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In pursuit of prodromal Parkinson's disease

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In *The Lancet Neurology*, Anette Schrag and colleagues[1] provide a valuable contribution to the pursuit of prodromal Parkinson's disease. Why is this important? Many clinical trials involving thousands of patients and millions of dollars have assessed a range of drugs for their putative neuroprotective effects in Parkinson's disease.[2] These drugs have targeted several different pathophysiological processes, including oxidative stress, mitochondrial dysfunction, apoptosis, excitotoxicity, inflammation, and failure of trophic support. Despite impressive preclinical effects, none of these agents has modified disease progression in patients with Parkinson's disease. The many possible reasons for these failures include poor target engagement, inappropriate dose, and targeting of the wrong biological pathways, further exacerbated by inadequate animal models that might not represent the pathogenesis of the human disease. However, an important concern that applies to the discovery of effective neuroprotective therapy in all neurodegenerative diseases is the possibility that these treatments have been administered too late in the degenerative process. Patients participating in such trials for Parkinson's disease have previously been viewed as having early disease, since they are generally enrolled within months to 2–3 years of the onset of their motor symptoms. However, it is now increasingly acknowledged that at this so-called early clinical stage the disease has become well entrenched and potentially advanced beyond a point at which such treatments could be expected to have a substantial clinical effect, especially when given alone and directed towards only one pathogenic mechanism or pathway.[3] In support of this concern, such patients diagnosed as having early Parkinson's disease are known to have a greater than 50–60% deficit in the dopaminergic nigrostriatal pathway.[4] Consequently, interest has grown into the possibility of defining earlier stages of the disorder based on the understanding that the disease might actually begin in the peripheral autonomic nervous system and the olfactory bulb and spread from there to the CNS, typically affecting lower brainstem structures well before the involvement of the substantia nigra.[5] Substantial evidence supports the occurrence of various symptoms many years before the development of classical motor parkinsonism. Increased attention to the issues of where the disease process begins, how it spreads through the nervous system, and how it can be diagnosed at earlier prodromal stages has encouraged active discussions about the need to redefine Parkinson's disease[6] and establish new research criteria[7] that can be applied in future clinical trials of disease-modifying therapies.

Schrag and colleagues now describe the largest and most comprehensive assessment of the prediagnostic features of Parkinson's disease reported so far.[1] By using data recorded in The Health Improvement Network UK primary care database, they were able to compare the incidence of symptoms in up to 8166 individuals with Parkinson's disease and 46 755 without the disease at 2, 5, and 10 years before the diagnosis. 2 years before clinical diagnosis, many patients may have had overt but unappreciated clinical features of Parkinson's disease. However, 5 years before the diagnosis of the disease, patients who went on to develop Parkinson's disease had a higher incidence of several symptoms than did control participants, including tremor, balance problems, depression, anxiety, constipation, postural hypotension, dizziness, erectile dysfunction, fatigue, and urinary dysfunction. At 10 years before disease onset, the incidence of constipation (risk ratio 2·01, 95% CI 1·62–2·49) and tremor (7·59, 1·11–44·83) were higher in those who went on to develop the disease than in controls.

Although this study largely confirms previous findings, such as those from the Honolulu-Asia Aging Study[8] and from the Mayo Clinic,[9] its size is impressive and the data were collected prospectively in the course

of routine primary care, without recall or selection bias towards the diagnosis of Parkinson's disease. The findings further emphasise the frequency and complexity of the early premotor or prodromal phase of the disorder. Unfortunately, the study design did not allow the investigators to calculate relative risks for combinations of clinical features. Indeed, without a reliable diagnostic biomarker, we will probably need such information if patients who are presumed to have prodromal Parkinson's disease are ever to be enrolled in neuroprotective trials in the future. An important limitation of this type of study is the uncertainty of the accuracy of the diagnosis of Parkinson's disease. In a similar population with older disease onset, Adler and colleagues[10] reported only 26% accuracy for the clinical diagnosis of Parkinson's disease in untreated patients or those not clearly responsive to treatment, and only 53% accuracy in early (<5 years' duration) Parkinson's disease responsive to medication. Therefore, many patients diagnosed with Parkinson's disease in Schrag and colleagues' study might not have actually had the disease of interest. This possibility emphasises the crucial need for reliable and widely applicable diagnostic biomarkers. When these become available, they will probably be applied first to populations enriched for the clinical symptoms emphasised in the present study, as well as other features known to be associated with α-synuclein pathology, such as olfactory dysfunction,[11] rapid eye movement sleep behaviour disorder,[12] and selected genetic factors,[13] in hope of defining those patients who are most likely to benefit from the early application of effective neuroprotective strategies.

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I declare no competing interests.

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Corrections

Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol *2014; 13: 575–86*—The appendix of this Article was incomplete. The appendix has been updated as of Dec 8, 2014.