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NEWS AND COMMENTARY

Biomarkers in the diagnosis of CTE

Antemortem biomarker support for a diagnosis of clinically probable chronic traumatic encephalopathy

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative condition associated with repetitive mild traumatic brain injuries (mTBI) that occur in high-impact collision sports like football, hockey, soccer and boxing. Warfighters exposed to blast injuries from improvised explosive devices can develop a similar condition. While the rising awareness of mTBI and CTE has galvanized research into the mechanism and pathology by which mTBI leads to CTE, there is still the issue of how to confirm the clinical diagnosis in living persons. As with many neurodegenerative diseases, CTE can be diagnosed definitively only upon direct examination of brain tissue secured by biopsy or autopsy. Clinically, advances have been made in diagnosing CTE, and these include a range of neuropsychological tests, blood biomarkers and brain imaging using magnetic resonance imaging (MRI) and positron emission tomography (PET), although the clinical characteristics of CTE are broad and overlap with many symptoms common in retiring athletes and former warfighters.

A number of PET tracers have recently been developed that bind to aggregated tau in neurofibrillary tangles (NFTs), the pathological hallmarks of CTE. These include [11C]PBB3, [18F] FDDNP, [18 F]AV-1451/T807 and a series of ligands from Tohoku ([18 F]THK-523, THK-5105, THK-5117 and THK-5351). $^{1-5}$ These tracers have been validated in both animal models of Alzheimer's disease (AD) and postmortem tissue from AD patients, where binding was more elevated in neocortical areas in patients with AD compared with cognitively normal controls.^{1,6,7} While tauopathy imaging seems to be a constructive application in the staging of AD,⁸ there is little known about the usefulness of tauopathy imaging in diagnosing and staging other neurodegenerative diseases such as CTE. It is also important to note that these are early days in the use of such tauopathy markers; these markers have not been validated in people who have had a positive tauopathy scan and then had an autopsy confirming the findings, and no tauopathy tracer has been approved by any regulatory agency.

Recently, we reported on a 39-year-old retired National Football League (NFL) player who had suffered 22 concussions and who presented with progressive neuropsychiatric symptoms and was determined to have a decline in executive functioning, processing speed and fine motor skills. Structural analysis of longitudinally acquired MRIs revealed cortical thinning in the left frontal and lateral temporal areas, as well as volume loss in the basal ganglia, areas that corresponded to the clinical symptoms. [¹⁸F]Florbetapir PET imaging for amyloidosis was negative. [¹⁸F]AV-1451/T807 PET imaging revealed multifocal areas of tracer retention outlining the cortical gyri and sulci, with apparent localization to the gray-matter–white-matter junction, a distribution considered pathognomonic for CTE (see cover).^{9,10}

The fact that the scattered regions of [¹⁸F]AV-1451/T807 retention correlated with what we know of the disseminated pathological localization of clusters of NFT at the depths of the sulci in the cortex is an encouraging finding in our search for noninvasive ways to confirm the clinical diagnosis. However, we do not yet have sensitivity data to allow us to approximate our accuracy of findings of the multisite tauopathy deposition. Determination of a radiological signature of CTE, or the use of tauopathy tracers to make clinical diagnoses analogous to those made with amyloid PET imaging in AD, is still awaited. Large-scale studies are needed to determine both quantitative measures of tauopathy burden as well as gualitative patterns that can distinguish among non-specific uptake, normal aging and any one of the various different tauopathies. In AD, an emerging topography of in vivo [¹⁸F] AV-1451/T807 uptake, with progression of deposition from the medial temporal lobes to increasingly larger temporal, parietal and frontal regions, does seem to correspond to what is known of the progressive spread of NFTs as the clinical disease progresses.4,8 Autopsy examination and pathological - radiological analysis of such cases are eagerly anticipated.

In CTE, validation of a positive tau scan also critically requires postmortem examination of brains of people scanned during life, to determine whether the tracer retention correlates with the presence of tau and NFTs in the brain. However, the populations affected by CTE are young, with little risk for early mortality apart from increased suicide rates. Waiting decades for pathological – radiological correlation will delay the numerous potential benefits from developing and harnessing *in vivo* diagnostics in the present. Developing methods to detect and quantify tauopathy burden during life will enable us not only to estimate prevalence and to track the natural history of CTE, but also to test the efficacy of novel therapies as they emerge. Moreover, active athletes or warfighters found to have positive [¹⁸F]AV-1451/T807 imaging might want to consider avoiding further exposure to trauma.

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In conclusion, ours and other studies of *in vivo* imaging of tauopathy deposition in the brains of retired athletes and former warfighters can provide insight into the pathogenesis, diagnosis and potential treatment of tauopathies such as CTE. Whether tauopathy imaging can provide useful diagnostic or prognostic screening information and/or clinically important outcome measures for anti-tauopathy therapies are major questions for the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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