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The new definition and diagnostic criteria of Parkinson's disease

We thank *The Lancet Neurology* for highlighting the changes in Parkinson's disease diagnosis given in the new International Parkinson Disease and Movement Disorder Society diagnostic criteria.[1] The criteria were created in response to the huge advances in our understanding of Parkinson's disease over the past 20 years, especially the identification of α-synuclein, advances in genetics, recognition of non-motor Parkinson's disease, and the realisation that prodromal stages exist. The Movement Disorder Society recognised that these advances challenge the fundamental definition of Parkinson's disease and created a task force to examine potential changes to the Parkinson's disease definition,[1] develop revised diagnostic criteria,[2] and develop research criteria for prodromal Parkinson's disease.[3] The final task force reports were recently published.[2,3] But, what has changed and what remains the same?

Several key definition decisions were made.[4] Parkinson's disease was defined as a synucleinopathy. Despite numerous challenges (rare genetic forms without synuclein deposition, synuclein deposition possibly occurring later than other changes, or inability to document deposition during life), synuclein deposition remains the main final arbiter of diagnosis. However, an exception category was created to include genetic cases (parkin, LRRK-2, etc) that meet clinical Parkinson's disease criteria but have no synuclein deposition on autopsy.

Dementia was removed as an exclusion criterion for Parkinson's disease, even if it is the first presenting symptom. Just as many non-motor features of Parkinson's disease might start before motor signs emerge, dementia might also manifest before motor onset. Patients diagnosed with dementia with Lewy bodies should be considered as also having Parkinson's disease if they meet the Movement Disorder Society Parkinson's disease criteria.

The task force recognised that Parkinson's disease is highly variable, and therefore should potentially be classified into subtypes. However, we felt that there was still insufficient information to formally delineate a specific subtype classification. Parkinson's disease was, however, divided on the basis of stage of disease into clinical Parkinson's disease (with motor parkinsonism), prodromal Parkinson's disease (motor or non-motor symptoms are present but clinical Parkinson's disease criteria has not yet been met), and preclinical Parkinson's disease (neurodegeneration present, but asymptomatic).

The new diagnostic criteria for Parkinson's disease have been published, and constitute the first Parkinson's disease diagnostic criteria of the Movement Disorder Society. Their goal was to help standardise clinical research (entry into clinical trials, etc) and to aid bedside diagnosis. Because there is not yet a reliable objective test for Parkinson's disease, expert opinion still remains the gold standard. So, the clinical criteria were designed to mimic and codify the process of an expert clinician. Several unique features bear special mention.[2] Parkinsonism remains defined as bradykinesia plus rigidity and rest tremor or both. However, postural instability is not a core feature of parkinsonism due to Parkinson's disease (because if present early, it suggests alternate causes). Also, unlike parkinsonism in general, to diagnose bradykinesia due to Parkinson's disease, some decrement in speed or amplitude is also required. Similarly to previous criteria, the Movement Disorder Society criteria combine positive features (supportive criteria) and negative features. However, good clinicians do not only check boxes; rather, they weigh the diagnostic strength of various atypical signs. Therefore, negative features were divided into absolute exclusions (which rule out probable Parkinson's disease) and red flags (which rule out probable Parkinson's disease if numerous or unopposed by supportive features). The criteria permit some flexibility, allowing individual criteria to be interpreted in the context of the whole patient, for example low-dose quetiapine does not merit exclusion for probable drug-induced parkinsonism. Timing was also incorporated because some features argue against Parkinson's disease when present in early Parkinson's disease, but are common in advanced Parkinson's disease.

Finally, to account for the long prodromal stage of Parkinson's disease and to set the stage for earlier intervention in the future, the first ever Movement Disorder Society research criteria for prodromal Parkinson's disease were proposed.[3] The criteria's approach is unique because it uses statistical methods (the Bayesian naive classifier) to estimate the likelihood that a patient has prodromal Parkinson's disease. The Bayesian model has already been used for numerous analyses of different health-related outcomes. However, to our knowledge, use of a mathematical formula to calculate probability of disease has never been incorporated into diagnostic criteria for neurological diseases. The criteria involve three steps:

1 The probability of having prodromal Parkinson's disease is estimated based on age (ie, the prior probability).
2 Diagnostic information is obtained on as many variables as possible. These can include environmental risk variables (eg, sex, smoking, caffeine use), genetic risk variables (from family history or results of genetic testing), prodromal symptoms and signs (eg, constipation, hyposmia, motor testing), or biomarker testing (eg, dopaminergic imaging). The diagnostic strength of each variable is expressed as a likelihood ratio; positive tests have a likelihood ratio of more than 1, and negative tests have a likelihood ratio of less than 1. If information is unavailable, borderline, or uncertain, the likelihood ratio is simply not applied for that test (likelihood ratio=1).
3 Once all information is collected, all likelihood ratios are multiplied by each other. The total likelihood ratio is then compared with the threshold required to give more than an 80% probability of having prodromal Parkinson's disease (this ranges from likelihood ratio 95–1000, depending on age). If this threshold is met, probable prodromal Parkinson's disease is diagnosed.

Why use this method? The essential difficulty frequently encountered when trying to predict disease likelihood is the radical differences in diagnostic accuracy of the various markers. Specificity ranges from 75–80% (depression, constipation) to 99·7% (polysomnogram-proven random eye movement sleep behaviour disorder). The Bayesian naive classifier allows systematic weighting of different diagnostic values. This approach also has the notable advantage of being evidence-based; only markers shown to predict Parkinson's disease in prospective studies with measurable diagnostic accuracy are included. Finally, the field of prodromal Parkinson's disease is still in its relative infancy; the method provides a scaffold upon which results of new diagnostic tests for prodromal Parkinson's disease can be continually added.

Because the field of Parkinson's disease is constantly evolving, diagnostic methods need to be constantly updated. The first official Movement Disorder Society clinical criteria provide a framework for a common global clinical diagnostic workup. The research criteria for prodromal Parkinson's disease will allow the systematic diagnosis of this so far prediagnostic phase. Both criteria will no doubt change as future knowledge grows.

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