Neuropathological progression of clinical Parkinson disease subtypes

Eduardo De Pablo-Fernández, Andrew J. Lees, Janice L. Holton and Thomas T. Warner

Many attempts have been made to identify clinical subtypes of Parkinson disease (PD), but little progress has been made in determining whether they are simply a reflection of the clinical heterogeneity of PD or whether they represent different diseases hiding under one rubric. In a recent News & Views article (Clinical Parkinson disease subtyping does not predict pathology. *Nat. Rev. Neurol.* **15**, 189–190 (2019))[1], Alberto Espay and Connie Marras discussed our recent clinicopathological study showing that PD subtyping at diagnosis can provide useful information on subsequent disease progression and survival[2]. They stated correctly that the severity of Lewy and Alzheimer disease (AD) pathologies did not differ between the clinical subtypes but, importantly, they failed to mention that these pathological changes were reached over a considerably shorter disease duration in the diffuse malignant subgroup than in the other subtypes. This was one of the key findings of our study.

All patients with PD, despite differences in the disease course in the early and middle stages, eventually enter an accelerated terminal phase of illness, often associated with falls and cognitive impairment[3,4]. By the time of death, most patients with PD have reached an equivalent terminal neuropathological stage but, analogous to clinical progression, the rate of neuropathological deterioration differs among different subgroups, and it was this finding that allowed us to conclude that different neuropathologies were important determinants of clinical PD subtypes[2]. Despite different rates of clinical and neuropathological progression, we could not establish pathological features that would allow a neuropathologist 'blinded' to the clinical details to accurately categorize the clinical subtype.

Neuropathological studies have inherent limitations given the inability to serially examine brain tissue over time to evaluate the dynamic neurodegenerative processes, which prevents analysis of differences in pathological severity and distribution among subtypes at earlier stages of the disease. We agree that other important factors such as regional cell loss independent of Lewy and AD neuropathologies must be involved, and we have previously demonstrated that the age of the patient is an important determinant of prognosis and also of clinical subtype definition[2,3].

There is a reply to this letter by Espay, A. J. & Marras, C. *Nat. Rev. Neurol.* https://doi.org/10.1038/s41582-019-0198-9 (2019).

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Competing interests
The authors declare no competing interests.

Reply to 'Neuropathological progression of clinical Parkinson disease subtypes'

Alberto J. Espay and Connie Marras

In our recent News & Views assessment of the important work by De Pablo-Fernández and colleagues on 111 pathology-proven Parkinson disease (PD) cases from the Queen Square Brain Bank (Clinical Parkinson disease subtyping does not predict pathology. *Nat. Rev. Neurol.* **15**, 189–190 (2019))[1,2], we stated that although the study served to confirm the predicted trajectory of the three data-driven severity subtypes of PD — mild, intermediate and diffuse malignant — it failed to suggest there were pathological correlates to each subtype.

In their Correspondence article (Neuropathological progression of clinical Parkinson disease subtypes. *Nat. Rev. Neurol.* https://doi.org/10.1038/s41582-019-0197-x (2019))[3], De Pablo-Fernández and colleagues state that we failed to mention that these pathological changes were reached over a considerably shorter disease duration in the diffuse malignant subgroup than in the other subgroups. We did acknowledge that the mean rates of progression and survival mirrored the early subtypes: longest survival and slowest progression in the mild motor-predominant group, shortest survival and fastest progression in the diffuse malignant group, and intermediate progression and survival in the intermediate group. Inferences on the timing of pathological changes before death, however, are not possible from this cross-sectional post-mortem evaluation of pathology.

Importantly, any differences in the rate of neuropathological deterioration among subgroups cannot be used to conclude that the neuropathology features themselves were important determinants or correlates of clinical PD subtypes. In fact, the neuropathological features were similar across the three subtypes.

Protein aggregates that are identified at post-mortem and are relied upon for nosology might not be pathogenic but could potentially be universal compensatory responses to a wide range of biological stressors[4]. This idea was supported by the data from the study by De Pablo-Fernández and colleagues[2]. Amyloid and tau pathology were associated with older age at death: individuals with more Alzheimer disease pathology lived longer[2]. This finding is paradoxical to our current disease model but aligns with a future systems biology approach to diseases of brain ageing[5]. If 'PD' is to be accepted as the nosological entry point to many diseases, most of which have Lewy pathology in common, we will need to vigorously engage in an individualized search 'upstream' to identify molecular and biological subtypes and truly usher in the era of precision medicine[6].