A Case of Possible Chronic Traumatic Encephalopathy and Alzheimer’s Disease in an Ex-Football Player

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The pathologic progression of CTE is divided into 4 stages. In CTE stage I, the brain is grossly normal, with only a few p-tau deposits in the lateral and frontal cortices. As the disease progresses, there is widespread cortical deposition of p-tau and TDP-43. In the final CTE stage IV, there is marked atrophy of the frontal and medial temporal lobes, as well as the medial anterior thalami. The majority of patients in stage IV have sepal abnormalities, including cavum septum pellucidum with or without fenestration, and pallor of locus coeruleus and substantia nigra.

Although CTE is mainly a neuropathologic diagnosis, there are clinical manifestations corresponding to each progressive stage of CTE. In stage I, patients are either asymptomatic or might complain of mild memory and depressive symptoms, but as the diseases advances to stage III, there are prominent memory loss and executive functioning deficits. In the final CTE stage IV, profound cognitive, and motor deficits have been reported, which are often comorbid with psychotic symptoms. There are also reported CTE cases comorbid with Alzheimer disease (AD) pathology. In a cohort of CTE patients, reported by Stein and colleagues, amyloid β peptide (Aβ) deposition in diffuse or neuritic plaque form was reported in 52% of the cases. Despite the reported pathologic comorbidity of AD and CTE, there are relatively few case reports of patients with these comorbid diseases. Furthermore, the presence of neuritic plaques were found to be associated with increased CTE tauopathy, and comorbid Lewy body disease and dementia.

The patient began to have significant short-term memory deficits 4 years before being seen in the clinic. His wife also started to notice behavioral changes, including unusual emotional reactivity and irritability in everyday situations. As his episodic memory symptoms continued to worsen, he had increasing difficulty with retaining details of conversations, and following multistep instructions. His wife emotionally recalled an episode, during which the patient was unable to remember the name of his nephew. A sociable person by nature, he started to become more reclusive and withdrawn, and actively avoided social settings. As the disease progresses, there is widespread cortical deposition of p-tau and TDP-43. In the final CTE stage IV, there is marked atrophy of the frontal and medial temporal lobes, as well as the medial anterior thalami. The majority of patients in stage IV have sepal abnormalities, including cavum septum pellucidum with or without fenestration, and pallor of locus coeruleus and substantia nigra.

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reported worsening speech disturbances within the past 4 years. He had an extensive career as a business executive with an MBA degree, who had worked in multiple well-known companies managing purchasing, supply chains, and sustainability. He also managed his household financial affairs, but his wife had to take control of this because of his significant difficulties with processing numbers, calculations and multitasking.

Mr C.W. had his first concussion at the age of 5, and from the age of 5 until 1 year before being seen in the clinic, he suffered at least 20 concussions. The majority of them sustained playing in football teams, in his high school and college years playing in a quarterback position. In addition to his football involvement, Mr C.W. also played left field in baseball in high school, college, and a competitive league after college made up of former D1 college players, sustaining a few reported head injuries in collisions with other players and the outfield wall. His most recent concussion occurred at the age of 61 because of a fall, while walking with his dog. The concussions involved brief loss of consciousness, but the patient was unable to provide the exact durations.

There was a reported maternal history of dementia, not formally diagnosed, and Mr C.W.’s sister is currently undergoing further assessment for mild cognitive impairment.

His Montreal Cognitive Assessment (MoCA) score was 13/30, with significant deficits involving multiple domains including episodic memory, visuospatial functioning, attention, executive functioning, and phonemic fluency. The more extensive neuropsychological assessment indicated significant dysnomia, significant deficits in auditory comprehension, verbal and phonemic verbal fluency, as well as deficits in working memory, clock drawing, cognitive estimation, and novel problem solving (Table 1).

His serum levels for vitamin B12, folate, thyroid stimulating hormone, and free T4 were all within normal limits. The cerebrospinal fluid had significantly elevated total Tau (1045 pg/mL), phosphorylated Tau (125.05 pg/mL), and a decreased A-beta 42 to total Tau Index11 (0.25), which were consistent with diagnosis of AD.

The magnetic resonance imaging of brain without intravenous contrast with 3D volumetric analysis indicated total hippocampal volume measuring at the 11th percentile of the patient’s age-matched controls, with significant asymmetry (~12.1%) with smaller left hippocampal volume (Fig. 1). Moreover, the lateral ventricles were mildly enlarged with accompanying volume loss and a prominent cavum septum pellucidum (Fig. 2).

### DISCUSSION

This case report presents a unique but reported combination of memory, speech and executive functioning deficits comorbid with mood and subtle personality changes likely because of an underlying pathology of CTE and AD in a patient in his 60s.

The patient’s history of multiple mild TBI episodes with accompanying loss of consciousness in a subset of those episodes, is consistent with a history of CTE.5 Stern et al12 proposed that CTE presents clinically in 2 distinct subtypes. The first involves younger individuals who initially present with predominantly mood and behavioral symptoms; the second involving older patients with mostly memory and cognitive deficits. On the basis of this classification and consistent with the reported age onset, the presented case likely belongs to the second category.

Although CTE is a postmortem neuropathologic entity, the working diagnosis of the patient is “possible” CTE with comorbid AD, with features of “probable” CTE, based on the previously proposed CTE likelihood criteria by Montenigro et al.13,14 These suggestive features include a history of multiple impacts, leading to progressive memory and speech deficits over a time course lasting longer than 12 months, absence of prior psychiatric history including mood/anxiety disorders, post-traumatic stress disorder or substance use. There are additional supportive features including elevated cerebrospinal fluid phospho-tau/total-tau, cavum septum pellucidum, and cortical atrophy.14 There are multiple recent published cases of CTE comorbid with AD.9,15,16 However, the reported clinical presentation of dysarthria, dysnomia, personality alterations in a patient suffering from possible CTE with comorbid AD is unique. This case highlights the importance of obtaining a detailed history of TBIs, capturing subtle presenting symptoms, as well as characteristic neuroimaging findings. CTE is increasingly being recognized to be a distinct tauopathy. The characteristic CTE neuropathologic lesions include perivascular accumulation of tau in neurons, astrocytes, and cell-processes in sulci depth. Although, the clinical presentation could resemble AD, or FTD, its tau pathology is distinct from AD, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, Guamanian Parkinsonism Dementia Complex, and primary age-related tauopathy.10,17 Furthermore, according to a recent report by Falcon et al.18 using cryoelectron

### TABLE 1. Detailed Neuropsychological Assessment Reveals Global Cognitive Deficits

| Test                                         | Raw Score | Standard Score | Percentile |
|----------------------------------------------|-----------|----------------|------------|
| Factor                                       |           |                |            |
| Verbal learning/memory                       | 40        | SS = 54        | < 1        |
| Visual learning/memory                      | 38        | SS = 54        | < 1        |
| Hopkins adult reading test                  | 23        | Std = 111      | 77         |
| Trails A                                     | 44        | t = 41         | 18         |
| WAIS-IV digit span                          |           |                |            |
| Digits forward                              | 6         | t = 43         | 24         |
| Digits backward                             | 3         | t = 27         | 1          |
| Cognitive estimation task                    | 14        | t = 19         | < 1        |
| Calibrated ideational fluency               |           |                |            |
| Phonemic fluency total                      | 11        | t = 24         | < 1        |
| Semantic fluency total                      | 10        | t = 19         | < 1        |
| Boston naming test-30 item                  | 22        | t = 21         | < 1        |
| NAB language module                         |           |                |            |
| Language index                              | 29        | Std = 51       | 0.05       |
| Oral production                             | 7         | t = 19         | < 1        |
| Auditory comprehension                      | 77        | t = 19         | < 1        |
| Naming                                      | 23        | t = 19         | < 1        |
| Reading comprehension                       | 13        | t = 42         | 21         |
| Writing                                     | 9         | t = 25         | 1          |
| Bill payment                                | 10        | t = 19         | < 1        |
| Clock drawing                               | 2/5       | t = 19         | < 1        |
| Clock copy                                  | 4/5       | t = 20         | < 1        |
| Rey complex figure-copy                     | 29        | t = 38         | 12         |
| Hopkins verbal learning test                 |           |                |            |
| Total recall                                | 2         | t = 19         | < 1        |
| Delayed recall                              | 0         | t = 21         | < 1        |
| % retention                                 | 0         | t = 25         | 1          |
| Recognition discrimination                  | 7         | t = 30         | 2          |
| Brief visual                                |           |                |            |
| Total recall                                | 1         | t = 19         | < 1        |
| Delayed recall                              | 2         | t = 19         | < 1        |
| % retention                                 | 100       | t = 53         | 62         |
| Recognition discrimination                  | 2         | t = 19         | < 1        |
| Geriatric depression scale                  | 2/15      | t = WNL        |            |
| Wisconsin card sorting test-64              |           |                |            |
| Categories                                  | 0         |                | < 1        |
| Perseverative responses                     | 13        | t = 41         | 19         |
| Failure to maintain set                     | 0         |                |            |
| Total errors                                | 32        | t = 36         | 8          |

The neuropsychological battery demonstrated severe memory, executive functioning, language, and visuospatial deficits. WAIS indicates Wechsler adult intelligence scale; WNL, within normal limits.
microscopy, tau filaments in 6 CTE patients was found to contain a distinct hydrophobic domain that is unique only to this pathology, and absent in AD patients. A recently published case report using 18F-MK6240 tau positron emission tomography ligand, has reported a frontally predominant pattern of tau/phosphor-tau accumulation, distinct from posterior temporoparietal predominant pattern of prodromal AD.16

Other diagnostic possibilities include behavioral variant frontotemporal dementia (bvFTD) and logopenic variant primary progressive aphasia. However, the patient presented here has overlapping symptoms of both bvFTD and logopenic variant primary progressive aphasia, making the individual diagnostic entities less likely. Furthermore, bvFTD patients typically do not develop speech-related deficits, or episodic memory deficits until late stages of the disease process.19

A number of promising tau specific neuroimaging positron emission tomography ligands, including 18F-MK6240,THK5317, THK5351, AV1451, PBB3, and flortaucipir could change the diagnostic and assessment landscape of CTE.16,20-22 Moreover, recent advances in serum markers of TBI will likely provide the opportunity to assess, and monitor injured patients over time, which, in turn, may provide a more comprehensive time window to the disease etiology, which is currently lacking. The wider utility of TBI biomarkers will also make future timely disease preventative interventions a viable possibility.23 As awareness and understanding of CTE evolves, preventative measures including safe practice techniques, destigmatizing the reporting of mild TBI symptoms in both sport and combat settings, as well as vigilant and timely care of patients post trauma will need to be incorporated in our everyday practice.

This case highlights the importance of early recognition of symptoms in light of prior history of brain injuries. The onset of new affective symptoms in the absence of any prior psychiatric history, as well as severe and progressive cognitive deficits including speech, memory and executive functioning decline, warrants extensive neuropsychiatric assessments. Given the comorbidity of AD in this case, it is entirely plausible that the patient could have benefitted from enrollment in current ongoing clinical trials using experimental regimens such as Aducanumab.24 This in turn highlights the importance of early recognition of symptoms, and exploring potential and appropriate clinical interventions in a timely manner.

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