

Updated Diagnostic Criteria for Parkinson's Disease: Implications for Clinical Trials

Idiopathic Parkinson's Disease (IPD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD). Despite its prevalence, approximately 5 to 10% of patients with IPD are misdiagnosed, and conversely, up to 20% of patients diagnosed with IPD reveal alternative diagnoses upon autopsy, such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, AD type pathology, and cerebrovascular disease. Well-established diagnostic criteria such as the UK PD Society Brain Bank criteria¹ have been in use in clinical trials for over 20 years; however, it has been suggested that an accuracy of 90% is the best that can be achieved with clinical assessment and clinical diagnostic criteria. In an effort to update these criteria to reflect our more recent understanding of IPD and increase diagnostic specificity, the Movement Disorders Society (MDS) has recently published Clinical Diagnostic Criteria for Parkinson's disease (MDS-PD), designed specifically for use in clinical research, but also as a general guide to clinical diagnosis of IPD consequent to Lewy body pathology.² In these updated criteria, motor abnormalities remain central, but there is an increasing recognition given to non-motor manifestations. As with

previous diagnostic criteria, the MDS-PD criteria utilise a two-step process for diagnoses. First, parkinsonism (defined as bradykinesia in combination with either rest tremor, rigidity or both) is required. However, this definition of parkinsonism fails to take into consideration a loss of postural reflexes, flexed posture, and freezing phenomenon. Having established that the patient has parkinsonism, the MDS-PDs created supportive and absolute exclusion criteria, as well as a red flag list that is applied to determine whether or not the patient meets criteria for IPD as the cause of their parkinsonism. There are two levels of certainty, including clinically established PD, defined as parkinsonism with at least two supportive criteria, absence of absolute exclusion criteria and no red flags, and clinically probable PD, defined as parkinsonism with no absolute exclusion criteria and presence of red flag counterbalanced by supportive criteria. Supportive criteria include: a) clear and dramatic beneficial response to dopaminergic therapy; b) presence of levodopa induced dyskinesia, c) rest tremor of limb; and d) either olfactory loss or cardiac sympathetic denervation documented by metaiodobenzylguanidine (MIBG) scintigraphy.





Two of the four supportive criteria are treatment response-related (*ex juvantibus*) taken from step 3 of UK Brain Bank Criteria, making diagnosis of IPD in early stage of disease as difficult as it was before the emergence of the MDS-PD criteria. In addition, MDS-PD criteria neglect the insidious unilateral onset progressing to bilateral, as well as a role of structural neuroimaging to rule out other basal ganglia disorders. In practice, an early IPD patient with no resting tremor can be still easily misdiagnosed using the MDS-PD criteria. Therefore, diagnostic accuracy varies considerably according to disease duration (lower on first visit than after longer follow-up), the expertise of the physician, and evolution of the understanding of IPD.² Although MDS-PD criteria were developed in an attempt to reduce diagnostic errors among clinical sites participating in clinical trials, it is likely that experienced clinicians can diagnose IPD with greater accuracy than formal diagnostic criteria.³

This is problematic as the early and accurate diagnosis of IPD is a priority in clinical trials of PD drugs and creates an urgent need for valid PD biomarkers with predictive validity for diagnosis of IPD. Until now, several non-motor clinical features have been shown to be associated with IPD risk: the combined occurrence of REM-Sleep Behaviour

Disorder (RBD) and hyposmia in otherwise asymptomatic subjects has been shown to associate with development of clinically defined IPD in substantial proportions over a relatively short time. There is increasing evidence for the existence of a clinically silent phase of IPD, with accompanying brain tissue pathological changes leading to neuronal dysfunction and cell death. This “preclinical IPD” may last for indefinite periods of time and may cause motor or non-motor symptoms that are in themselves unspecific and do not meet diagnostic criteria for IPD. This stage, called “prodromal IPD” has been recently defined by Movement Disorders Society Research Criteria,⁴ exclusively for clinical research purposes.

The criteria are based upon the likelihood of prodromal IPD defined at >80% certainty. Certainty estimates rely upon calculation of an individual’s risk of having prodromal IPD using Bayesian naive classifiers. In this methodology, a previous probability of prodromal disease is delineated based upon age. The probability of prodromal IPD is then calculated by adding diagnostic information, expressed as likelihood ratios. This diagnostic information combines estimates of background risk (environmental, genetic, etc.) and results of diagnostic marker testing. Diagnostic markers are clinical symptoms and signs, including ancillary diagnostic tests which have prospective evidence of the ability to predict clinical IPD.

Once all relevant information is obtained, each individual likelihood ratio (LR) (i.e. sex, smoking history, exposure to pesticide, olfaction, anxiety, somnolence and many others) can then be multiplied together to generate a total LR of prodromal IPD for an individual patient. This total LR is combined with baseline probability to calculate the final probability for the individual.

While the concept of MDS-research criteria prodromal IPD are promising, there are several limitations⁴ including quality of underlying data, lack of knowledge about marker’s independency and duration of the prodromal stage of disease. These criteria generally require patients to have had a relatively thorough evaluation of markers for prodromal IPD, and if information regarding markers is unavailable, it is difficult to meet the threshold for prodromal IPD. Finally it is difficult to distinguish a prodromal marker from an IPD risk marker, a limitation that is mitigated here by treating prodromal and risk markers similarly. For all of these reasons, further validation of the model will be essential.⁴

Accurate diagnosis of prodromal PD is essential to assess the many drugs claiming to have neuroprotective effects. This latent phase of neurodegeneration in IPD is of particular relevance in relation to the development of disease-modifying or neuroprotective therapies which would require intervention at the earliest stages of disease. Ideally a disease-modifying effect should be separable from a symptomatic effect. A method widely used in order to distinguish a symptomatic effect from a

neuroprotective effect is to demonstrate that the effect is maintained in the active treatment group relative to placebo after sufficient washout of the study drug at the end of the treatment period. A neuroprotective effect should be maintained, whereas a symptomatic effect would not be maintained. Several clinical trial designs have been used so far,⁵ including long-term classical parallel group design, a washout design, delayed start design, and biomarker study like REAL PET or CALM-PD-CIT study.

There are a number of obstacles that hamper the successful discovery of disease-modifying therapies. The precise cause and pathogenesis of PD are not known and there may well be more than one; indeed, the development of effective neuroprotective therapy will probably require a conceptual change, accepting the potential contribution of multiple pathogenic mechanisms and consequently, the need for combination therapies rather than the use of a single drug.⁶ A further limiting factor in the field is a lack of animal models that accurately reflect the age-related slowly progressive neurodegenerative process in humans. There are major limitations with all of the outcome measures used so far in 'neuroprotective trials'; unfortunately, none of the available clinical or imaging measures accurately assesses all aspects of the complex neurodegenerative process.⁶ Thus, a critical need for this field to successfully move forward is the development of valid and reliable biomarkers that accurately reflect both the presence and status of disease.⁷ Moreover, the slow but quite variable progression of clinical signs and symptoms, subject to different age of disease onset⁸ and the availability of very effective symptomatic therapies, also seriously complicate the assessment of efficacy of any treatment designed to slow the progression of the disease.

Much effort has been directed to the development of treatments that can stop or slow the progression of established disease. Since there is no biomarker of IPD progression, regulatory authorities are forced to accept primary endpoints based on clinical measures of parkinsonism alone, either as a change on motor UPDRS-3 or time to L-dopa+/DA-agonists.⁹ The change in UPDRS may be evaluated by a slope analysis. Extrapolation of the slope beyond the observation period requires a linear progression rate. The proposed trial duration should be sufficiently long, probably up to 24 months, but because most patients with IPD require symptomatic therapy within several months to one year of diagnosis, such studies typically should enrol only those early in the course of disease who do not require symptomatic therapy. If a delay in disease progression is shown, this does not imply that a new agent is also a disease-modifier. This requires the demonstration of an effect on the underlying pathophysiology of the disease by, e.g., biochemical markers or neuroimaging measures. Therefore, for a disease-modifying claim, a two-step procedure is foreseen; first, a delay in clinical measures of disease progression should be shown; second, an

effect on the underlying pathophysiology process which correlates to a meaningful and persistent change in clinical function.⁹

Despite the shortcomings, the MDS-PD criteria will stimulate new research into earlier stages of IPD, with the ultimate goal of designing clinical trials to test intervention for disease prevention in at-risk individuals.

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