Nature Reviews Neurology **11**, 1 (2015); published online 16 December 2014; doi:10.1038/nrneurol.2014.238

PARKINSON DISEASE

Facilitating detection of prodromal Parkinson disease in primary care clinics

The hallmark features of Parkinson disease (PD) are preceded by a prodromal phase lasting several years. A new study, published in *The Lancet Neurology*, retrospectively analysed primary care data from across the UK, and identified symptoms that were more common in patients later diagnosed with PD than in other patients.

"A number of studies have reported symptoms or diagnoses that can predate typical features of PD by several years," explains study author Anette Schrag. "However, it has been unclear whether these features are clinically relevant enough to allow identification in primary care."

Schrag's team at University College London, UK, analysed The Health Improvement Network database, which contains anonymized longitudinal medical records for over 11 million people. In this database, the investigators identified 8,166 patients diagnosed with PD, and selected 46,755 demographically matched people as controls.

The investigators examined each individual's medical records for possible preclinical manifestations of PD, including motor symptoms, autonomic dysfunction and neuropsychiatric disturbances. To corroborate and extend the descriptions from clinical exams, the authors also took note of prescriptions for drugs like anxiolytics, antidepressants and erectile dysfunction medications.

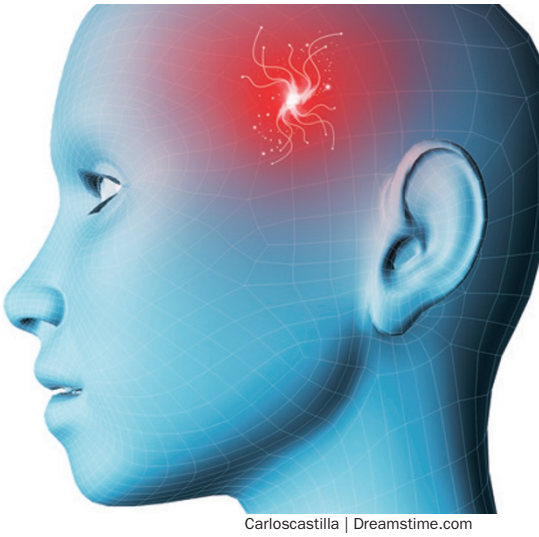
The specificity of every symptom or clinical feature was determined by calculating symptom incidence during each of the 10 years leading up to an 'index date'. For patients with PD, the index date was the date of their formal diagnosis of PD, or their first prescription for antiparkinsonian medication. For controls, a randomly selected clinic visit was used as the index date.

Several clinical complaints were found to be more common in patients eventually diagnosed with PD than in controls. "These symptoms include motor symptoms such as balance problems, shoulder pain or stiffness, and tremor; but also neuropsychiatric symptoms such as depression and anxiety; autonomic features such as hypotension, constipation and urinary disturbances; and other features such as insomnia and fatigue," explains Schrag.

At 2, 5 and 10 years before the index date, the symptom that consistently conferred the highest risk of PD was tremor. "Ultimately, these data may help identify patients at earlier stages of PD to offer them inclusion into potential clinical trials with neuroprotective treatments before the greatest part of neuronal cell death has occurred," concludes Schrag.

Schrag's team also looked for evidence of other clinical features that have been reported to indicate prodromal PD, including cognitive decline, rapid eye-movement sleep behaviour disorder and anosmia (an impaired sense of smell). The prevalence of these symptoms was only 1%, thus precluding further analysis. Although this absence of evidence is not evidence of absence, the low prevalence of anosmia is particularly noteworthy in light of recent findings by Danna Jennings and colleagues. Jennings *et al.* surveyed 10,139 people to assess olfaction and other putative features of prodromal PD. The investigators then used the survey data to recruit 203 healthy people with hyposmia, and 100 controls with intact olfaction, to undergo single-photon emission CT scans with the ^{123}I-β-CIT ligand.

The investigators observed that dopamine transporter binding in the striatum was markedly reduced in the participants with hyposmia. In some individuals, hyposmia might thus be an early indication of the progressive loss of dopaminergic neurons that is the pathogenetic hallmark of PD. However, follow-up studies are necessary to establish the proportion of the participants with hyposmia who go on to be diagnosed with PD.



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Jennings and colleagues futher observed that a combination of factors was more predictive of dopaminergic deficits than was hyposmia as an isolated symptom: dopaminergic dysfunction was present in 11% of participants with hyposmia overall, but was seen in 40% of male participants with hyposmia and chronic constipation.

Although these experiments do not reveal a specific symptom or pattern that could be used to reliably identify patients with prodromal PD, the results suggest that early clinical detection is feasible. Earlier diagnosis of PD would improve our understanding of the insidious onset of this disease, and might enable clinicians to intervene in time to prevent the manifestation of overt symptoms.

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Original article Schrag, A. *et al.* Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol*. doi:10.1016/S1474-4422(14)70287-X

Further reading Jennings, D. *et al.* Imaging prodromal Parkinson disease: the Parkinson Associated Risk Syndrome Study. *Neurology* **83**, 1739–1746 (2014) | Silveira-Moriyama, L. & Lees, A. J. How reliable are prodromal indicators of Parkinson disease? *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2014.235