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Title Page

Title: Late presentation of chronic traumatic encephalopathy in a former association football (soccer) player.

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Abstract

Background: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterised by widespread accumulation of hyperphosphorylated tau that typically occurs in people who have suffered repetitive head impacts. To date, very few cases have been reported in association football (soccer) players.

Objectives: To describe the clinicopathological features of a case of CTE in an 84-year-old former football player who was clinically diagnosed as having dementia with Lewy bodies (DLB).

Methods: A retrospective review of the patient's primary care and hospital medical records was performed along with a comprehensive neuropathological examination.

Results: This patient presented age 84 with symmetrical parkinsonism and cognitive impairment that was exacerbated by prochlorperazine. His condition was rapidly progressive with recurrent falls within 1 year. Other features included headaches, depression, anxiety,

suicidal ideation, disturbed sleep and aggression. He received a clinical diagnosis of DLB and died approximately 2 years after the onset of symptoms. A post-mortem examination revealed stage 4 CTE.

Conclusions: While the contemporaneous onset of parkinsonism and cognitive symptoms in the context of possible neuroleptic sensitivity is suggestive of DLB, the additional symptoms of aggressive behaviour, depression and suicidality in a former football player are consistent with the neuropathological diagnosis of CTE. This case, which is notable for the late presentation, demonstrates that CTE may masquerade as other dementias and highlights the importance of seeking a history of repetitive head impacts.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterised by widespread accumulation of hyperphosphorylated tau in neurons and astroglial cells that typically occurs in people who have suffered repetitive head impacts. CTE has received widespread media attention because of highly publicised cases in former athletes involved in contact sports, particularly boxing, American football and rugby union. CTE neuropathological change (CTE-NC) has also been reported in military personnel exposed to repeated blasts and as a consequence of self-injurious behaviour[1,2]. We report a case of CTE in an 84-year-old former association football (soccer) player who was clinically diagnosed as having dementia with Lewy bodies (DLB).

Case report:

This former professional football player was 84 when he presented to the emergency department with confusion and a 4-5 month history of reduced mobility. He played as a centre forward during a professional career that spanned at least 10 years. His cognitive symptoms

were thought to be exacerbated by prochlorperazine, which he had started taking 2 months earlier for vertigo. His other past medical history included hypertension and hyperlipidaemia. He was seen by a neurologist who noted symmetrical rigidity in the arms more than the legs, difficulty performing finger and foot tapping tasks, and his gait was described as shuffling and ataxic. His eye movements were normal and there was no tremor. His score on a questionnaire of cognitive decline in the elderly was indicative of dementia. MRI of the brain showed generalised cerebral atrophy, small vessel disease and an old lacunar infarct in the left basal ganglia. Given the combination of motor and cognitive symptoms along with possible neuroleptic sensitivity, a diagnosis of DLB was made and rivastigmine was started. He attended the psychiatry service 3 months later with a 2-3 week history of low mood and suicidal ideation without features of psychosis. Over the next year he developed anxiety, headaches, pain and tingling in his feet and recurrent falls. Levetiracetam was started following a vacant spell that was classified as a seizure. His condition progressed rapidly over the next 6 months such that he became uncooperative with personal care and was physically aggressive towards his carers. By this time, he was living in a care home and was also noted to have fluctuating cognition and disturbed sleep. He died from his illness age 86, following a disease duration of approximately 2 years from the time of his initial presentation.

Pathological findings:

Whole unfixed brain weight was 1,344g. Macroscopic examination of the left half of the brain revealed mild global cerebral atrophy, prominent atrophy of the amygdala and hippocampus, and severe pallor of the substantia nigra and locus coeruleus. Although, these macroscopic appearances could be consistent with DLB, on histological examination (figure 1), there was no evidence of α-synuclein pathology in brainstem, medial temporal lobe or neocortical regions. Instead, there was widespread tau pathology in the form of subpial, subcortical white matter

and periventricular subependymal thorn-shaped astrocytes and neuronal pre-tangles, tangles and threads in the grey matter. There was an overall irregular spatial distribution of tau pathology with some emphasis of astrocytic tau pathology at the depths of cortical sulci and neuronal tau pathology in the superficial cortical layers. Whilst this type of astrocytic tau pathology is similar to that seen in age-related tau astrogliopathy (ARTAG), the extent and distribution was unusual for typical ARTAG in this case based on: 1) the presence of neuronal tau pathology in the form of pre-tangles and tangles preferentially affecting the superficial neocortical laminae (layers II-III); 2) the perivascular distribution of astrocytic tau pathology at the depths of some of the cortical sulci; 3) the extent of the subpial and periventricular thorn-shaped astrocytes across hemispheric and brainstem regions; 4) the presence of frequent pre-tangles in CA2; and 5) the presence of frequent tangles with proximal dendritic swellings in the CA4 region. Based on these findings and in the context of his possible exposure to repetitive head impacts through playing professional football, a neuropathological diagnosis of stage 4 CTE[3,4] was made. TDP43 pathology was restricted to occasional cytoplasmic inclusions in the dentate gyrus along with rare inclusions and scattered threads in the cortex of the parahippocampal gyrus. There was no TDP43 pathology seen in the amygdala or frontal lobe. In addition, there was amyloid-β pathology corresponding to Thal phase 5 and CERAD score 2, which combined with Braak and Braak stage IV (at most) neurofibrillary tangle tau pathology, was indicative of an intermediate level of Alzheimer's disease (AD) neuropathology (A3, B2, C2). Finally, there was evidence of small vessel disease comprising mild, patchy hyaline arteriolosclerosis in the subcortical white matter, large vessel disease consisting of mild atherosclerosis in leptomeningeal blood vessels and frequent cerebral amyloid angiopathy (CAA) in cortical, as well as cerebral and cerebellar leptomeningeal vessels.

Discussion:

Hyperphosphorylated tau accumulation in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci is considered pathognomonic for CTE[4]. As demonstrated in this case, pre-tangles and neurofibrillary tangles in CTE preferentially affect the superficial cortical layers II–III (in contrast to layers III-IV in AD), the CA2 and CA4 regions of the hippocampus, and are also seen in subcortical nuclei[4]. Other supportive features, as observed in this case, include thorn-shaped astrocytes in subpial and periventricular regions and TDP43 immunoreactive neuronal cytoplasmic inclusions in medial temporal structures[4]. In addition to the characteristic distribution of pathology in CTE, the cryo-EM structure of tau fibrils extracted from post-mortem human tissue also appears to distinguish CTE from other tauopathies including AD and ARTAG[5], although very few cases have been studied with this technique to date. While the precise mechanisms responsible for hyperphosphorylated tau accumulation following repetitive head impacts have yet to be determined, a large study of American football players has shown that the severity of tau pathology corresponds with older age at death, more years of playing American football, the frequency of dementia, and the presence of co-morbid neurodegenerative disease[3]. However, CTE neuropathological change (CTE-NC) is not inevitable in people exposed to repetitive head impacts through boxing or other sports and as such, it has been suggested that as yet undetermined genetic and environmental factors may be important[6].

Although the contemporaneous onset of parkinsonism and progressive cognitive symptoms in the context of possible neuroleptic sensitivity was suggestive of DLB in this case, the additional neurobehavioral dysregulation characterised by aggressive behaviour in a former football player is compatible with traumatic encephalopathy syndrome (TES), the clinical correlate of CTE[7]. Although parkinsonism, depression and suicidality are not considered core features of TES, they are frequently present in individuals CTE neuropathology and are supportive of the diagnosis[7]. While football players may be exposed to repeated head impacts

through heading of the ball and head-player contact[8], reports of CTE are rare despite the sport's worldwide popularity and epidemiological evidence showing that mortality from neurodegenerative disease and prescription of dementia-related drugs was higher in Scottish former professional football players when compared to controls[9]. To our knowledge, fewer than 20 cases of CTE-NC in former football players have been reported to date. Cases of CTE-NC have been identified in young men in their twenties, one of whom (reported in abstract form) was a former high school football player who suffered numerous concussions playing football and developed psychiatric, behavioural and mild cognitive symptoms before an accidental but fatal overdose age 24, while another was a semi-professional player who died from motor neuron disease age 29[10,11]. In other cases, the age at presentation varied from the 6th to 8th decade and disease duration ranged from approximately 5-16 years[12-15]. Co-pathologies were frequent, and an alternate neuropathology was considered the primary driver of the clinical phenotype in 3/5 cases of football-associated CTE-NC in one series[15]. Co-existing AD-neuropathologic change was particularly frequent[12-15], however AD neuropathological change is common with ageing and its clinical relevance in the context of CTE is uncertain. The present case is notable for the particularly late presentation, highlighting that CTE may go unrecognised in cases of dementia among former football players. This case also demonstrates the importance of seeking a history of repetitive head impacts in patients with a clinical syndrome compatible with CTE. Further clinicopathological studies, combined with imaging and fluid biomarkers, will be required to determine the overall risk of CTE in association football players.

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1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

PWC: 1C, 3A

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Queen Square Brain Bank protocols have been approved by the NHS Health Research Authority, Ethics Committee London-Central (REC reference 18/LO/0721) and informed consent was obtained for publication. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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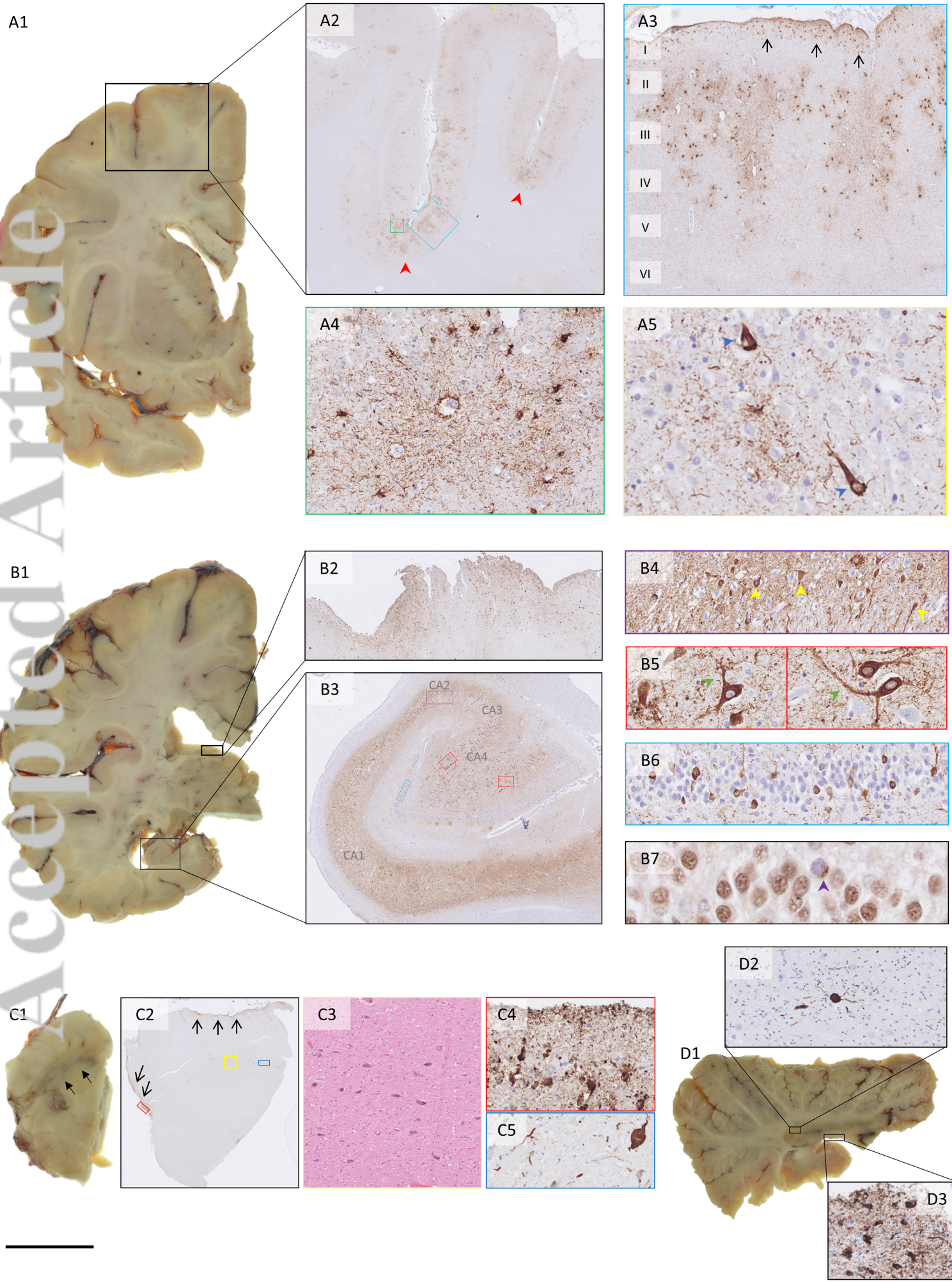
Figure legend:

Figure 1: Macroscopic and microscopic CTE pathology. Mild global cerebral atrophy with enlargement of the lateral ventricle can be seen (A1, B1), along with prominent atrophy of the hippocampus (B1), and severe pallor and neuronal loss in the substantia nigra (C1, arrows; C3). Widespread phosphorylated tau (AT8, MN1020, 1:600; Invitrogen) pathology is seen in the frontal cortex (A2, A3), consisting of thorn-shaped astrocytes, pre-tangles, tangles and threads. Astrocytic tau pathology shows some emphasis in the depths of the cortical sulci (A2, red arrowheads), where thorn-shaped astrocytes can be seen in a perivascular distribution (A4). Neuronal tau pathology shows emphasis in superficial neocortical laminae at the crests of the gyri (A5, blue arrowheads). Subpial thorn-shaped astrocytes are seen in the neocortex (A3, black arrows, superior frontal gyrus), midbrain (C2, black arrows and C4) and pons (not shown). Thorn-shaped astrocytes are also present in the subependymal white matter adjacent to the lateral (B2) and fourth (D3) ventricles. In the hippocampus (B3), a dense meshwork of threads, tangles and pre-tangles (yellow arrowheads) are evident in the CA2 region (B4), with pre-tangles seen in the dentate gyrus (B6) and in the CA4 region where proximal dendritic swellings can also be seen (B5, green arrowheads). Occasional TDP43 (2E2-D3, H00023435-M01, 1:500; Abnova) immunoreactive neuronal cytoplasmic inclusions are seen in the dentate

gyrus (B7, purple arrowhead). Occasional tangle, pre-tangle and thread pathology can be also be seen in the substantia nigra (C5) and dentate nucleus (D2). There was widespread amyloid-β pathology corresponding to Thal phase 5, but no α-synuclein pathology was present (not shown). Scale bar: 5.5mm in A2, 700μm in A3, 170μm in A4, 85μm in A5, 1.4mm in B2, 2mm in B3, 250μm in B4, 120μm in B5, 140μm in B6, 50μm in B7, 8mm in C2, 500μm in C3, 110μm in C4, 160μm in C5, 250μm in D2 and 140μm in D3.



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