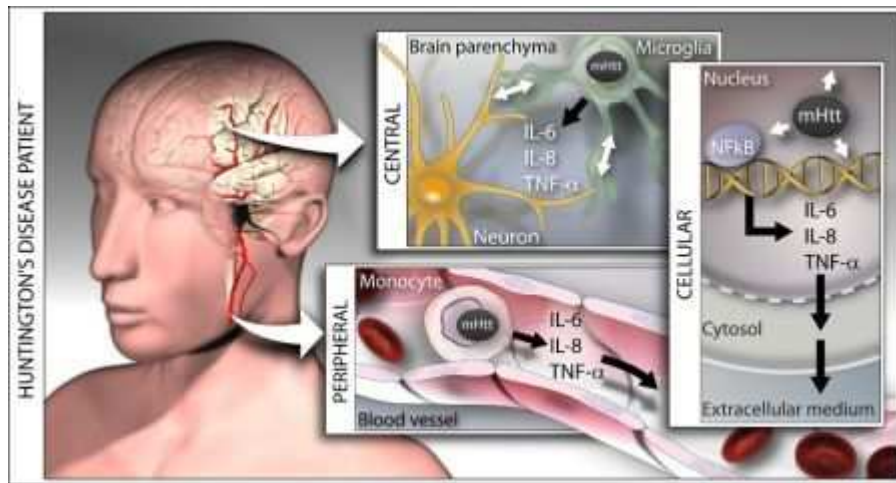


Immune System Over-activated in HD

Two teams of researchers, working separately and then combining their results for a significant journal article, provide evidence of an over-activated immune system in both the blood and brains of HD patients and HD mice.

Researchers at the University of Washington and researchers at the University College of London used a variety of methods to study the immune system, examining blood plasma and cerebrospinal fluid in HD patients, premanifest gene carriers, and controls as well as in multiple mouse models. In addition, brain tissue samples from autopsy were analyzed as were samples from the mice.

They found that certain cytokines, proteins which are secreted as part of an immune system response, were elevated in both plasma and the brain. These cytokines were elevated in those who were gene positive but not showing clinical symptoms as compared to a control group of individuals without the HD gene. Strikingly, these elevations were found in premanifest gene carriers who were an average of 16 years from their predicted age of onset. Levels were elevated still further in HD patients as compared to premanifest gene carriers.



It appears that the presence of the HD protein causes the cells to be over-responsive when the immune system is activated. The researchers stimulated isolated white blood cells from people and YAC128 mice and found that the cells produced more of the cytokine IL-6 than did cells from normal controls. They repeated the experiment with microglia cells from the R6/2 mice and got the same response.

In the blood, the cytokine elevation was associated with white blood cells. In the brain it was associated with microglia. The microglia are often said to be the immune cells of the brain, but their function is a little more complicated than that. The microglia, like glia cells, function to protect and support neurons, but they also function as immune cells.

However, they are not as powerful as the immune cells in the blood because neurons are too fragile to withstand a response of that intensity.

The role of microglia in HD is not fully understood but it is believed that they contribute to pathology since microglial activation is associated with the areas of the brain affected by HD and is found early in the brain in premanifest gene carriers, and because it increases with the severity of the disease. The theory is that activated microglia could lead to excitotoxicity, the production of free radicals and oxidative damage, and caspase activation and apoptosis.

Dr Sarah Tabrizi, who led the research for the UCL Institute of Neurology team commented that: "Finding increased cytokines in the blood was interesting, but the idea that the HD gene could be causing immune overactivity directly from within the white blood cells is important, because if the same thing is happening in the brain, cells that are there to protect neurons could be damaging them instead."

"It looks like we've unearthed a new early pathway by which the HD gene could cause damage, through abnormal overactivity of the immune system. What's more, this new pathway is quite easy to detect in the blood of patients, so we may have found a unique window from the blood into what the disease may be doing in the brain."

Dr. Thomas Moeller lead the research team at the University of Washington. "When we found increased levels of cytokines in the brains of Huntington's disease patients, we were very excited," Dr. Moeller said. "Inflammation in the brain has been increasingly recognized as an important component in other neurodegenerative diseases such as Alzheimer's or Parkinson's disease. These findings might open the door to novel therapeutic approaches for Huntington's disease that target inflammation."

Huntington's patients may eventually benefit in three ways. Further research may confirm that the pathway by which the cytokines become elevated is a therapeutic target for drug development. Should that happen, a blood test for these cytokines could be a good indicator of when the treatment should be started. In addition, levels of the cytokines could become a biomarker for more objective and more rapid measurement of disease progression in clinical trials.

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- *Marsha L. Miller, July 21, 2008*