Diagnosing Synucleinopathies: Will Parkinson's Disease or Dementia with Lewy Bodies Become 'Biologically' Defined?

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INTRODUCTION

Parkinson's disease (PD) is the second-most common neurodegenerative disease after Alzheimer's disease (AD), with an estimated 6.1 million people affected worldwide.[1] PD is also the fastest-growing neurodegenerative disorder, with an expected two-fold increase in prevalence over the next generation.[1,2] The pathological hallmark of both PD and the overlapping condition of dementia with Lewy bodies (DLB) is the presence of intraneuronal and axonal inclusions, called Lewy bodies and Lewy neurites, in the substantia nigra and other brain areas that contain pathological aggregates of misfolded α-synuclein as their main constituents.[3] Accordingly, both PD and DLB are classified among the synucleinopathies, which also include multiple system atrophy (MSA), where synuclein aggregates in glial cytoplasmic inclusions are a pathological hallmark.[4]

For decades, the mainstay of symptomatic therapy for motor symptoms of PD treatment has been dopamine substitution by administration of the dopamine precursor levodopa and other drugs that help maintain levels of dopamine and dopamine receptor activity in the striatum.[5] While these therapies are able to provide long-term symptomatic control, they cannot slow or prevent the progression of the underlying pathology, thus increasing disability from a progressive combination of motor and non-motor symptoms over time. For this reason, there is a pressing need to identify disease-modifying treatment strategies; however, in the past, numerous clinical trials pursuing a multitude of different drug targets to slow disease progression have failed. The identification of novel targets and non-pharmacological strategies has led to a recent surge in disease-modification efforts, with 60 trials currently listed on ClinicalTrials.gov, including investigational therapies targeting pathological α-synuclein (McFarthing et al., unpublished data).

One of the major challenges, which may have contributed to the failure of past disease-modifying trials, is related to the timing of intervention. Current clinical diagnostic criteria for PD require the presence of cardinal motor features of the disease, but there is ample evidence to suggest that the underlying pathological events may start many years prior to the full expression of PD motor symptoms.[6] There is justifiable concern that the start of disease-modifying interventions after PD motor symptoms are fully established may correspond to a relatively late time point on the trajectory of progressive PD pathology, and thus may have a reduced likelihood of success. Intervening at the earliest stages of the biological processes driving PD pathology would require diagnostic criteria that are anchored on reliable biomarkers of disease, potentially even enabling the identification of pre-clinical disease in asymptomatic subjects. The concept of a 'biological' definition of disease independent of the presence of defining clinical features has been pioneered by the Alzheimer's field by developing a framework of biomarkers for Abeta- and tau-pathology, and imaging evidence for neurodegenerative brain changes.[7] Similar efforts are now underway for Parkinson's disease, and may have far-reaching implications not only for the planning of clinical trials but also for future implementation of PD risk screening programmes and ultimately efforts aimed at disease prevention.

LIMITATIONS OF CLINICAL DIAGNOSTIC CRITERIA

Current diagnostic criteria for PD are based on the clinical presentation of bradykinesia combined with limb rigidity and/or resting tremor, enforced by supportive criteria such as responsiveness to levodopa and the absence of exclusion criteria.[8] When compared to diagnoses based on postmortem studies, however, the accuracy of the clinical criteria is suboptimal and error rates have been as high as 20%.[9] The latter is mainly due to clinical overlap between PD and other neurodegenerative conditions such as MSA or progressive supranuclear palsy. Similarly, clinical criteria for MSA have yielded accuracies of 94% in late disease stages, but this was only around 85% in early disease.[10] In addition, current clinical criteria for PD are insensitive to the early appearance of non-motor symptoms prior to defining motor features like hyposmia, constipation, rapid eye movement sleep behaviour disorder, or autonomic dysfunction. Although these have been addressed in attempts to define diagnostic criteria for 'prodromal' PD,[11,12] the predictive value for established PD is still limited.

DIAGNOSING PARKINSON'S DISEASE: THE ROLE OF BIOMARKERS

There are two biomarker categories that have already entered the arena of clinical routine: molecular testing for genetic PD subtypes and neuroimaging.

Genetic testing is particularly relevant in patients with a family history of Parkinsonism or early age at onset (defined as onset before the age of 50 years). Knowledge of the underlying gene defect within a family enables more effective counselling of patients, and increasingly, clinical trials are targeting specific genetic forms of PD, like *GBA*-PD or PD subjects with *LRRK2* mutations.[13]

Molecular imaging using dopaminergic tracers has evolved into a routine diagnostic tool for PD, but has limited specificity since nigrostriatal dopaminergic denervation is also present in other types of degenerative Parkinsonism. Nonetheless, it is sensitive to early neurodegenerative change as shown by multiple longitudinal studies in subjects at risk for PD, like those with hyposmia or rapid eye movement sleep behaviour disorder. Recent advances in MRI techniques, including machine-learning algorithms to analyse volumetric, diffusion tensor, as well as multimodal magnetic resonance data, have improved differential diagnostic accuracy between different types of neurodegenerative Parkinsonism.[14] In addition, novel magnetic resonance techniques have also enabled the detection of nigral pathology in PD by using iron-sensitive sequences, diffusion tensor, or

neuromelanin imaging. Free water and neuromelanin MRI have also been studied as progression markers of nigral pathology in PD, producing promising results that may support their use as outcomes in disease-modifying PD trials.[15] The availability of PET tracers for amyloid beta and tau as key proteins driving disease pathology has been a major step forward in the ability to detect the effects of disease-modifying interventions in AD, and has also become a cornerstone of biological definitions of AD. Recent efforts to develop PET tracers for pathological brain depositions of α-synuclein have begun to bear fruit, and ACI-12589 has been shown to detect pathological α-synuclein and, so far, has been able to distinguish MSA from other synucleinopathies.[16]

Seed amplification assays (SAA) for detecting α-synuclein aggregates in cerebrospinal fluid (CSF) were first reported in 2016 and have since consistently demonstrated high diagnostic accuracy for PD and DLB versus controls.[17] In addition, some studies have reported promising specificity in distinguishing between different synucleinopathies like PD and MSA by differences in the kinetics of SAA's. These assays have also been reported to yield positive results in other biofluids like serum or blood, as well as in skin biopsies.[18,19]

TOWARDS A BIOLOGICAL DEFINITION

Two recent proposals for biological definitions of PD are intended to facilitate very early diagnosis of PD.[20,21] One of them specifically also includes other Lewy-type synucleinopathies like DLB by putting different clinical expressions under the new umbrella term 'neuronal synuclein disease',[21] a terminology that has somewhat blurred boundaries towards MSA, where synuclein pathology also occurs in neurons. The neuronal α-synuclein disease integrated staging system (NSD-ISS) is anchored on the presence of pathological α-synuclein in CSF, striatal dopaminergic denervation as assessed by dopamine transporter imaging with DAT-SECT, and the presence of and degree of functional impairment from clinical symptoms. PD subtypes that lack synuclein pathology, like a proportion of cases with *LRRK2*-PD, would fall outside this biological classification system. Inherently, this system considers PD as one of several syndromatic expressions of the biological disease process. The 'SynNeurGe' framework, on the other hand, is designed to include the full spectrum of what is now recognised clinically as PD, combining the presence or absence of α-synuclein in CSF, evidence of underlying neurodegeneration assessed by dopaminergic imaging, and pathogenic genetic variants linked to PD. This framework also lists a broader spectrum of biomarkers and reviews the current evidence of their diagnostic performance, indicating that future refinements of the SynNeurGe classification will likely become possible by incorporating additional biomarkers.

Both frameworks have not yet been validated in prospective studies regarding their predictive value for symptomatic disease in biologically defined subjects without clinical symptoms, and thus are only appropriate for research purposes at present. Once validated, however, a framework based on a biological definition of PD or a broader spectrum of synucleinopathies that enables early diagnosis would be invaluable in supporting research and development, and improving the design of clinical trials in a number of ways, including pathogenic subtype-specific drug targeting and patient stratification. This approach is already underway in symptomatic patients with *LRRK2* or *GBA* mutation, but the concept of biologically defined disease would open the door to a new type of disease-modification approach targeting asymptomatic individuals or those with subtle signs and symptoms that do not meet the threshold of current diagnostic criteria. Ultimately, this could pave the way towards population-based risk screening and disease prevention strategies. However, there are still major issues that need to be addressed before such scenarios can be implemented. They include uncertainties regarding the validity and scalability of currently proposed biomarker anchors, specifically the alpha-

synuclein SAAs, as well as ethical concerns around the possibility of false positive or false negative biomarker results and their harmful effects. Above all, diagnosing a disease in people without symptoms at a time where there is very limited information on the risk of biomarker-positive individuals developing clinically relevant disease, and where there are no effective preventive interventions, is difficult to justify from an ethical perspective. This highlights the need for careful, long-term, prospective studies to understand the meaning of biological disease markers both at the population level and in specific risk groups.

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