

Study Links Neurodegeneration in Head Trauma and ALS

By: Katie Moisse, PhD

Nearly four years since researchers identified the mystery component of toxic protein aggregates in ALS and frontotemporal lobar degeneration (FTLD)-affected motor neurons as TAR DNA-binding protein (TDP-43), a new study has suggested the protein is a player in head injury too.

Repetitive head injuries, like those tolerated by boxers, football players and hockey players, can lead to chronic traumatic encephalopathy (CTE) — a condition marked by neurofibrillary tangles of tau protein and behavioral changes akin to those seen in frontal lobe dementia.

But Boston-based researchers have reported that TDP-43 also accumulates in CTE patients' brain neurons, and, in some cases, motor neurons in the spinal cord. In their report, published August 18 in the online *Journal of Neuropathology and Experimental Neurology*, they provide evidence that trauma-induced CTE and changes in brain TDP-43 expression could lead to downstream motor neuron degeneration resembling ALS.

The 16-strong research team, led by Ann McKee, MD, from the Bedford Veterans Administration Hospital in Bedford, MA, measured tau and TDP-43 expression in post-mortem brain and spinal cord tissue from 12 former athletes with CTE. Three of the subjects — a professional boxer and two professional football players — were also diagnosed with ALS. Tissue from 12 people who were neurologically normal at the time of death and 12 people with sporadic ALS served as controls.

As expected, the researchers detected abnormal tau expression in brain neurons from all 12 CTE subjects. But they also observed it in spinal neurons in all eight of 12 cases for which spinal cord tissue was available. This is in contrast to the rare tau-positive motor neurons they observed in spinal tissue from only four of 12 normal controls.

When the researchers looked for TDP-43, they saw normal patterns of expression in controls. But seven of the nine CTE subjects without MND displayed TDP-43 expression reminiscent of that seen in sporadic ALS motor neurons throughout the brain and brain stem — but not in the spinal cord, for which tissue was only available for five of the nine cases.

Perhaps the most striking finding the authors reported is that in all three subjects diagnosed with CTE that went on to develop a progressive and ultimately fatal motor neuron disease (MND) years later, they detected abnormal TDP-43 expression throughout the brain, brain stem *and* spinal cord. It should be noted that the clinical symptoms of these individuals resembled sporadic ALS, although the boxer was ultimately diagnosed with atypical ALS with dementia.

"This is the first pathological evidence that repetitive head trauma experienced in collision sports might be associated with the development of a motor neuron disease," they reported.

The study attracted significant attention from the North American press. Several reports in the media put forth the provocative question of whether Lou Gehrig — the New York Yankee who died from a progressive motor neuron disease diagnosed as ALS resulting in the popular term "Lou Gehrig's disease" — in fact suffered from a condition related to multiple head injuries sustained during his professional baseball career.

This is not, however, the first report that has suggested a link between ALS and trauma. In a study published in 2007 in *the American Journal of Epidemiology*, participants who reported having sustained repeated head injuries were three times more likely to have ALS than those who reported being injury-free. In other studies, the incidence of ALS among professional soccer players in Italy and professional football players in North America was reportedly higher than what would be expected in the normal population.

Nor is this the first report that has documented abnormal neuronal TDP-43 expression in neurodegenerative conditions other than ALS or FTLD. According to the McKee and colleagues, it is also a feature of Alzheimer's disease, hippocampal sclerosis, parkinsonism-dementia complex (PDC) of Guam,

Pick's disease, corticobasal degeneration, argyrophilic grain disease and Lewy body disease.

Although researchers have learned much about TDP-43 since Manuela Neumann, MD, and Tetsuaki Arai, MD, PhD, and colleagues, first published evidence for its role in neurodegenerative disease, its function is not completely clear. It is known to bind RNA, including low molecular weight neurofilament (NFL) RNA, which increases following nerve injury. TDP-43 RNA and protein levels also increase after nerve injury in mice, suggesting that the protein might be a key player in the neuronal response to injury.

"Conceivably, traumatic axonal injury may also accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm and thereby enhance its neurotoxicity," McKee and colleagues report.

Nerve injuries and ALS share many features other than TDP-43 abnormalities, such as inflammation, glutamate excitotoxicity, whereby neurons are injured by sustained activation of glutamate receptors leading to a toxic influx of calcium, and oxidative stress. And while the events that trigger motor neuron degeneration in ALS remain unclear, it is widely accepted that several genetic, environmental and behavioural factors are at play. Whether repetitive head trauma alone provokes neurodegeneration or whether it must occur in association with other genetic risk factors remains to be determined, McKee and her team wrote.

The study supports the notion that an injury can prompt abnormal TDP-43 expression leading to neurodegeneration. The authors propose that the neurodegeneration exhibited by the three athletes who had CTE and went on to develop motor neuron disease spread from their brains to their spinal cords. This begs the question: could the accumulation of injuries over time cause ALS?

Although the three athletes with MND were diagnosed with ALS based on their symptoms, McKee and colleagues suggest they actually suffered from something else: CTE+MND.

"This report suggests that the play of contact sports, including boxing, football, and hockey, might be associated with a widespread TDP-43 proteinopathy that, in some individuals, is manifest as MND," they wrote.

But whether the two conditions are in fact separate entities or, rather, overlapping degrees of the same syndrome remains unclear. CTE+MND is marked by tau abnormalities traditionally not associated with ALS. And while McKee and colleagues observed tau and TDP-43 abnormalities in the same patients, they rarely saw them in the same neurons. Moreover, their data also establish that having abnormal tau alone in spinal cord neurons is not sufficient for the development of MND.

Other research groups have made similar observations in a subset of familial and sporadic ALS patients, and the two proteins are known to play a role in ALS-PDC of Guam and ALS with frontotemporal dementia. Furthermore, a study recently published in *Human Molecular Genetics* suggests that mice expressing mutant SOD1 (the most commonly used mouse model of ALS) and mice expressing mutant tau share several genetic and behavioral features.

It is important to note that mutations in the TDP-43 gene cause familial ALS. But how this fits in with the idea of injury provoking progressive and fatal motor neuron degeneration remains unclear. The study by McKee and colleagues adds to the complexity of this elusive protein whose discovery has, perhaps, generated more questions than answers. But it also paves the way for additional research into TDP-43's normal function and its role in neurodegeneration.

"This study in *the Journal of Neuropathology and Experimental Neurology* is a very interesting piece of work, and it opens the door to some very exciting research questions," said Denise Figlewicz, PhD, vice-president of research for the ALS Society of Canada.

"As the authors state in their introduction, a link between ALS and head trauma has been considered as a possibility for several decades. It has been challenging to establish the connection based on epidemiological studies, for the same reasons that any epidemiology of ALS has been difficult – multiple possible causes, and the low numbers of study subjects," Figlewicz said.

"ALS Canada researchers have contributed to international breakthroughs in the search to find a cure for ALS, including studies of the role of TDP43 in cellular and animal models of ALS, and hopefully this study will bring us one step closer to finding treatments and a cure for this devastating disease."

Posted On: Friday, August 20, 2010

Modified: Friday, August 20, 2010

Category: [ALS Research](#)

Posted By: [Andrew Romano](#)