Study identifies pathology of Huntington's disease

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A study led by researchers at Boston University School of Medicine (BUSM) provides novel insight into the impact that Huntington's disease has on the brain. The findings, published online in *Neurology*, pinpoint areas of the brain most affected by the disease and opens the door to examine why some people experience milder forms of the disease than others.

Richard Myers, PhD, professor of neurology at BUSM, is the study's lead/corresponding author. This study, which is the largest to date of brains specific to Huntington's disease, is the product of nearly 30 years of collaboration between the lead investigators at BUSM and their colleagues at the McLean Brain Tissue Resource Center, Massachusetts General Hospital and Columbia University.

Huntington's disease (HD) is an inherited and fatal neurological disorder that typically is diagnosed when a person is approximately 40 years old. The gene responsible for the disease was identified in 1993, but the reason why certain neurons or brain cells die remains unknown.

The investigators examined 664 autopsy brain samples with HD that were donated to the McLean Brain Bank. They evaluated and scored more than 50 areas of the brain for the effects of HD on neurons and other brain cell types. This information was combined with a genetic study to characterize variations in the Huntington gene. They also gathered the clinical neurological information on the patients' age when HD symptoms presented and how long the patient survived with the disease.

Based on this analysis, the investigators discovered that HD primarily damages the brain in two areas. The striatum, which is located deep within the brain and is involved in motor control and involuntary movement, was the area most severely impacted by HD. The outer cortical regions, which are involved in cognitive function and thought processing, also showed damage from HD, but it was less severe than in the striatum.

The investigators identified extraordinary variation in the extent of cell death in different brain regions. For example, some individuals had extremely severe outer cortical degeneration while others appeared virtually normal. Also, the extent of involvement for these two regions was remarkably unrelated, where some people demonstrated heavy involvement in the striatum but very little involvement in the cortex, and vice versa.

"There are tremendous differences in how people with Huntington's disease are affected," Myers said. "Some people with the disease have more difficulty with motor control than with their cognitive function while others suffer more from cognitive disability than motor control issues."

When studying these differences, the investigators noted that the cell death in the striatum is heavily driven by the effects of variations in the Huntington gene itself, while effects on the cortex were minimally affected by the HD gene and are thus likely to be a consequence of other unidentified causes. Importantly, the study showed that some people with HD experienced remarkably less neuronal cell death than others.

"While there is just one genetic defect that causes Huntington's disease, the disease affects different parts of the brain in very different ways in different people," said Myers. "For the first time, we can measure these differences with a very fine level of detail and hopefully identify what is preventing brain cell death in some individuals with HD."

The investigators have initiated extensive studies into what genes and other factors are associated with the protection of neurons in HD, and they hope these protective factors will point to possible novel treatments.

Provided by Boston University Medical Center