

# Letters

## OBSERVATION

### Pathologically Confirmed Chronic Traumatic Encephalopathy in a 25-Year-Old Former College Football Player

Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy associated with repetitive head impacts.<sup>1</sup> Presently, CTE only can be diagnosed pathologically; however, research efforts, such as the ongoing Understanding Neurological Injury and Traumatic Encephalopathy (UNITE) Study,<sup>2</sup> are investigating ways to diagnose CTE during life. As part of the UNITE Study, a panel of clinicians, blinded to neuropathology, make retrospective clinical consensus diagnoses using published criteria, including proposed clinical research criteria for CTE.<sup>3</sup> Here, we present an informative case from the UNITE Study.



Editorial

**Report of a Case |** A 25-year-old man with a congenital bicuspid aortic valve and a family history of addiction and depression died of cardiac arrest secondary to *Staphylococcus aureus* endocarditis. He played American football for 16 years, beginning at age 6 years, including 3 years of Division I college football (red shirt, freshman, and sophomore) as a defensive linebacker and special teams player. He experienced more than 10 concussions, all while playing football, the first occurring at age 8 years and none resulting in hospitalization. During his freshman year of college, he had a concussion with momentary loss of consciousness followed by ongoing headaches, neck pain, blurry vision, tinnitus, insomnia, anxiety, and difficulty with memory and concentration. When he returned to play after a few days, symptoms persisted. A neurologist prescribed cyclobenzaprine and topiramate, which offered limited benefit. He stopped playing football at the beginning of his junior season owing

Table. Neuropsychological Testing<sup>a</sup>

Test	Score <sup>b</sup>	Interpretation <sup>c</sup>
Intellectual functioning		
WAIS-III/7		
Estimated visual IQ	102	Average
Estimated performance IQ	100	Average
Estimated full-scale IQ	101	Average
WTAR	103	Average
Memory		
WMS-III		
Logical memory I	8	Low average
Logical memory II	8	Low average
CVLT-II		
Total trials 1-5	22	Impaired
Trial 1	4	Borderline
Trial 5	4	Impaired
Short-delay free recall	5	Impaired
Short-delay cued recall	5	Impaired
Long-delay free recall	4	Impaired
Long-delay cued recall	5	Impaired
BVM-T-R		
Trial 1	8	Average
Trial 2	10	Average
Trial 3	11	Average
Delayed recall	11	Average
Language		
BNT-2	47	Impaired
D-KEFS letter fluency	26	Low average
D-KEFS category fluency	32	Average

(continued)

Table. Neuropsychological Testing<sup>a</sup> (continued)

Test	Score <sup>b</sup>	Interpretation <sup>c</sup>
Attention/executive functioning		
TMT		
Part A speed (errors)	14 s(0)	High average
Part B speed (errors)	84 s(1)	Impaired
Symbol digit modalities test		
Written	36	Impaired
Oral	57	Low average
Stroop color and word test		
Word score	46	Average
Color score	46	Average
Color-word score	51	Average
Interference	53	Average
Visuospatial		
Rey figure copy	8	Low average
BVMT-R copy	12	Within expectation
Judgment of line orientation	28	High average

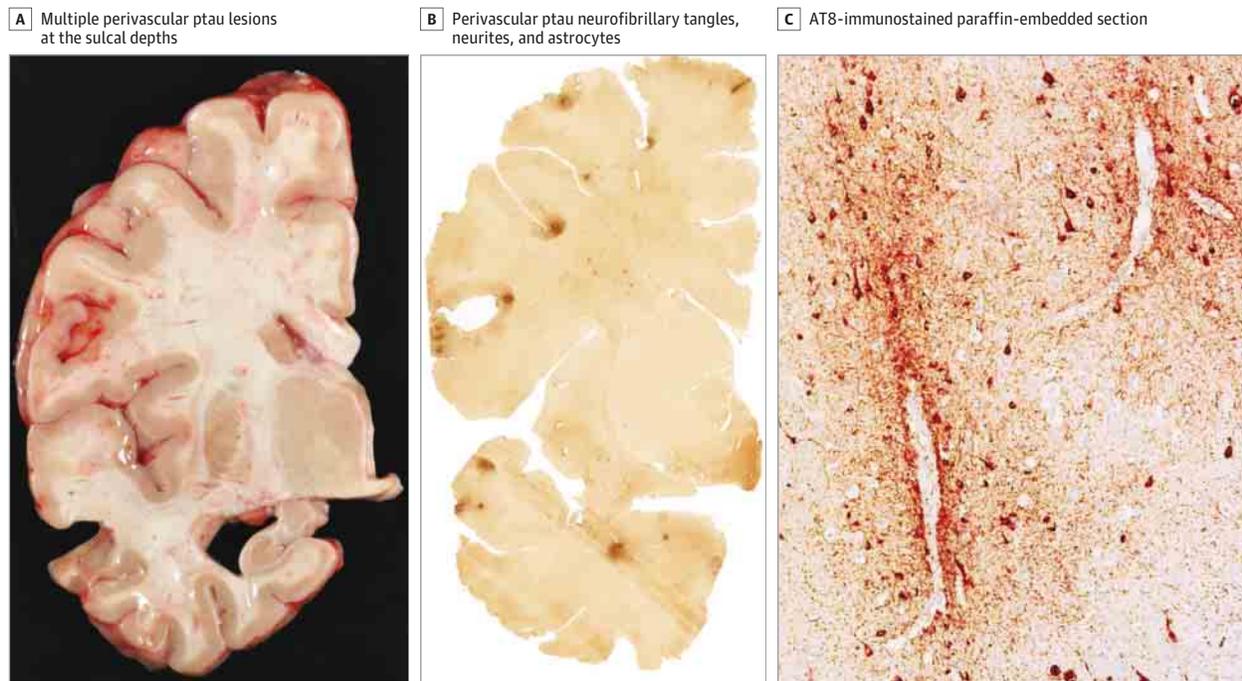
Abbreviations: BNT, Boston Naming Test; BVM-T-R, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

<sup>a</sup> Summary: Intelligence was average and reading ability was commensurate. Visuospatial abilities were average. There were deficits in verbal episodic encoding, although verbal episodic retrieval and visual memory were intact. There were deficits in set-shifting and processing speed. Selective attention was intact. There were deficits in naming. Letter and category fluency were intact.

<sup>b</sup> All scores are raw, unless otherwise indicated.

<sup>c</sup> Interpretations are based on normative data accounting for age and education level. Percentile conversions are as follows: very superior >98%; superior, 91%-97%; high average, 75%-90%; average, 25%-74%; low average, 9%-24%; borderline, 2%-8%; and impaired <2%.

Figure. Neuropathological Findings of Chronic Traumatic Encephalopathy (CTE)



A, The brain showed mild ventricular dilation and hippocampal atrophy. Pathological lesions of hyperphosphorylated tau (ptau) consisting of neurofibrillary tangles, neurites, and astrocytes around small blood vessels were found at the sulcal depths of the frontal and temporal lobes. Free-floating 50- $\mu$ m section immunostained for AT8 (B) and paraffin-embedded 10- $\mu$ m section immunostained for AT8 (C; original magnification  $\times 200$ ). These ptau lesions are considered to be pathognomonic for CTE based on the preliminary

National Institute of Neurological Disorders and Stroke consensus criteria for the pathological diagnosis of CTE.<sup>1,5,6</sup> Characteristic CTE ptau pathology was also found in the parietal lobes, entorhinal cortex, anterior hippocampus, hypothalamus, nucleus basalis of Meynert, substantia nigra, locus coeruleus, and median raphe. There was no immunopositivity for amyloid- $\beta$ , TAR DNA-binding protein 43, or  $\alpha$ -synuclein.

to ongoing symptoms. He began failing courses despite having earned above-average grades in high school (3.8 GPA) and earlier in college. He left school with a GPA of 1.9, 12 credits short of earning his bachelor degree.

His symptoms persisted and included apathy, anhedonia, decreased appetite, hypersomnia, feelings of worthlessness, and passive suicidal ideations. He had difficulty maintaining a job and eventually stopped seeking employment. He began using marijuana daily to alleviate headaches and anxiety and to improve sleep. At age 23 years, he became verbally and physically abusive toward his wife, a change from his prior demeanor. At age 24 years, he underwent neuropsychological evaluation (Table). He became increasingly dependent on his wife, although basic activities of daily living remained intact.

His next of kin provided written informed consent for participation and brain donation. Institutional review board approval for brain donation was obtained through the Boston University Alzheimer's Disease Center and CTE Program and the Bedford VA Hospital. Institutional review board approval for postmortem clinical record review, interviews with family members, and neuropathological evaluation was obtained through the Boston University School of Medicine.

Consensus members unanimously supported postconcussive syndrome (PCS) as the primary diagnosis, with possible CTE and major depression as contributing diagnoses. Although CTE was considered, the lack of delay in symptom on-

set, his young age, and his family history of depression reasoned against CTE as the primary diagnosis. Consensus members thought that neuropsychological performance, while impaired, did not discriminate postconcussive syndrome or major depression from CTE (Figure).

**Discussion** | Focal lesions of CTE have been found in athletes as young as 17 years<sup>1</sup>; however, widespread CTE pathology, as found in this case, is unusual in such a young football player. Although idiopathic depression and postconcussive syndrome commonly present in a similar fashion,<sup>4</sup> the presence of widespread CTE pathology argues against but does not exclude them as potential etiologies of the clinical syndrome. While the case suggests that CTE should be considered in the differential diagnosis of a young adult with extensive repetitive head impact exposure and persistent mood and behavioral symptoms, it does not allow us to infer the likelihood of CTE in this setting.

While proposed clinical research criteria for CTE include impairment in memory and executive function on neuropsychological testing,<sup>3</sup> to our knowledge, this is the first published case of pathologically confirmed CTE to include a neuropsychological test profile. It remains to be determined whether impairment in learning and executive function with preserved verbal episodic retrieval is a common presentation of CTE.

Studies of clinicopathological correlation, such as the UNITE Study,<sup>2</sup> should help identify clinical features that are

sensitive and specific for CTE pathology. Prospective studies that include neuropsychological testing with imaging and fluid biomarkers will be essential to future improvements in diagnosis of CTE during life.

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