Tracking the course of prodromal Parkinson’s disease

This scientific commentary refers to ‘Trajectories of prediagnostic functioning in Parkinson disease’, by Darweesh et al. (doi:10.1093/brain/aww291).

No therapeutic interventions have been shown to modify disease progression in Parkinson’s disease when applied to patients after the clinical diagnosis has been made. This failure to translate promising preclinical findings from bench to bedside may, in part, reflect the fact that the underlying pathology in such patients has advanced beyond a point at which...
neuroprotective treatments can have a meaningful effect. After all, it is known from autopsy studies that patients with Parkinson’s disease have a profound loss of dopaminergic nigrostriatal neurons within only a few years of diagnosis (Kordower et al., 2013). New strategies are urgently needed to identify patients earlier in the course of their disease and understand the pattern(s) of their clinical deterioration. In this issue of *Brain*, Darweesh and colleagues present findings from a nested case-control study that help to elucidate the temporal sequence of prediagnostic decline prior to Parkinson’s disease diagnosis (Darweesh et al., 2016).

This study was embedded in the prospective Rotterdam Study, a population-based cohort study in which 78% of residents aged 55 or older from the Ommoord district in Rotterdam were enrolled. After excluding cases of parkinsonism and dementia at baseline, 6456 individuals were followed-up between 1990 and 2013. They underwent five study visits in which daily functioning, motor features, and non-motor features (such as cognition, mood and autonomic function) were assessed. There was an impressive rate of follow-up at each visit of 89–95%. Screening for possible parkinsonism relied on several overlapping strategies: in-person evaluation during study visits (including testing for parkinsonian signs by research nurses using standardized protocols), use of anti-parkinsonian medications (based on pharmacy records), and alerts from continuous monitoring of health records. In the event of screening positive in any of these modalities, participants were examined by a research physician specialized in neurological disorders to establish whether they did in fact have parkinsonism, after which the final diagnosis was decided by a consensus panel. In all, 109 cases of incident Parkinson’s disease were diagnosed during the 23-year follow-up period.

The study compared the differences in prediagnostic trajectories between
Parkinson’s disease cases and selected matched controls (ratio of 1:10). From 7 years before diagnosis, those with Parkinson’s disease reported difficulties with complex tasks requiring a combination of motor and non-motor skills (earliest differences were seen with travelling). Problems with basic activities of daily living became more common ~5 years before diagnosis (earliest differences were seen with eating) and increased thereafter. This deterioration in daily functioning was paralleled by the emergence of motor impairments, initially in the upper limbs (finger tapping, reduced arm swing) and then more generally (tremor, poverty of movement, imbalance, rigidity, postural abnormalities, falls). A more rapid decline in cognitive scores was observed as early as 7 years before diagnosis in Parkinson’s disease cases compared to controls, with tasks affecting executive function and processing speed primarily affected. Anxiety symptoms, depressive symptoms and use of laxatives only became significantly different in the last few years before diagnosis.

This study builds on work from Schrag and colleagues (2014) who, using a large primary care database in the UK, found that tremor and constipation pre-dated the diagnosis of Parkinson’s disease by up to 10 years. A variety of other motor and non-motor features were also found to be more common at 5 and 2 years prior to diagnosis. Similarly, other studies have characterized the evolution of prodromal clinical markers in cohorts known to be at higher risk of Parkinson’s disease, such as those with rapid eye movement sleep behaviour disorder (Postuma et al., 2012) and glucocerebrosidase mutations (Beavan et al., 2015).

As the authors acknowledge, this study does not capture the full burden of prodromal symptoms in Parkinson’s disease as many important domains such as sleep and olfactory disturbance were not included. Having said that, some of the results are in line with previous prospective studies. In common with the Rochester Epidemiology Project (Shiba et al., 2000), Darweesh et al. observed anxiety and depression preceding Parkinson’s disease but, in contrast to the earlier project, they found that these complaints developed in close proximity to the time of diagnosis. This raises the possibility that the changes might have been partly caused or exacerbated by unappreciated loss of motor or cognitive functioning (i.e. reactive or secondary) rather than having a distinct neuroanatomical basis in α-synuclein-related degeneration. As in the Honolulu-Asia Aging Study (Ross et al., 2012), constipation (based on laxative use as a proxy measure) was found to be more common in Parkinson’s disease cases. Comprehensive evaluation of other autonomic parameters was not performed.

As for all clinical studies of Parkinson’s disease, the potential for misdiagnosis must be considered. Even when specialists in movement disorders use defined criteria, the accuracy of a clinical diagnosis of Parkinson’s disease remains ~85% when compared to neuropathological findings as the gold standard, and is substantially lower in those with disease duration <5 years (53%) or those who have not received any/adequate dopaminergic replacement (26%) (Adler et al., 2014). It is noteworthy that the age-specific incidence rates of Parkinson’s disease in this study were higher than most other population-based cohorts. One possible explanation for this is that some individuals had an incorrect diagnosis, and with this in mind it is disappointing that the study did not specify the number of individuals diagnosed with atypical parkinsonian syndromes such as progressive supranuclear palsy, multiple system atrophy and corticobasal syndrome; nor did it report the number of patients in whom the original diagnosis of Parkinson’s disease was revised. Furthermore, given the high average age at diagnosis (78 years), the possibility of vascular brain disease or other pathologies (e.g. Alzheimer’s disease) contributing to mild parkinsonian signs may also have been more of an issue (Louis et al., 2006).

Despite these caveats, this is an important study and the results are extremely valuable. How might they change our approach to the identification and management of Parkinson’s disease? First, the study informs us that motor symptoms in Parkinson’s disease may impact on daily activity far earlier than previously thought. This should be borne in mind when assessing patients because it may signal the need for earlier symptomatic treatment rather than the ‘wait and watch’ approach that many neurologists still espouse. Second, the finding of cognitive deficits early in the prediagnostic course could argue—depending on the anatomical basis of these complaints—against the Braak hypothesis of caudal-rostral spread...
of pathology. Further work is needed to clarify the clinical-pathological correlations of early premotor/prodromal features, whether the spread of α-synuclein pathology through the nervous system is responsible for all Parkinson’s disease symptoms, or whether dual pathologies (especially in the elderly population studied) contribute in any way to the prodromal course. Finally, the study adds to the belief that large-scale population screening has the potential to identify individuals at-risk (or in the early stages) of Parkinson’s disease. In 2015, the Movement Disorders Society published research criteria for the diagnosis of prodromal Parkinson’s disease (Berg et al., 2015). Subsequent efforts to retrospectively apply these criteria in elderly populations have shown that they are capable of identifying individuals who go on to develop disease (Mahlknecht et al., 2016). Enriching these cohorts using additional risk factors known to be associated with synucleinopathies is likely to further facilitate the identification of high-risk individuals. Several studies such as the Parkinson’s Associated Risk Study (PARS), the Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study, and PREDICT-PD are now exploring this possibility. Once definitive diagnostic biomarkers are available (e.g. imaging or measurement of α-synuclein from biospecimens or peripheral tissue biopsies), these individuals could undergo more definitive diagnostic characterization and then be enrolled in clinical trials at what is now considered a ‘prodromal stage’ of their disease. By targeting the right patients at the right time, we should be optimistic that effective neuroprotective therapies will be found in the years ahead.

**References**


**Doppelgängers and dissociations: lesion network mapping illuminates misidentification delusions**

This scientific commentary refers to ‘Finding the imposter: brain connectivity of lesions causing delusional misidentifications’, by Darby et al. (doi:10.1093/brain/aww288).

Patients with misidentification delusions claim that the identities of places or people (including the self in some cases) are altered or duplicated. The most well-known of these delusions is Capgras delusion, wherein patients claim that familiar others have been replaced by doppelgängers or imposters. Misidentification delusions are often