specific synuclein pathology with involvement of olfactory or lower brain stem structures, as well as the peripheral autonomic nervous system prior to any change in the nigrostriatal dopamine projection, these observations have begun to challenge the classical diagnostic and clinical concept of Parkinson’s disease. In particular, there is reason to hypothesize that individuals without any distinctive motor features but the combined presence of hyposmia, RBD and constipation might in reality represent patients in the earliest “extranigral” stages of Parkinson’s disease. A new definition and concept of PD needs to be developed that would take into account the prominent non-motor facet of the disease as well as the distinction of a preclinical and premotor phase of the illness. What is needed for such a new concept to be successfully established is a set of biomarkers with high sensitivity and specificity for the future development of classical motor PD. Recent progress has been made in the field of genomics—imaging, tissue biopsies and proteomic/metabolism marker are an active field of study. Such concepts are needed not least to open up new opportunities for defining at-risk subjects as the future targets for neuropreventive strategies that might ultimately lead to a reduced prevalence of and morbidity from Parkinson’s disease.

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