New research implicates myelin in early evolution of Huntington's disease

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Last month, Dr. George Bartzokis, director of the UCLA Memory Disorders and Alzheimer's Disease Clinic, suggested in the journal Alzheimer's & Dementia that the breakdown of a type of myelin that develops late in life promotes the buildup of toxic amyloid plaques long associated with Alzheimer's disease. Myelin is the "insulation" that wraps around nerve axons in the brain.

Now, in a new report currently online in the journal Neurochemical Research, Bartzokis turns his attention to Huntington's disease. Again, he suggests that a breakdown of myelin is the cause, but with a twist — it is the myelin that develops early in the formation of the brain that breaks down prematurely and eventually leads to the disease's symptoms.

Huntington's disease (HD) is a rare, inherited neurological disorder that ultimately deprives individuals of their ability to control their movement, behavior and thinking. It affects approximately 30,000 people in the U.S., with another 150,000 at risk. While it is known that HD is caused by a mutation in a gene called Huntingtin (Htt), the exact mechanism by which the Htt gene causes or contributes to neuronal cell death and HD symptoms remains unclear. Bartzokis' research suggests it is Htt's affect on myelin that may prove to be the cause.

The earliest parts of the developing brain include systems of neurons that control movement and behavior. These neurons have long axons — finger-like projections that serve as the primary transmission lines of the nervous system — covered with thick myelin sheaths. The sheaths are nourished by an ongoing supply of a protein called brain-derived neurotrophic factor, which travels down a neuron's axon.

Bartzokis believes the Htt gene interferes with this nourishment-delivery system, resulting in a breakdown of the myelin that depends on it. That, in turn, disrupts cell signaling, which results in the neuron's death.

The problem is compounded by the continual production of other cells that continue to make myelin. In HD, increasing numbers of these cells, called oligodendrocytes, are produced in an attempt to remyelinate axons whose myelin sheaths have broken down. This results in strikingly elevated numbers of oligodendrocytes years before the appearance of HD symptoms.

Such elevation is detrimental because oligodendrocytes are rich with iron, which, while required for myelination, is also a well-known catalyst of free-radical-induced tissue damage. Iron accumulates during normal aging, and abnormal iron metabolism is believed to be involved in many human disorders. This is true for both highly prevalent, chronic disorders of aging, such as Alzheimer's and Parkinson's diseases, and acute disorders, such as stroke, where the extent of tissue damage is also related to iron levels.

To spot myelin destruction, neuron death and iron accumulation in the brains of HD subjects, Bartzokis used two magnetic resonance imaging (MRI) machines operating at different field strengths. Measurements of myelin breakdown and iron content were taken from the brains of 11 HD subjects and compared to a control group of 27subjects. Bartzokis found that both the breakdown and the iron accumulation matched the typical progression of the disease from early to late myelinating regions.

Thus, according to Bartzokis, earlier myelinated axons, such as the ones controlling movement, bear the brunt of damage from the mutant gene in the disease.

"And the early symptoms of Huntington's are problems with controlling movement, behavior and

eventually thinking," he said.

The implications of this are important, Bartzokis noted, since there is a decades-long period during which therapeutic interventions could modify the course of the disease, long before clinical evidence — such as behavioral, cognitive and motor problems — appear. Thus, it may be possible to develop medication that could be administered in the very early stages using non-invasive in vivo neuroimaging markers of both myelin breakdown and levels of iron.

Source: University of California - Los Angeles