Researchers show first clear relationship between amount of CTE pathology, severity of symptoms

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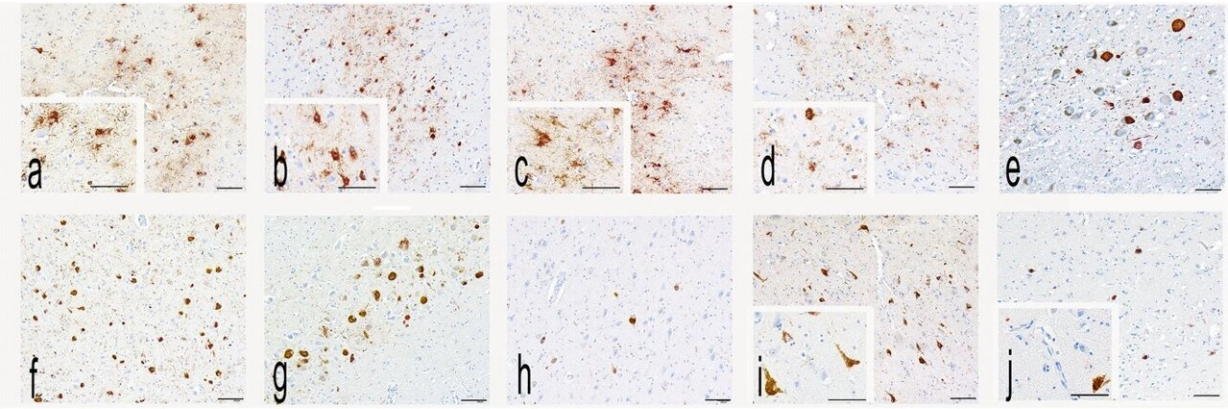

Regional Hyperphosphorylated Tau Pathology in CTE. Photomicrographs of AT8 immunostained cortical neurofibrillary tangles (NFTs), neurites, and astrocytic inclusions around small central vessels within the depths of sulci in a 71- year-old former professional American football player with stage IV CTE in the dorsolateral frontal cortex (**a**), inferior frontal cortex (**b**), inferior parietal cortex (**c**), superior temporal cortex (**d**), globose NFTs and neurities in the locus coeruleus (**e**), NFTs in the CA1 (f), CA2 (**g**) CA4 (**h**) hippocampal subfields, NFTs and neurites in the entorhinal cortex (**i**) layer 4 and basal nucleus of the amygdala (**j**). Scale bar = 100μm. Credit: *Molecular Neurodegeneration* (2024). DOI: 10.1186/s13024-023-00697-2

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease

defined by hyperphosphorylated tau (p-tau) protein accumulating in a particular pattern in specific regions of the brain. Currently, CTE can only be diagnosed at autopsy. Like similar brain diseases, the clinical symptoms in life of people diagnosed with CTE after death can vary, and there has been robust debate as to what symptoms, if any, are caused by CTE pathology.

In a new study from the BU CTE Center, researchers provide the most definitive evidence to date that CTE p-tau pathology is primarily responsible for cognitive and functional symptoms, explaining up to 49% of the variation seen in individual patients. For context, studies of Alzheimer's disease have suggested that all pathologies, including p-tau, explain about 50% of symptoms.

"For the first time, we were able to show a clear dose-response relationship between the amount of CTE pathology and the severity of cognitive and functional symptoms, including problems with memory and executive function. These findings provide a clear step forward toward diagnosing CTE in life," explains corresponding author Jesse Mez, MD, MS.

Neuropathologists rated the amount of p-tau pathology across 11 brain regions commonly affected in CTE in 364 brain donors with autopsy-confirmed CTE. Family and friends of brain donors completed seven standardized scales assessing their loved one's cognitive, functional, mood, and behavioral symptoms. The researchers then examined the relationship between global and regional p-tau pathology and scores on multiple scales.

They found that the amount of p-tau pathology across the brain, but most predominantly in the frontal lobe, was associated with more cognitive and functional symptoms and that the amount of p-tau pathology in the frontal lobe was associated with more neurobehavioral symptoms.

However, neurobehavioral symptoms were less correlated than cognitive symptoms, with p-tau pathology only explaining about 14% of the variation in neurobehavioral symptoms.

Memory and executive function symptoms are included as core features of the 2021 NINDS Traumatic Encephalopathy Syndrome criteria, proposed by a group of multidisciplinary experts to diagnose CTE in life. Currently, the criteria are not yet approved for use outside of research. These findings help validate the criteria, with the hope that they can eventually be used on living patients to help provide a diagnosis and treatment plan.

According to the researchers, these findings provide crucial insights into diagnosing CTE in life.

"Diagnosis is crucial before we can test therapies. With validated in-life diagnostic criteria, we will be able to design clinical trials for therapies," says Mez.

The work is published in the journal *Molecular Neurodegeneration*.

More information: Michael L. Alosco et al, Cognitive, functional, and neuropsychiatric correlates of regional tau pathology in autopsy-confirmed chronic traumatic encephalopathy, *Molecular Neurodegeneration* (2024). DOI: 10.1186/s13024-023-00697-2

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