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Feature Article Commentary

The search for sensitive biomarkers in presymptomatic Huntington disease

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Huntington disease (HD) is a severe neurodegenerative disorder for which there is a critical need of disease modifying drugs. Clinical onset typically occurs between the age of 30 and 50, and the disease evolves over 15 to 20 years with worsening psychiatric, motor, and cognitive symptoms (Novak and Tabrizi, 2010).

Huntington disease is caused by a mutation in a single gene, *HTT*, with full penetrance, making it feasible to identify presymptomatic individuals who will develop the disease but do not yet show yet any clinical symptoms. This provides a unique opportunity to prevent or slow brain damage before clinical onset. Our understanding of the pathogenesis of HD, although still incomplete, has improved tremendously since the identification of the mutation in 1993 (The Huntington's Disease Collaborative Research Group, 1993). A number of molecules have been shown to slow down disease in animal models and are potential candidates for neuroprotective therapeutic trials in humans (Mochel and Haller, 2011; Roze *et al*, 2008).

However, such preventive clinical trials are hampered by the lack of sensitive markers for the disease in its early stages, and even more so in its presymptomatic period. Therapeutic trials using clinical scores such as the Huntington's Disease Rating Scale (UHDRS) and TFC (Total Functional Score) typically require studying large cohorts over long periods of time. At least two large studies (Predict-HD and Track-HD) are underway to identify more sensitive biomarkers. These studies have been extremely useful and have provided much needed data. Nonetheless, recently published results from both studies emphasize that there is still an important need for variables showing significant short-term changes during the presymptomatic period (Paulsen *et al*, 2010; Tabrizi *et al*, 2012).

The featured article by Chaumeil *et al* (2012) in the present issue reports interesting changes in pH in the brain of patients with HD at a mild-to-moderate stage of the disease (stages I to II) using ^{31}P magnetic resonance spectroscopy. The authors also report similar and progressive changes in pH in the brain of rats treated with 3-nitropropionic acid. In addition to providing new insights into the disease process, these results provide a new candidate biomarker. Two recent proton magnetic resonance spectroscopy studies in HD patients, one at 3 T and the other one at 7 T, as well as earlier studies at lower magnetic field cited in those two papers, showed that significant neurochemical changes in HD brain occur only after the appearance of clinical symptoms (Sturrock *et al*, 2010; van den Bogaard *et al*, 2011). Therefore, further studies are now needed to determine how early changes in pH reported by Chaumeil *et al* (2012) occur in HD and whether pH is a sensitive biomarker at earlier stages of the disease and in presymptomatic individuals.

Overall, it is unlikely that a single biomarker will be sufficient to monitor disease progression. More likely, a combination of biomarkers will be necessary. Magnetic resonance spectroscopy is a noninvasive technique that gives unique access to biochemical processes in the brain and is certainly one of the directions to further explore in the search for suitable biomarkers for neuroprotective therapeutic trials in HD.

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