Critical appraisal of brain pathology staging related to presymptomatic and symptomatic cases of sporadic Parkinson's disease

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Summary, Clinical Parkinson's disease (PD) is a well-characterised syndrome that benefits significantly from dopamine replacement therapies. A staging procedure for sporadic PD pathology was developed by Braak et al. assuming that the abnormal deposition of x-synuclein indicates the intracellular process responsible for clinical PD. This paradigm has merit in corralling patients with similar cellular mechanisms together and determining the potential sequence of events that may herald the clinical syndrome. Progressive pathological stages were identified - 1) preclinical (stages 1-2), 2) early (stages 3-4, 35% with clinical PD) and 3) late (stages 5-6, 86% with clinical PD). However, preclinical versus early versus late-stage cases should on average be progressively older at the time of sampling, a feature not observed in the cohort analysed. In this cohort preclinical cases would have developed extremely late-onset PD compared with the other types of cases analysed. While the staging scheme is a valuable concept, further development is required.

Requirement for staging disease progression

Parkinson's disease (PD) is currently characterised by several cardinal motor symptoms, including rigidity, bradykinesia and/or resting tremor, that benefit significantly from dopamine replacement therapies. However, it is clear that considerable neuronal destruction occurs prior to the onset of these motor symptoms with commensurate compensatory mechanisms accounting for the delay in clinical onset (Jankovic, 2005). It is therefore necessary to recognise this presymptomatic disease stage to advance knowledge on the cellular mechanisms underlying the disease process.

Clinical demographics of sporadic Parkinson's disease

Sporadic PD is one of the most reliable and stable neurological diagnoses with 92% of the clinical features remaining unchanged for 5–10 years (Jankovic et al., 2000). While the incidence of sporadic PD significantly increases with age, the average age of onset for levodopa-responsive motor symptoms is around 60 years old. Fewer studies have assessed the average age at death for sporadic PD patients, but recent large-scale risk analysis using death and mortality as outcomes suggest that patients survive to 76 years of age on average (Wirdefeldt et al., 2005). These data show that, in the relatively homogeneous group of patients with dopa-

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