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PARKINSON DISEASE

Progression markers for early PD — finding the right tools for the job

Measurement of disease progression in patients with early Parkinson disease (PD) requires careful selection of the most relevant markers across multiple domains, according to new research published in *Neurology*. Of 30 candidate progression markers that were tested by Brit Mollenhauer and colleagues, just 10 were found to be reliable indicators of disease progression in this patient group.

Traditionally, diagnosis and monitoring of PD has relied largely on assessment of motor and dopaminergic function. Mollenhauer *et al.* decided to adopt a broader approach, incorporating nonmotor symptoms (NMS), cognitive measures, sleep parameters, volumetric imaging, and cerebrospinal fluid (CSF) biomarkers.

The participants for the new study were drawn from the *De Novo* Parkinson (DeNoPa) cohort. "This cohort started in 2009, with the aim of identifying markers for diagnosis and progression in a *de novo* PD cohort and healthy controls," explains Mollenhauer. "The healthy control arm is important, as we wanted to separate PD-specific progression from normal ageing."

Baseline data — published in 2013 — had been obtained from 159 patients with recently diagnosed PD and 110 age-matched, neurologically healthy controls, recruited at a single centre. From the original study participants, 123 patients with PD and 106 controls underwent repeat assessments after 24 months. Mollenhauer and colleagues compared the baseline and follow-up data to identify any longitudinal changes that might signify PD progression.

Over the 2-year follow-up period, the patients with PD exhibited significant changes in NMS, sleep measures (including daytime sleepiness and REM sleep behaviour disorder), and grey matter and hippocampal volumes. Improvements in depression scores were also observed, possibly mirroring the so-called 'honeymoon period' that people with PD frequently experience after initiation of dopaminergic therapy.

Interestingly, scores on the MDS-UPDRS 1 (Movement Disorder Society United Parkinson's Disease Rating Scale part 1) indicated a worsening of NMS, whereas the NMS Scale (NMSS) detected improvements in the severity of NMS. These seemingly conflicting results could reflect the more limited range of NMS assessed by the MDS-UPDRS 1 compared with the NMSS, as well as the differential effects of dopaminergic treatment on various NMS.

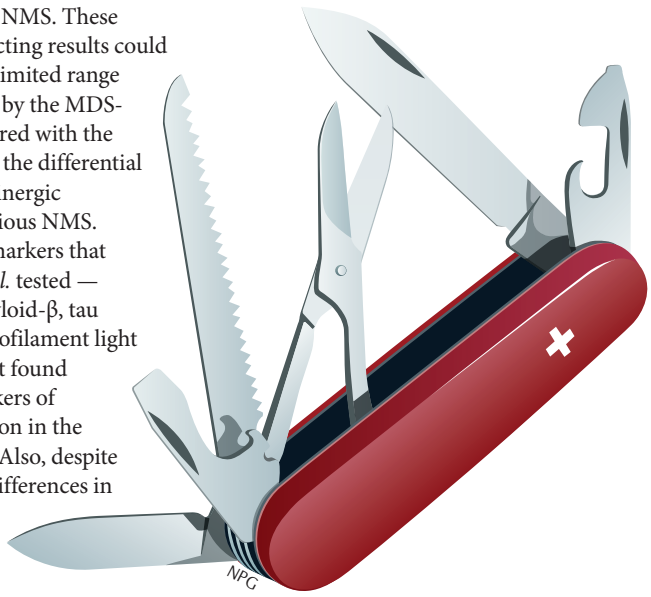
The CSF biomarkers that Mollenhauer *et al.* tested — α-synuclein, amyloid-β, tau protein and neurofilament light chain — were not found to be useful markers of disease progression in the DeNoPa cohort. Also, despite cross-sectional differences in cognitive performance between controls and patients with PD, no significant longitudinal changes in this parameter were observed.

The new findings indicate that monitoring of disease progression in the early stages of PD requires a multimodal approach that goes beyond motor symptoms, and might require a different set of markers from those that have proved valuable for diagnosis. The authors acknowledge that their panel of potential markers now needs to be validated through longitudinal studies in larger cohorts.

"We are continuing with the biennial follow-up, and we are very lucky that the patients and controls are very committed: we just finalized the 4-year follow-up, with 95% of the participants coming back at the end of 2015," says Mollenhauer. "We will also continue to systematically explore new biofluid marker candidates through unbiased cross-omic analyses and targeted approaches."

Heather Wood

> "monitoring of disease progression in the early stages of PD requires a multimodal approach"



ORIGINAL ARTICLES Mollenhauer, B. *et al.* Monitoring of 30 marker candidates in early Parkinson disease as progression markers. *Neurology* http://dx.doi.org/10.1212/WNL.0000000000002664 (2016)
FURTHER READING Mollenhauer, B. *et al.* Nonmotor and diagnostic findings in subjects with *de novo* Parkinson disease of the DeNoPa cohort. *Neurology* **81**, 1226–1234 (2013)