Optimal time to treat Huntington's disease identified
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By the University College London May 26, 2020

The earliest brain changes due to Huntington's disease can be detected 24 years before clinical symptoms show, according to a new UCL-led study.

The researchers say their findings, published in *The Lancet Neurology*, could help with clinical trials by pinpointing the optimal time to begin treating the disease.

There is currently no cure for Huntington's, a hereditary neurodegenerative disease, but recent advances in genetic therapies hold great promise.

Researchers would ultimately like to treat people before the genetic mutation has caused any functional impairment. However, until now, it was unknown when the first signs of damage emerge—but as there is a genetic test for Huntington's susceptibility, researchers have a unique opportunity to study the disease before symptoms appear.

Professor Sarah Tabrizi (UCL Huntington's Disease Centre, UCL Queen Square Institute of Neurology), the study lead, said: "Ultimately, our goal is to deliver the right drug at the right time to effectively treat this disease—ideally we would like to delay or prevent neurodegeneration while function is still intact, giving gene carriers many more years of life without impairment. "As the field makes great strides with the drug development, these findings provide vital new insights informing the best time to initiate treatments in the future, and represent a significant advance in our understanding of early Huntington's."

The Wellcome-funded study, led by UCL researchers in collaboration with colleagues from the University of Cambridge and University of Iowa, investigated a large cohort of Huntington's mutation carriers at a much younger age than previously examined in detail. 64 people with the mutation took part alongside 67 others without the mutation who served as control subjects for comparison.

The study involved the most extensive testing of Huntington's ever performed, including tests of thinking, behaviour, brain scans and proteins in spinal fluid. The mutation carriers were, on average, 24 years ahead of the predicted disease onset, based on their age and a genetic test. They exhibited no changes in thinking, behaviour or involuntary movements commonly found in the disease, and there was very little evidence of brain scan changes.

But researchers did detect a subtle increase in the spinal fluid of a neuronal protein called neurofilament light (NfL), which is often the product of nerve cell damage.

Just under half (47%) of the mutation carriers had NfL values in their spinal fluid above the range of values found in the control group, at 24 years before disease onset, suggesting the authors have identified a crucial point at which brain changes first start occurring. NfL values correlated with predicted time to disease onset. The finding was supported by using the data to model predicted trajectories.

Co-first author of the study, Dr. Rachael Scahill (UCL Huntington's Disease Research Centre) added: "Other studies have found that subtle cognitive, motor and neuropsychiatric impairments can appear 10-15 years before disease onset. We suspect that initiating treatment even earlier, just before any changes begin in the brain, could be ideal, but there may be a complex trade-off between the benefits of slowing the disease at that point and any negative effects of long-term treatment."

Huntington's disease is caused by a single known genetic mutation, which codes for the production of the toxic mutant huntingtin protein that slowly damages neurons in disease sufferers. The disease usually develops in adulthood and causes abnormal involuntary movements, psychiatric symptoms and dementia. Patients usually die within 20 years of the start of symptoms. No effective treatments exist to slow it down.

Professor Tabrizi led the first human safety trial, completed in 2017, of a drug developed to reduce the levels of the huntingtin protein in the nervous system, which successfully lowered levels of the toxic huntingtin protein in participants. She is now one of the lead investigators on a major global phase 3 clinical trial, testing the long-term safety and clinical efficacy of the drug, and whether it slows disease progression.

Reference: [note: this document can be downloaded from the below URL. It is 502 pages

Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington's disease Young Adult Study (HD-YAS): a cross-sectional analysis
https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(20)30143-5.pdf
Lancet Neurol 2020; 19: 502–12

Authors: Rachael I Scahill*, Paul Zeun*, Katherine Osborne-Crowley, Eileanoir B Johnson, Sarah Gregory, Christopher Parker, Jessica Lowe, Akshay Nair, Claire O'Callaghan, Christelle Langley, Marina Papoutsi, Peter McColgan, Carlos Estevez-Fraga, Kate Fayer, Henny Wellington, Filipe B Rodrigues, Lauren M Byrne, Amanda Heselgrave, Harpreet Hyare, Cristina Sampaio, Henrik Zetterberg, Hui Zhang, Edward J Wild, Geraint Rees, Trevor W Robbins, Barbara J Sahakian, Douglas Langbehn, Sarah J Tabri

Summary

Background Disease-modifying treatments are in development for Huntington's disease; crucial to their success is to identify a timepoint in a patient's life when there is a measurable biomarker of early neurodegeneration while clinical function is still intact. We aimed to identify this timepoint in a novel cohort of young adult premanifest Huntington's disease gene carriers (preHD) far from predicted clinical symptom onset.

Methods We did the Huntington's disease Young Adult Study (HD-YAS) in the UK. We recruited young adults with preHD and controls matched for age, education, and sex to ensure each group had at least 60 participants with imaging data, accounting for scan fails. Controls either had a family history of Huntington's disease but a negative genetic test, or no known family history of Huntington's disease.

All participants underwent detailed neuropsychiatric and cognitive assessments, including tests from the Cambridge Neuropsychological Test Automated Battery and a battery assessing emotion, motivation, impulsivity and social cognition (EMOTICOM). Imaging (done for all participants without contraindications) included volumetric MRI, diffusion imaging, and multiparametric mapping. Biofluid markers of neuronal health were examined using blood and CSF collection. We did a cross-sectional analysis using general leastsquares linear models to assess group differences and associations with age and CAG length, relating to predicted years to clinical onset. Results were corrected for multiple comparisons using the false discovery rate (FDR), with FDR <0·05 deemed a significant result.

Findings Data were obtained between Aug 2, 2017, and April 25, 2019. We recruited 64 young adults with preHD and 67 controls. Mean ages of participants were 29·0 years (SD 5·6) and 29·1 years (5·7) in the preHD and control groups, respectively. We noted no significant evidence of cognitive or psychiatric impairment in preHD participants 23·6 years (SD 5·8) from predicted onset (FDR 0·22–0·87 for cognitive measures, 0·31–0·91 for neuropsychiatric measures). The preHD cohort had slightly smaller putamen volumes (FDR=0·03), but this did not appear to be closely related to predicted years to onset (FDR=0·54). There were no group differences in other brain imaging measures (FDR >0·16). CSF neurofilament light protein (NfL), plasma NfL, and CSF YKL-40 were elevated in this far-from-onset preHD cohort compared with controls (FDR<0·0001, =0·01, and =0·03, respectively). CSF NfL elevations were more likely in individuals closer to expected clinical onset (FDR <0·0001).

Interpretation We report normal brain function yet a rise in sensitive measures of neurodegeneration in a preHD cohort approximately 24 years from predicted clinical onset. CSF NfL appears to be a more sensitive measure than plasma NfL to monitor disease progression. This preHD cohort is one of the earliest yet studied, and our findings could be used to inform decisions about when to initiate a potential future intervention to delay or prevent further neurodegeneration while function is intact.