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LETTER TO THE EDITORS

Longitudinal clinicoradiological findings in pathologically confirmed chronic traumatic encephalopathy

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Dear Sirs,

Chronic traumatic encephalopathy (CTE) is a degenerative tauopathy associated with repetitive head trauma. It is associated with sport concussions and currently diagnosed on a post-mortem basis through pathological analysis [1, 2]. Ongoing research aims to identify potential in vivo biomarkers which may be used to improve the specificity of the premortem diagnosis of traumatic encephalopathy syndrome (TES) [3]. Due to the limitations of retrospective data collection, significant gaps remain in the literature regarding accurate longitudinal clinical and radiologic data in CTE [4]. Here, we describe longitudinal clinical, cognitive, and radiological data, including fluorodeoxyglucose-positron emission tomography (FDG-PET) and MRI, in a former professional football player meeting 2021 consensus criteria for TES [3] who presented with short term memory deficits at age 69 and was followed to age 82 when he was pathologically diagnosed with CTE.

Clinical assessments and cognitive testing were performed at St. Joseph's Hospital and the University of Western Ontario, London, Ontario, Canada between 2006 and 2014 and subsequently in a long-term care facility. The patient was initially enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study in 2006 and completed ADNI visits through 2009. Part of the data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. All research protocols were approved by the human subjects research ethics board of University of Western Ontario.

MRI scans were collected every 6–12 months in accordance with the ADNI protocol between 2006 and 2011 (http://adni.loni.usc.edu/). The patient also completed an FDG-PET/hybrid magnetic resonance imaging scan in 2014.

A 1 mm^3 three-dimension (3D) T1-weighted anatomical MRI image was acquired during PET imaging with a 3D magnetization-prepared rapid gradient-echo sequence for compensation of partial volume effects and spatial normalization of PET to a common template. The PET data were reconstructed to a 2 mm^3 image volume and analyzed following our previous image processing pipeline for FDG-PET [5]. The PET image corrected for partial volume effect was spatially smoothed by a 3D Gaussian kernel (10 mm full-width-half-maximum) and count-normalized to the mean cerebellum gray matter value to reduce inter-subject variability and allow for comparison to healthy volunteers. To better delineate areas of decreased FDG-PET representing areas of glucose hypometabolism, the PET image of the

A portion of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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patient was compared voxel by voxel to PET images of 10 healthy adults ranging from 57 to 77 years old (4 males) using the Crawford and Howell modified *t*-test [6] described in Anazodo et al. [5].

At autopsy, the brain was retrieved and then fixed in 10% neutral formalin for two weeks. After fixation, the brain was sliced and examined, with samples blocked for formalin-fixed paraffin-embedded sections. All paraffin sections were stained with Luxol fast blue/ Hematoxylin–eosin. Immunohistochemistry was performed for the relevant sections using primary antibodies for phosphorylated tau PHF (1:4000, polyclonal; Dako, Carpinteria, CA, USA), alpha-synuclein (1:200 LB509; Invitrogen, Pittsburgh, PA, USA), TDP-43 (1:4000; Cedarlane, Burlongton, Ontario), neurofilament (1:2000, M762; Dako, Carpinteria, CA, USA), P62 (1:500, polyclonal; Enzo, Farmingdale, N, USA), NeuN (1:400, MAB377, Sigma–Aldrich, Oakville, Ontario) and beta-amyloid (1:50, 6F/3D; Dako Carpintera, CA, USA) utilizing Autostainer Link48 visualized with the Dako Envision Flex kit detection system (Dako, Carpinteria, CA, USA).

The patient had been a successful athlete, father, and businessman who played university-level American-style football for four years and was a professional athlete with a Canadian Football League Team for one year in his early twenties. He was known to have experienced approximately 13 concussions during that time, including several with loss of consciousness and at least 2 warranting overnight observation in hospital. He proceeded to have a successful business career, advancing to an executive leadership position at a large company, and was engaged in significant philanthropy.

Beginning at age 69, his family noted short term memory deficits, including forgetting his golf tee-times, paying bills twice, and repeating questions. At the time of his first clinical presentation to a geriatrician at age 72, his neurologic examination was normal although he had deficits in delayed recall (Table 1). He was diagnosed with amnestic mild cognitive impairment (MCI), considered possibly due to Alzheimer's disease, and enrolled in the ADNI longitudinal study.

Two years after initial presentation, at age 74, evaluation was significant for ongoing short-term memory deficits and new aggression, delusional thinking, hyperorality, reduced personal hygiene, and lack of insight. He displayed new road rage and was argumentative with strangers. He was unable to safely drive, manage his finances, and use a computer or his voicemail. His family noted general disinhibition, delusional paranoia, copious butter consumption, compulsive fingernail cleaning, and new falls. His frontal behavioral inventory score was elevated at 29, with a score of 16 for negative behavior and 13 for disinhibition. Neurologic examination otherwise remained unremarkable. On mini mental status examination (MMSE), he scored 27/30 and deficits in delayed recall were again prominent (Table 1). MRI demonstrated mild atrophy in the anterior temporal and medial frontal lobes. Genetic testing for *C9ORF72, CHMP2B, FUS, GRN, MAPT, SIGMAR1, TARDBP, UBLQN2, VCP, OR PSEN1* revealed no disease associated mutations.

At age 75, he had worsening disinhibition, with rude comments being made to strangers and arguments with authority figures. Paranoid and delusional thinking continued, including beliefs that friends had stolen his memorabilia, changed over the ownership of one of his cars, and that a high school sports team moved to distance themselves from him. Neurologic evaluation demonstrated garrulousness and inappropriate comments but was otherwise normal apart from bilateral grasp reflexes. Cognitive testing showed impaired immediate and delayed recall, intact performance on the Trail making A and B tasks, and impaired performance on the Stroop test (Table 1).

By age 76, the patient had been started on 40 mg of citalopram daily for his agitation and irritability. His family noted that his irritability had greatly improved to the point of happiness or silliness, although inappropriate behaviors continued. Cognitive testing again showed impairments in delayed recall, though more so for registration and retrieval (see Table 2).

By 77 years of age, he had become inactive and a motivated around the house, though with an escalation in his inappropriate behavior. His vocabulary had reportedly diminished, although he had intact naming and comprehension on examination. Repeat neuropsychological evaluation now revealed erratic and impulsive responses with inconsistent effort. Additionally, he now demonstrated impairments in attention, trail making, and phonemic fluency (Table 1). At age 79, physical aggression had increased despite treatment with selective serotonin uptake inhibitors, trazodone, and quetiapine. He required hospitalization two months and had eventual discharge to a nursing home. By age 80, he was non-ambulatory and did not initiate conversation. His neurologic examination was notable for parkinsonism which persisted despite cessation of risperidone. He died at age 82 and underwent clinical autopsy which revealed changes consistent with CTE, as well as widespread tauopathy, TDP-43 type B, and hippocampal sclerosis.

MRI of the brain in 2006 was reported as mild to moderate generalized atrophy, most prominent in the parietal lobes and cerebellum. Neuroradiological review of annual MRIs from 2006 to 2011 reported minimal progression of atrophy (Fig. 1). Comparisons of FDG-PET/MRI images were made at age 72 and age 80, and at age 80 with an older healthy control group (ages 57–77). Reduced FDG-PET signal was observed predominantly in the frontal lobes, and anterior and medial temporal lobes, including the temporal poles, amygdala and ventral hippocampus at the time of

Table 1 Longitudinal cognitive testing and clinical dementia rating scores

Date	Age (years)	CDR Sum of Boxes (0–18)/ Global CDR Score (0–3)	MMSE (range 0–30)	Memory [range 0 (no impairment) – 3 (severe impairment)]	Executive Function (range 0 (no impairment) – 3 (severe impairment))	Language[b]	Visuospatial	Depression
2006	72	1/0.5	30	Impaired Logical Memory[a] Immediate: 8/25, delay 2/25 ADAS-COG 0/10 delayed word recall CDR Memory 0.5; CDR Orientation 0	Mild Impairment CDR Judgement and Problem Solving 0.5 CDR Community Affairs 0 CDR Home and Hobbies 0 CDR Personal Care 0	Intact Fluent, intact naming, repetition, comprehension and writing (clinical bedside evaluation and items on MMSE and MoCA)	Intact Clock draw; intersection pentagons	Not endorsed 0 GDS; 0 CDS
2007	73	2/0.5		Impaired CDR Memory 0.5; CDR Orientation 0.5	Mild Impairment CDR Judgement and Problem Solving 0.5 CDR Community Affairs 0.5 CDR Home and Hobbies 0 CDR Personal Care 0			
2008	74	2.5/0.5	27	Impaired CDR Memory 0.5; CDR Orientation 0.5	Mild Impairment CDR Judgement and problem solving 0.5 CDR Community Affairs 0.5 CDR Home and Hobbies 0.5 CDR Personal Care 0	Intact Fluent spontaneous speech. Intact naming, repetition, comprehension and writing on MMSE, MoCA		Not endorsed 0 GDS; 5/38 CDS (reflecting irritability, severe short temper)
2009	75	4.5/0.5		Impaired Impaired immediate and delayed recall on river mead prose recall CDR Memory 1.0; CDR orientation 0.5	Mixed Intact on Trails A and B; Impaired on Stroop (<1%); CDR Judgement and problem solving 0.5 CDR Community Affairs 0.5 CDR Home and Hobbies 1 CDR Personal Care 1	Intact Fluent, intact naming, repetition, comprehension and word definition on bedside clinical evaluation		

Table 1 (continued)

Date	Age (years)	CDR Sum of Boxes (0–18)/ Global CDR Score (0–3)	MMSE (range 0–30)	Memory [range 0 (no impairment) – 3 (severe impairment)]	Executive Function (range 0 (no impairment) – 3 (severe impairment))	Language[b]	Visuospatial	Depression
2010	76		26	Impaired Impaired immediate and delayed recall on river mead prose recall	Mixed Intact Trails B 85th %tile; Stroop impaired, 5th percentile; WCST-mild impairment learning first category, sorted successfully 5 of 6 categories	Mixed Intact naming (WAB) Fluent spontaneous speech Moderate to severe impairment of semantic fluency; mild to moderate impairment of letter fluency	Intact Clock draw	
2011	77		25	Impaired Mild impairment on immediate recall, Severe impairment on adapted river mead paragraph delayed recall; 0/3 on MMSE; 2 points lost on orientation; severe impairment on ACE-R memory	Impaired Poor attention during memory testing. Interruptive during testing, hypersexual remarks. Trails A 25th percentile, Trails B 35th %	Impaired Moderate to severe semantic fluency impairment; frequent curses given for f/a/s; mild anomia for low frequency words on stroke card; intact naming on Western Aphasia Battery	Intact Intact clock drawing and intersecting pentagons; 14/16 on ACE-R visuospatial	

[+]Logical memory test adapted from River mead paragraph recall

[a]scores reflect number of details from a story recalled immediately after story is read, and after a 30-min delay

[b]Language assessed through: controlled oral word association test for f/a/s and animals

WAB Western Aphasia Battery (where indicated), *CDR* Clinicians Dementia Rating Scale (higher scores indicate greater impairment), *MMSE* mini-mental status exam (lower scores indicate greater impairment), *GDS* Geriatric Depression Scale (higher scores indicate greater symptoms of depression), *CDS* Cornell scale for depression in dementia (higher scores indicate greater symptoms of depression), *ACE-R* Addenbrooke's Cognitive Exam Revised (lower scores = greater impairment), *ADAS-Cog* Alzheimer's Disease Assessment Scale-Cognitive Subscale, *Trails A* Trail making test A, *Trails B* Trail making test B, *WCST* Wisconsin Card Sort Task

Table 2 Application of TES and CTE criteria to patient's clinical features and neuropathologic findings

Consensus diagnostic features	Primary diagnostic criteria		Patient characteristics
Traumatic Encephalopathy Syndrome (TES) (Katz et al. 2021)			
Substantial Exposure to Repetitive Head Impacts	**Involvement in high-exposure contact or collision sports** (includes American (tackle) football), minimum of 5y of organized play with > =2 years at high school level or beyond	✓	Played organized American (tackle) football including 4 years of high school, 4 years of University (All-star fullback), and 1 year at the Canadian Professional Football League Known history of multiple concussions (approximately 13) while playing football, with loss of consciousness and at least 2 overnight hospitalizations
Core Clinical Features	**Cognitive Impairment** (all required): -Significant decline from baseline functioning as reported by self, informant or clinician - Deficits in episodic memory and/or executive function (may include additional domains) supported by impaired performance on standardized mental status examination **Neurobehavioral Dysregulation** -Significant change from baseline functioning as reported by self, informant or clinician - Poor regulation or control of emotions and/or behaviour, including explosiveness, impulsivity, rage, violent outbursts, short fuse, preferably substantiated by standardized measures. Not a transient response to life events **Progressive Course** - Evidence of progressive worsening over at least 1 year in the absence of continued exposure to repeated head injury or traumatic brain injury. Supported by serial standardized testing or clear history of change in functioning	✓ ✓ ✓	Post-concussions and after retirement from football, patient was a high functioning business executive. Progressive decline in cognitive abilities beginning in late 60 s noted by family and clinicians -Deficits in memory and executive function by history and objective cognitive testing (Table 1) Behavioural changes noted initially by family, then friends and clinicians including: -Impaired emotion and behaviour regulation with anger outbursts and verbal aggression (rated moderate on FBI). New road rage. Argumentative with strangers Irritability/short temper (rated as severe on FBI) Aggression (rated as moderate on FBI). Impulsivity (rated severe on FBI). Impulsivity (on FBI) Symptoms and progressive functional decline based on history and repeated standardized testing (Table 1) over 15-year course
Not fully accounted for by other disorder	Pattern of cognitive deficits and behavioural dysregulation is not fully accounted for by other pre-existing, established or acquired disorders or conditions Comorbid diagnosis of another neurodegenerative disease does not exclude a TES diagnosis, though TES may be excluded if the clinical features are fully accounted for by another neurodegenerative disorder based on clinical judgement, clinical features, or available biomarkers Comorbid diagnosis of substance use disorder, PTSD, mood or anxiety disorders does not exclude a TES diagnosis unless determined to account for all core clinical features	✓	Prior to patient's autopsy results, differential diagnosis included neurodegenerative disorders including Alzheimer's disease or Frontotemporal Dementia. Amyloid biomarkers were not available pre-mortem. Genetic testing for familial dementias (FTD and AD) was unremarkable Possible comorbid clinical symptoms of Frontotemporal Dementia including disinhibition N/A. No comorbid diagnosis of substance use, PTSD, mood or anxiety disorder
Level of Functional Dependence/ Dementia	Based on cognitive impairment and neurobehavioral dysregulation Independent Subtle/mild functional limitation Mild dementia Moderate Dementia Severe dementia	✓	Subtle/mild functional limitation at time of presentation due to memory deficits. Gradually progressive course over 15 years ultimately to severe dementia, resident in long term care

Table 2 (continued)

Consensus diagnostic features	Primary diagnostic criteria		Patient characteristics
Supportive Features used in determining provisional levels of certainty for CTE pathology	**Delayed onset-** Core clinical features begin following a clear period of stable functioning (years) after the repeated head injury exposure ends **Motor signs:** -Parkinsonism -Other motor signs: dysarthria, ataxia, imbalance -Motor neuron disease **Psychiatric Features** -Anxiety: pervasive worries, excessive fears, agitation, or obsessive or compulsive behaviour - Apathy: loss of interest in usual activities and motivation or drive - Depression: overly sad, dysphoric, hopeless, with or without suicidal thoughts -Paranoia: delusional beliefs of suspicion, persecution or unwarranted jealously	✓ ✓ ✓	Cognitive and behavioural changes began approximately 35–40 years after end of RHI exposure Parkinsonism as course progressed Apathy (3 = severe rating on FBI) Compulsive behaviour Paranoid delusions regarding unwarranted jealousy about spouse, suspicion football team was avoiding him
Second CTE Neuropathologic Consensus Criteria (Bieniek 2021	**Pathognomonic CTE Lesion:** -= p-tau aggregates in neurons with or without thorn-shaped astrocytes, at the depth of a cortical sulcus around small blood vessel, deep in the parenchyma, and not restricted to the subpial and superficial region of the sulcus **Neuronal p-tau pathology** (< 5 = low/mild CTE, > = 5 high/severe CTE): NFT in gyral side adjacent to CTE lesion NFT in gyral crest adjacent to CTE lesion NFT in superficial cortical laminae (layer II) NFT in CA4 of hippocampus (with dendritic swellings) NFT in CA2 of hippocampus NFT in entorhinal cortex NFT in amygdala NFT in thalamus NFT in mammillary body NFT in cerebellar dentate nucleus	✓	√ p-tau aggregates in depths of cortical sulci including perivascular glial p-tau inclusions Neuronal p-tau pathology > 5 consistent with high/severe CTE): √ NFT in gyral side adjacent to CTE lesion √ NFT in gyral crest adjacent to CTE lesion √ NFT in superficial cortical laminae (layer II) √ NFT in CA4 of hippocampus (with dendritic swellings) √ NFT in CA2 of hippocampus √ NFT in entorhinal cortex √ NFT in amygdala √ NFT in thalamus √ NFT in mamillary body - NFT in cerebellar dentate nucleus (not done)

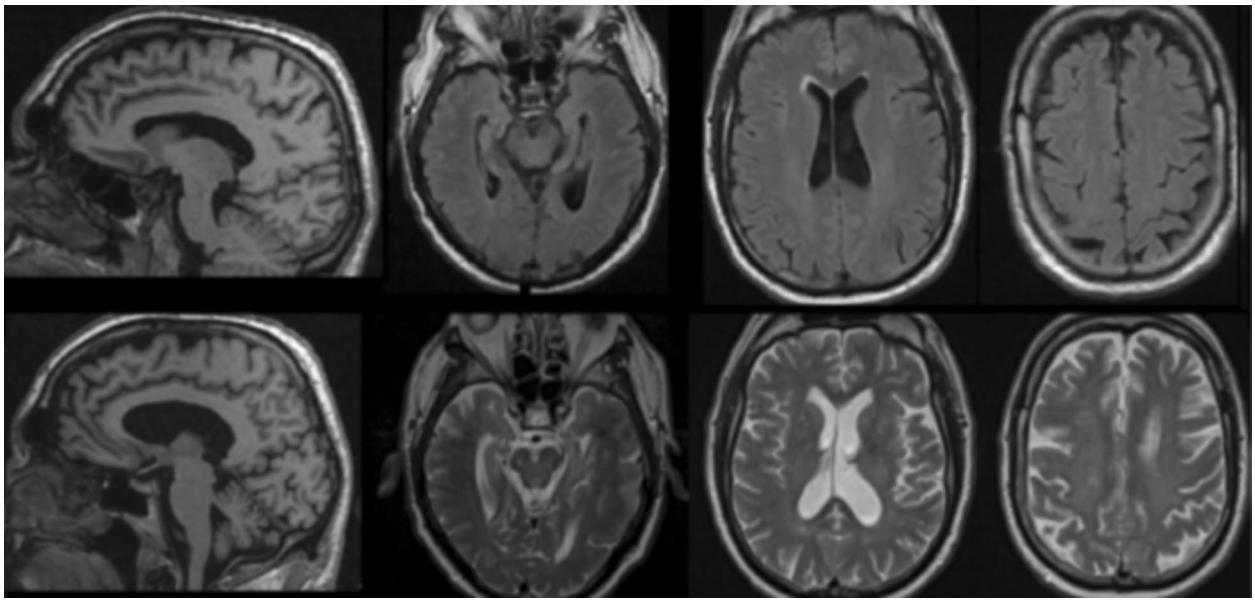

Fig. 1 MRI images at the time of first presentation at age 72 (top panel) and age 77 (bottom panel). Mild to moderate diffuse atrophy was observed, most notable in the parietal lobes. Mild progression of atrophy was observed over the 5 year period

presentation. Later in the course, hypometabolism was also observed in posterior cingulate cortex and the precuneus (Fig. 2).

The unfixed brain weight was 1243.5 g at autopsy. Mild atrophy of the bilateral frontal lobes, atrophy of the hippocampus, and marked atrophy of the mammillary bodies with significant dilation of the lateral and third ventricles were observed. Bilateral hippocampal sclerosis was noted on histological examination, and better highlighted by Neu-N immunohistochemistry (Fig. 3A, B). Subpial and cortical phosphorylated tau (pau) inclusions in the frontal (including orbitofrontal), temporal, parietal, and limbic cortices. Although these inclusions which involved neurons (including neurofibrillary tangles), glia, and neurites were prominent at the depth of sulci of the cerebral cortices (Fig. 3C), other parts such as the gyral side and crest of the cortices were also involved, including the superficial cortical layers. In the severely affected cortices at the sulcal depth, there were confluent areas of ptau inclusions which consisted of more glial than neuronal profiles (Fig. 3D), making it difficult to discern the perivascular distribution of these inclusions. However, in areas with less phosphorylated tau immunoreactivity in the background, perivascular glial and neuronal inclusions were demonstrated in the cortices at the depth of the sulci (Fig. 3E, F). Neurofibrillary tangles were also identified in the basal ganglia, mamillary bodies, hippocampus, amygdala, thalamus, and brainstem. Subpial and white matter perivascular glial clusters with ptau expression which represent age-related tau astrogliopathy (ARTAG) were also noted. TDP-43 expression in neuronal cytoplasm and neurites was mainly observed in the limbic regions, namely the amygdala, hippocampi (including dentate granule cells), and entorhinal cortex (Fig. 3G), with minimal involvement of neocortices. No Lewy body pathology and amyloid plaques were found. The neuropathological examination together with the clinical findings is consistent with a chronic traumatic encephalopathy.

Significant gaps in the CTE literature exist on prospective longitudinal clinical data as diagnosis is established on a post-mortem basis. Here, we have presented a former professional football player with clinical features consistent with TES and with pathologically confirmed CTE who had cognitive and behavioral decline beginning at 69 years of age after retiring from sports approximately 47 years prior. Given the extensive clinical and research evaluations conducted during the patient's 13-year journey, our report reveals a detailed pattern of symptoms, cognitive performance and functional deficits that support the recently developed criteria for TES as predictive of CTE. Further, our findings highlight the potential of FDG-PET detected regional hypometabolism as in the early symptomatic periods of TES.

Our patient's significant concussion exposure history, latency to symptoms, and combination of episodic memory, neurobehavioural dysregulation and progression represent the core features of TES [3]. The lack of amyloid pathology or alpha-synuclein pathology further supports the diagnosis of TES over Alzheimer's disease or Lewy body dementia, the other most common neurodegenerative dementias that can share some of these clinical features. The clinical presentation of our patient was also considered potentially

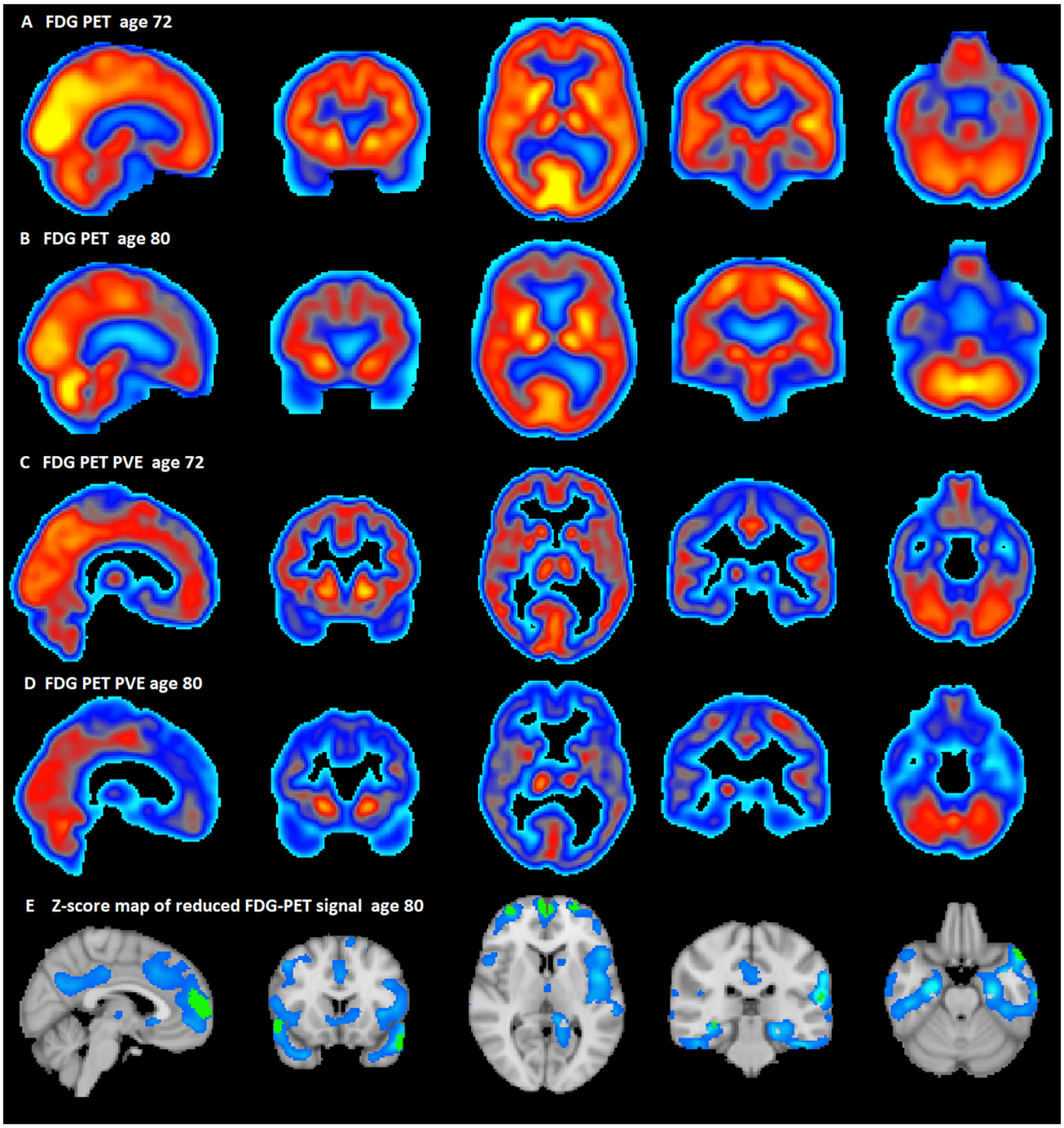

Fig. 2 FDG-PET maps from hybrid PET/MRI scan characterizing the relative distribution of FDG in the patient with CTE at age 72 and age 80. **A** Relative FDG-PET at age 72 (PET/CT). **B** Relative FDG-PET at age 80 (PET/MRI). **C** Relative FDG-PET corrected for partial volume effects (PVE) at age 72. **D** Relative FDG-PET corrected for PVE age 80. **E** *Z*-score maps depicting reduced FDG-PET signal in the patient at age 80 in comparison to a group of older healthy volunteers, demonstrating reduced FDG update in frontotemporal regions including inferior frontal gyri, medial prefrontal cortex, insula, caudate, temporal poles, and mesial temporal regions including the amygdala and ventral hippocampus (not pictured), posterior cingulate and precuneus. Relative PET images normalized to mean counts in pons at each timepoint. Panels **A**–**D** scaled from 0.25 to 1.75

consistent with behavioural variant Frontotemporal Dementia, which overlaps significantly with the cognitive and behavioural features of TES, though uncommonly involves paranoid or jealous delusions, as was a prominent feature of our patient. Further support for a diagnosis of CTE over FTLD is perivascular and sulcal-depths p-tau pathology,

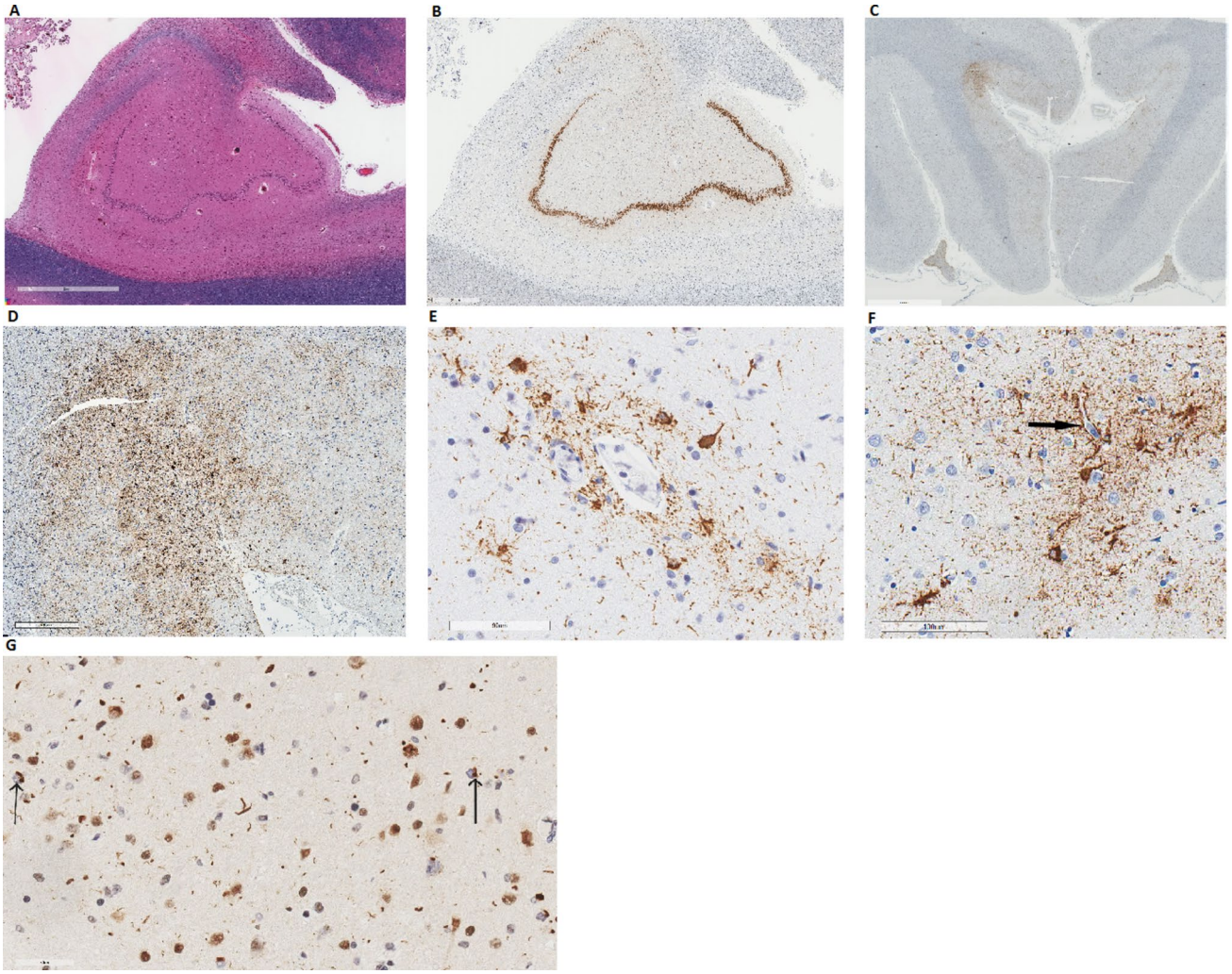

Fig. 3 Neuropathologic examination showing **A** hippocampal sclerosis, LFB&HE; **B** hippocampal sclerosis with loss of neurons in CA1, NeuN; **C** ptau expression, prominent at sulcal depth of one orbitofrontal cortex, and both olfactory nerves.; **D** ptau expression, prominent at sulcal depth, orbitofrontal cortex on the higher magnification of (**C**), showing confluent areas of glial and neuronal ptau with inconspicuous perivascular pattern; **E** inferior parietal cortex, perivascular ptau expression in glia and neurons (neurofibrillary tangles); **F** inferior temporal cortex, perivascular ptau in glia and neurons (vessel indicated by arrow); **G** entorhinal cortex, TDP-43 expression in neuronal cytoplasm (arrows) and numerous neurites (center)

which is not found in FTD or other non-CTE tauopathies [2]. Additionally, there was no significant frontal and temporal atrophy on gross examination and no superficial laminar spongiosis or gliosis in the neocortex (frontal and temporal) was identified. The TDP-43 pathology was sparse in the frontal and temporal cortex and mainly concentrated in the limbic areas (hippocampus, entorhinal cortex, amygdala), more consistent with LATE-NC (limbic-predominant age-related TDP-43 encephalopathy) stage 3 or associated with CTE rather than FTLD-TDP.

While multiple classifications of CTE exist, McKee et al. proposed one consisting of four clinical stages [7]. Our patient's presentation corresponded fairly well to this classification with initial complaints of mild memory impairment followed by behavioural outbursts. Towards the end of his disease course, he had psychotic features including paranoia and delusional thinking, and also had language deficits. Interestingly, depression was not a core feature of our patient's presentation despite its description within the classification—particularly within the first two stages. Additionally, our patient had early gait difficulties and falls prior to presumed Stage IV of advanced CTE. Further study is, therefore, needed to see if subtle motor findings may occur early in disease for other CTE patients.

The early prominent memory complaint in our patient is in contrast to a previous systematic review [8] of CTE cases and the view of some researchers [4] that cognitive impairment tends to emerge after development of neuropsychiatric

and behavioral symptoms. However, other case series have also described patients with short-term memory loss present in the early stages of the disease [7]. Stern et al. [9] suggested a framework of multiple subtypes of CTE, with one variant presenting at a younger age (mean age at death of 51.4) with behavioral and mood disturbances, and the other presenting later (mean age at death of 69.2) with prominent cognitive impairment. Additionally, our patient's advanced age of death of 82 could indicate that the prominent initial cognitive complaints in our patient are consistent with a presentation in the cognitive-variant group of CTE. Although Stern et al. stated it was unclear which neuropathologic changes led to these divergent presentations, the older cognition group had more extensive degenerative changes in the hippocampus and frontal cortex [9]. It is possible that the early memory complaints in our patient may have been due to hippocampal sclerosis, which has also been reported in other cases of CTE [10, 11]. Of interest, hippocampal atrophy was the most common finding in a series of 100 unarmed combatants with traumatic brain injury [12]. Together these findings suggest that hippocampal sclerosis with CTE should be considered in patients presenting with a history of significant concussion or TBI and the absence of amyloid biomarkers. Future studies should also seek to classify early cognitive or behavioral-predominant presentations with prevalence of hippocampal sclerosis to better understand this potential association. Although behavioral abnormalities are common, specific symptoms such as disinhibition, beyond impulsivity and anger-related emotion dysregulation, are not often seen in CTE [9].

In the first serial longitudinal FDG-PET imaging in a patient with confirmed CTE, we observed a clear pattern of bifrontal and bitemporal hypometabolism even at the MCI stage of impairment. Eight years later, progressive reductions in FDG-PET were observed in the frontal and temporal lobes, as well as in the posterior cingulate and precuneus. Studies of FDG-PET imaging in patients in the acute or subacute stages of TBI and mild TBI have shown conflicting findings, with some demonstrations of hypometabolism and others with hypermetabolism [13]. While some brain imaging studies exist for individuals at risk for CTE, few have been performed in patients with confirmed post mortem CTE and very few metabolic or perfusion studies have been reported [11]. One of the few available reports of antemortem PET imaging in an individual with pathologically confirmed CTE showed increased flortaucipir uptake in a frontotemporal-predominant pattern which corresponded to regions of neurodegeneration on MRI and hypometabolism on FDG-PET [14].Our findings suggest that FDG-PET may be relatively sensitive in early symptomatic stages of CTE and, therefore, useful both in the diagnosis as well as a potential biomarker of progression.

Our patient had a classic pattern of deep sulcal tau deposition, as well as widespread frontotemporal tauopathy and TDP-43 proteinopathies. This pattern of mixed pathologies is increasingly being identified in patients with CTE, in particular where death occurred at older ages. Although TDP-43 pathology is present in most patients with CTE in variable locations and to varying degrees depending on the stage of disease, relative confinement to the frontal and temporal lobes is atypical [15]. Mixed pathology in the setting of CTE has been reported in 37% of patients in a previous series, though typically involving amyloid pathology [15]. In one series, Alzheimer's type pathology and motor neuron disease pathology were observed in approximately 10% of patients with confirmed CTE, followed by alpha-synuclein pathology consistent with Lewy Body disease in 7%, and frontotemporal lobar degeneration in just 2% [15]. In another series, four retired professional soccer players who satisfied the diagnostic criteria for CTE had mixed pathology [16], with Alzheimer's disease and TDP-43 (diffuse in 3 cases, predominantly limbic in one) present in all cases, and hippocampal sclerosis [16]. In 2005, a 50-year-old professional football player with pathologically confirmed CTE had diffuse extracellular amyloid plaques and neurofibrillary tangles on autopsy [17]. Similarly, when Roberts et al. re-examined 14 of 15 patients from a previous series of exboxers which found neurofibrillary tangles without plaques using then contemporary pathological techniques, all had extensive beta amyloid plaques [18]. Given the absence of family history of FTD or AD, and normal genetic screening for FTD, we suggest that the concomitant presence of deep sulcal tau, the widespread frontotemporal tau and TDP-43 pathologies, as well as hippocampal sclerosis, represent a constellation of neurodegenerative changes most likely initiated by the patients history of multiple serious concussions decades earlier.

In summary, we report the longitudinal presenting symptoms, cognitive testing, MRI and FDG-PET findings in a patient with autopsy confirmed CTE, hippocampal sclerosis and mixed pathologies typically associated with Frontotemporal Lobar Degeneration. These data, in combination with others, demonstrate that cognitive and FDG-PET changes were observed 10 years ante-mortem, and may aid in ante-mortem diagnosis or outcome measures in future interventional trials. This patient and the others described above raise important questions about the relationship of hippocampal sclerosis and traumatic brain injury, as well as individual differences that lead to resilience in the years and decades immediately following the injury for some patients, and the factors that determine the various combinations of mixed pathologies comorbid with classic CTE changes.

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Author Contributions DK, AKS, AS, UA and LA contributed to the data analysis and drafting of the manuscript. AK, MB, LA and KSL contributed to the data acquisition. EF contributed to the concept and design, data analysis, and drafting of the manuscript.

Data Availability ADNI data used in this report is available through the LONI Image and Data Archive.

Declarations

Conflicts of interest The authors have no relevant conflicts of interest to report.

Ethical statement The ADNI study and the PET imaging studies presented in this report were approved by the Human Subjects Ethics Board of the University of Western Ontario.

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