

# Prodromal and advanced non-motor features of Parkinson's disease

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Publication about non-motor symptoms of Parkinson's disease (PD) began to expand around 20 years ago. While clinicians had always been aware of them, the increased level of interest helped to focus attention on some limitations of dopaminergic therapy, and on unmet needs in patient management. At about the same time, alpha-synuclein immunohistochemistry became available, greatly increasing knowledge about the Lewy cellular pathology that causes PD. The idea that certain non-motor symptoms could anticipate the motor deficit of PD is closely connected with the research of Braak and colleagues on the pathological progression of PD. Postulating that the alpha-synucleinopathy of PD represents a pathological continuum and that the laws which govern its progression can be determined,<sup>1</sup> they conceived a hierarchical, caudal to rostral six-stage scheme.<sup>2</sup> The earliest Braak stages involve the lower brainstem and anterior olfactory nucleus. The substantia nigra is not affected until Stage 3. Stage 6, with widespread neocortical Lewy body degeneration, is the pathological endpoint. The Braak model accords with observations that non-motor symptoms such as hyposmia, autonomic impairment and rapid eye movement sleep behaviour disorder (RBD) precede motor symptoms in some patients,<sup>3</sup> and that cognitive decline is usually an advanced PD feature.<sup>4,5</sup> There are exceptions to the Braak staging, and other researchers have proposed grading systems to increase the proportion of autopsy cases satisfactorily classified.<sup>6</sup> But overall, the caudal-rostral model of progression of Lewy pathology in PD has held up well. The predictive power of non-motor symptoms for development of PD may turn out to be important in developing disease-modifying treatments by extending the time window for clinical trials.

The article by Flores-Torres and co-authors<sup>7</sup> draws on a large prospective study of Mexican male health professionals to identify subgroups

with prodromal non-motor features of RBD, constipation and hyposmia. While much of the research was conducted remotely, participants self-administered a test of olfaction, and a sleep questionnaire tool shown to be specific and sensitive for RBD was employed. Assessments of cognition, both subjective and objective, were then conducted by telephone interview. Participants with prodromal non-motor features had worse cognitive function and more cognitive symptoms than those with none. The effects were generally greater when all three features were present. The influence of multiple prodromal features was particularly strong on subjective cognition. While the small group who had converted to clinical PD had greater cognitive deficits than those with maximum prodromal features only, this trend was actually reversed for objective memory scores. The paper broadly replicates other population-based studies.<sup>8-10</sup> Its relative strengths are the analysis of the influence of prodromal features, individually and in combination, and in the range of cognitive assessments employed.

The finding that the three non-motor prodromal features point to evidence for significant cerebral cortical pathology in the absence of parkinsonism seems at odds with a caudal-rostral scheme of progression of Lewy pathology. The clinicopathological correlations of cognition in PD are, however, more complicated. While neocortical Lewy pathology is present in PD dementia, so is Alzheimer's pathology (amyloid-beta and tau proteins).<sup>11</sup> The association of hyposmia with cognitive impairment is seen in PD, but also in early Alzheimer<sup>12</sup> and diffuse Lewy body diseases.<sup>13</sup> Diffuse Lewy body disease appears to result from a limbic-predominant pattern of Lewy pathology that initially bypasses the brainstem.<sup>14</sup> RBD, which is less common than hyposmia, has more specific associations with neurodegeneration. Its clinical localisation is to brainstem centres that regulate sleep, and its strong pathological correspondence



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is with alpha-synuclein deposition.<sup>15</sup> Pathological studies in established PD provide some clarification. In the presence of RBD, parkinsonian patients have increased amounts of Lewy pathology in *all* areas, not just the brainstem.<sup>16</sup> It is possible that identification of individuals with multiple prodromal non-motor features selects more for overall burden than for topography of underlying pathology. Another aspect of the Flores-Torres *et al* paper relates to the question of pathological burden—the age of the participants. The average age in this study was almost 80 years, so the assumption that many participants have prodromal PD implies an age of onset roughly two decades older than usual. Age rather than disease duration correlates best with cognitive decline, and older patients have a shorter interval of PD before dementia.<sup>17</sup> They tend to have higher degrees of both alpha-synuclein and Alzheimer's pathologies.<sup>18 19</sup>

This research highlights the fact that there is more to be learnt about relationships between the prodromal and advanced clinical features of PD. While cognitive decline is usually associated with the later stages of the disorder, the authors argue that detection of early cognitive deficits may increase the predictive power of the other non-motor features for development of PD. This could facilitate the evaluation of putative neuroprotective agents in the premotor phase of PD. The findings of Flores-Torres *et al* also suggest that, to a greater degree than has been appreciated, these 'prodromal' clinical features also have prognostic significance for cognitive decline and progression to the advanced PD state. This impression needs further exploration in population-based studies across younger age groups.

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