Biomarkers: casting the net wide

To have any hope of affecting the course of Parkinson's disease, early diagnosis is essential. **Rachel Jones** assesses progress so far.

When a patient is diagnosed with Parkinson's disease, they usually have two or three of the cardinal symptoms: resting tremor, rigidity and bradykinesia (slowed movement). By this stage, however, they have probably had the disease for years and up to four-fifths of the dopamine-producing neurons in the substantia nigra have been lost. There is currently no way to reverse this damage, but what if doctors could diagnose Parkinson's disease earlier, before so much harm has been done?

The search is on for a biomarker for early Parkinson's disease — a test that can reliably and specifically predict which patients are going to develop the disease while they are still in the early stages (Box 1). Such a biomarker would have several benefits: patients could be warned that they are likely to develop Parkinson's disease; longitudinal studies of these patients could help researchers develop treatments to slow or even halt the progression of the disease; and, if such treatments were to be developed, a reliable biomarker could allow treatment to begin earlier.

Box 1 | Biomarker definition

The Biomarkers Definitions Working Group has published definitions and guidelines[7]. Biomarkers must be sensitive enough to detect most cases of Parkinson's disease at an early stage, yet specific enough not to detect other neurodegenerative or motor disorders, and they must have strong predictive value. To be useful as a screening method, tests that use such a biomarker should be inexpensive, non-invasive and simple to apply. Ideally, a biomarker for Parkinson's disease would be related to the fundamental neuropathology of the disease, and should be validated by post-mortem examination.

A number of risk factors have been identified that might contribute to the development of Parkinson's disease, including genetic and environmental factors (see page S2). Exposure to these risk factors might be a good indication that subsequent, more sensitive biomarker-based tests are appropriate.

Candidate biomarkers

William Weiner, professor and chair of neurology at the University of Maryland and director of the Maryland Parkinson's Disease and Movement Disorders Center, describes the idea behind the development of a biomarker for Parkinson's disease. "Parkinson's definitely has a preclinical course — the tremor and so on develop after some time has passed. So in theory there might be several ways to detect the disease before this point. The theory is good — but all of these approaches are in clinical research, and none has been validated yet." So what are the leading approaches?

Leslie Findley, a neurologist at the Essex Neurosciences Unit in Romford, United Kingdom, believes that the sense of smell might hold the key to identifying early Parkinson's disease, as the olfactory bulb is one of the earliest structures to be damaged in the disease[1]. "Isolated loss of smell, with other potential causes excluded, is a good predictor of Parkinson's disease," says Findley. "In longitudinal studies, a significant proportion of these patients go on to develop the disease."

Chris Hawkes, honorary professor of neurology at Barts and the London School of Medicine and Dentistry, agrees — at least partially. "Olfaction is certainly a good predictor. The trouble is, it is not very specific for Parkinson's disease — patients with other conditions, such as Alzheimer's disease, can also be hyposmic, and the sense of smell decreases in old age."

Other early clinical signs and symptoms of Parkinson's disease include micrographia (small writing), sleep disorders and personality changes. None of these clinical features is sufficiently specific to predict Parkinson's disease in an individual patient reliably.

Smell is one of the first casualties of Parkinson's disease, and might serve as an early indicator of disease onset.

DR H.W. BERENDSE, DR S. BOESVELDT, DEPARTMENT OF NEUROLOGY, VU UNIVERSITY MEDICAL CENTER, AMSTERDAM, THE NETHERLANDS

Weiner believes that a battery of tests might be the way forward, with a combination of these clinical methods and others, such as imaging and biochemical techniques.

Imaging techniques

Several methods have been proposed to allow clinicians and researchers to view pathological changes in the brains of patients with Parkinson's disease. Standard structural imaging methods lack the sensitivity needed to identify changes in the substantia nigra that result from Parkinson's disease, let alone to spot such changes at an early stage.

More refined techniques show some promise. Two in particular — the identification of changes in iron deposition in the substantia nigra using magnetic resonance imaging (MRI), and the use of single photon-emission computed tomography (SPECT) scanning to visualize dopamine transporters in the nigrostriatal system — might be useful for diagnosing Parkinson's disease at an early stage.

Joanna Collingwood from Warwick University is a physicist working alongside clinicians on the use of high-resolution MRI techniques to visualize iron deposition in the brain (Fig. 1). "At autopsy, the concentration of iron in neurons in the substantia nigra is higher in patients with Parkinson's disease than in age-matched controls," she says. "We can, in principle, use MRI techniques to see changes in iron deposition in the substantia nigra of living patients with Parkinson's disease, but there are lots of issues to resolve before this can be used clinically to predict the disease."(ref. 2)

SPECT scanning is already used by some clinicians to aid in the diagnosis of Parkinson's disease. Patients with the disease show

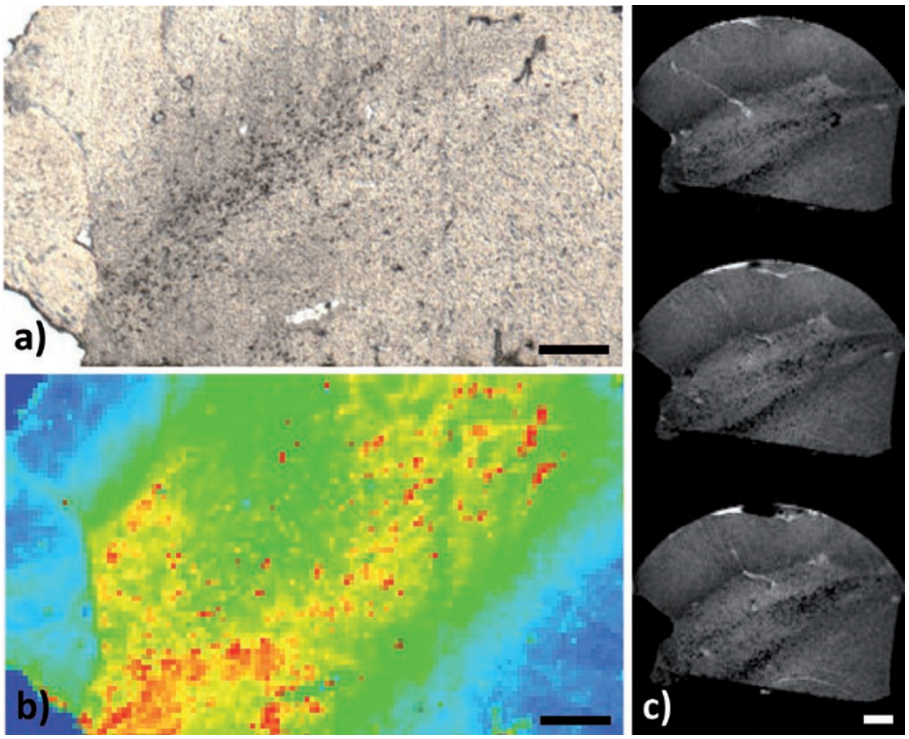

Figure 1 | Interpreting the contribution of iron to MRI signal in the substantia nigra of an elderly case without Parkinson's disease. a, Photograph showing brown deposits of neuromelanin, typically found in dopaminergic neurons (scale bar, 1 mm). **b**, Corresponding X-ray fluorescence map of iron distribution from low (blue) to high (red) concentration (scale bar, 1 mm). **c**, T2* MRI microscopy in original block of unfixed tissue (scale bar, 500 μm). For further details, see ref. 6. Picture credits: J. F. Collingwood (**a**–**c**), University of Warwick; M. R. Davidson (**b**), A. Mikhailova (**a**), J. P. Bullivant (**c**), V. Antharam (**a**, **c**), C. Batich (**c**) and J. Forder (**c**), University of Florida; J. Dobson (**b**), Keele University; and P. D. Quinn (**b**) and J. F. W. Mosselmans (**b**), Diamond Light Source.

a reduction of dopaminergic activity in the nigrostriatal system in these scans[3]. Neurologist Henk Berendse and colleagues from the VU University Medical Center in the Netherlands believe that a combination of nonspecific but quick and cheap olfactory testing and expensive, invasive but specific SPECT scanning offers a powerful predictive tool. Unfortunately, says Berendse, "Using this two-step approach for widespread screening would involve too many scans of healthy individuals, so we need other markers too."

Biochemical biomarkers

"A blood test for Parkinson's disease is undoubtedly something of a holy grail for researchers," says neurologist Douglas Mitchell of the Royal Preston Hospital in Lancashire, United Kingdom. His colleague from the University of Lancaster, David Allsop, agrees. His was the first group to show that α-synuclein, the protein that forms aggregates in the brains of patients with Parkinson's disease, could be detected in the blood[4]. Allsop and his collaborators have developed a test for the abnormal oligomeric forms of α-synuclein[5]. "Patients with existing Parkinson's disease have much higher levels of these oligomeric forms than healthy individuals," says Allsop.

He and Mitchell draw parallels with Alzheimer's disease, in which elevated levels of β-amyloid oligomers can be found in the cerebrospinal fluid of patients with mild cognitive impairment, which often precedes the disease. According to Mitchell, "The progress with early diagnosis of Alzheimer's disease might be a model of how the Parkinson's research could develop."

Although they have not yet investigated whether α-synuclein oligomers can be found in the blood before the onset of Parkinson's disease, they are looking at patients who have just been diagnosed to see whether the concentrations increase as the disease progresses.

Early-detection ethics

Imagine you go to your doctor for a routine check-up, or perhaps because you have noticed that you cannot smell your food as well as you previously could. The doctor wants to run some tests and, because you used to work with pesticides and are aged over 50, adds a blood test for α-synuclein oligomers to the list. A few weeks later, your doctor calls you back into the office to tell you that you almost certainly have Parkinson's disease — an incurable condition that will progressively worsen. So, you ask, what can I do? Well, currently nothing, comes the answer — except wait for the symptoms to appear, when you can take levodopa and other drugs to help manage them.

How would you feel? Would you rather not know? What about the life insurance that you were about to apply for? Do you have to tell prospective employers about this? A test for presymptomatic, or very early, Parkinson's disease might not seem like a good thing to a patient in this scenario. Of course, there are many potential disease-modifying treatments under development, but none that is ready for the clinic yet (see page S13). So until that day comes, is a test desirable?

"I don't know whether any of these tests will work, and I have a sense of unease about how this research might develop," says Weiner. He draws a parallel with Huntington's disease, which is caused by a single gene. People whose parents have the gene can be tested before they develop any symptoms. Extensive counselling is usually recommended to prepare patients for the outcome of the test, although fewer people take it than might be expected. "Before we had a test for Huntington's disease, about three-quarters of family members of patients said they would want to know whether they had the faulty gene — but in reality, a lot fewer actually take the test now that it is available."

There are positives to early diagnosis, Berendse points out: "Many patients with Parkinson's disease show initial, non-motor complaints that can be quite distressing. They might visit many doctors and undergo many tests before being accurately diagnosed, and these months or years of uncertainty are not trivial matters for a patient."

At least initially, one of the main benefits of a predictive biomarker for preclinical Parkinson's disease is in the development of disease-modifying treatments. Any candidate treatments designed to slow or halt the progression of the disease would need to be tested in patients with early disease to assess their ability to alter the course.

Collingwood speaks for many in the research community regarding the issue of early testing for Parkinson's disease: "I believe it is unethical to ignore opportunities for improved or earlier diagnosis if there is the possibility that a disease might be curable in future, or that protective therapies might be used to limit the extent or slow the progression of the disease." In the meantime, the search for biomarkers continues and researchers are starting to fathom their potential to catch Parkinson's disease early — this is no mere fishing trip.

Rachel Jones is a freelance writer in Welwyn, Hertfordshire, United Kingdom.

1. Posnen, M. M. *et al. Ann. Neurol.* **56,** 173–181 (2004).
2. Oakley, A. E. *et al. Neurology* **68,** 1820–1825 (2007).
3. Booij, J. *et al. Eur. J. Nucl. Med.* **24,** 68–71 (1997).
4. El-Agnaf, O. M. *et al. FASEB J.* **17,** 1945–1947 (2003).
5. El-Agnaf, O. M. *et al. FASEB J.* **20,** 419–425 (2006).
6. Collingwood, J. F. *et al. Mov. Dis.* **23** (suppl. 1), abstr. S62 (2008).
7. Biomarkers Definitions Working Group. *Clin. Pharmacol. Ther.* **69,** 89–95 (2001).