



REVIEW ARTICLE

Chronic traumatic encephalopathy: The unknown disease[☆]



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Abstract Chronic traumatic encephalopathy is a neurodegenerative disease produced by accumulated minor traumatic brain injuries; no definitive premortem diagnosis and no treatments are available for chronic traumatic encephalopathy. Risk factors associated with chronic traumatic encephalopathy include playing contact sports, presence of the apolipoprotein E4, and old age. Although it shares certain histopathological findings with Alzheimer disease, chronic traumatic encephalopathy has a more specific presentation (hyperphosphorylated tau protein deposited as neurofibrillary tangles, associated with neuropil threads and sometimes with beta-amyloid plaques). Its clinical presentation is insidious; patients show mild cognitive and emotional symptoms before progressing to parkinsonian motor signs and finally dementia. Results from new experimental diagnostic tools are promising, but these tools are not yet available. The mainstay of managing this disease is prevention and early detection of its first symptoms.

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PALABRAS CLAVE

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Encefalopatía crónica postraumática: aquella gran desconocida

Resumen La encefalopatía crónica postraumática es una enfermedad neurodegenerativa fruto de la acumulación de numerosos traumatismos craneoencefálicos, para la cual no existe un diagnóstico premortem definitivo ni un tratamiento específico. Entre los factores de riesgo asociados con la encefalopatía crónica postraumática se encuentran: la exposición a deportes de contacto, la presencia de la apolipoproteína E4 y la edad avanzada. Histopatológicamente, aunque comparte ciertas características con la enfermedad de Alzheimer, tiene una

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presentación más específica (depósito de proteína tau fosforilada en forma de ovillos neurofibrilares, asociados a acúmulo de elementos del neuropilo, acompañados en ocasiones de placas de beta-amiloide). Clínicamente se caracteriza por un curso lento que se inicia con síntomas cognitivos leves y emocionales, y progresa hacia la aparición de síntomas parkinsonianos y demencia. A pesar de que existen elementos diagnósticos prometedores, no son, actualmente, una realidad, y la clave en el manejo de esta enfermedad es la prevención y la detección precoz de sus primeros síntomas.

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Introduction

Chronic traumatic encephalopathy (CTE) is a nosological entity characterised by progressive neurological deterioration secondary to repeated head trauma.^{1,2} The wide spectrum of CTE includes dementia pugilistica (DP), a neurodegenerative disorder caused by the accumulation of phosphorylated tau protein at certain locations in the CNS as a result of the repeated traumatic brain injury (TBI) experienced by athletes playing contact sports. This condition was initially described in boxers in 1928 by Dr Harrison Martland,³ who coined the term 'punch drunk syndrome'; the term 'dementia pugilistica' came into use in the 1960s. As an aid to comprehension, we will treat the terms CTE and DP as synonyms. The term 'concussion' is ambiguous. Nevertheless, according to the National Center for Injury Prevention and Control, concussions are mild TBIs (GCS scores of 13 to 15) which are associated with a period of loss of consciousness, amnesia, and/or confusion immediately after the injury.

Recent years have seen growing public interest in the consequences of mild TBI on neurocognitive skills and potential associated long-term disability. This interest is shared by the scientific community. Although several cases describing histopathological changes and a number of studies in animal models have been conducted, data on the physiological basis, diagnostic methods, and prognostic and protective factors are scarce.

The purpose of our literature review was to thoroughly analyse predictive and risk factors for CTE and current diagnostic methods to help clinicians identify the initial stages of the disorder correctly in order to prevent disease progression. Likewise, our study aims to lay the foundations for future clinical guidelines for mild TBI associated with contact sports.

Epidemiology

Mild TBI is one of the most common neurological problems, accounting for 90% of all injuries to the brain parenchyma.⁴ To date, there are no epidemiological studies providing data on the frequency of CTE or DP.⁵ Around 17% of all retired professional boxers are estimated to have CTE⁶; this disease is rare in amateur boxers.⁵ In a review conducted by McKee et al.,⁷ 46 of the 51 patients diagnosed with CTE (90%) were athletes. Most of them played contact sports, mainly boxing and American football, and began practising these sports

at young ages.⁷ However, symptoms rarely appear before athletes retire.⁵

Risk factors

Several risk factors for CTE have been described, including retirement after the age of 28, a long professional career, or participating in a high number of matches.⁶ Episodes of concussions and head trauma increase the athlete's risk of developing CTE.⁷ There is a clear correlation between the number of knockouts and the risk of developing DP.⁸

In a study of a series of university players of American football, Crisco et al.⁹ observed that impact severity depended on the player's position on the team. These results agree with those reported in the histopathological study conducted by McKee et al.⁷: according to this study, the 5 football players diagnosed with CTE played similar positions, more specifically, positions prone to impacts that were less severe but more frequent.⁹ Likewise, we hypothesise that these differences may also be present in boxers depending on their weight class. Based on this theory, and extrapolating from results by Crisco et al.⁹ and McKee et al.,⁷ we suggest that boxers fighting in the lowest weight classes experience more (though less severe) blows and may therefore be at a greater risk for developing neurological symptoms compatible with CTE in the long term.

It seems reasonable to state that repeated head trauma is a necessary condition for developing CTE. However, not all athletes experiencing head trauma develop the disease. It would therefore be interesting to establish the factors associated with progression to CTE. One of the major questions in the study of DP or CTE is whether a single blow is able to cause the disease. Johnson et al.¹⁰ found that around one third of the individuals experiencing head trauma exhibited neurofibrillary tangles whereas this finding was rare in healthy controls with no history of TBI. In a study with animal models conducted by Laurer et al.,¹¹ neurocognitive and histopathological changes were present both in mice subjected to a single TBI and in those experiencing repetitive head trauma in under 24 hours, although changes were more marked in the second group. It is therefore logical to believe that the severity and presentation of CTE is linked to repeated concussions and that the risk increases with frequency of head trauma.

Age may be another potential risk factor. Although neurodegeneration caused by TBI at young ages will remain throughout an athlete's professional career,¹² it is also true

that since young individuals exhibit more neuronal plasticity, older athletes are at greater risk.¹³

Among the genetic factors involved, special mention should be made of the gene for apolipoprotein E (ApoE). ApoE is a protein 299 amino acids long encoded by a gene (*ApoE*) with 3 allele variants ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) presenting in white individuals with a frequency of 7%, 78%, and 15%, respectively.¹⁴ ApoE is produced by glial cells and constitutes a major transporter of lipids via the CSF. This protein is also responsible for maintaining the structural integrity of the microtubules within axons and neurons. The ApoE $\epsilon 4$ allele has bearing on the prognosis and presentation of certain neurological conditions, including Alzheimer disease (AD),¹⁵ subarachnoid haemorrhage,¹⁶ head trauma,^{17,18} and ischaemia secondary to head trauma.¹⁹ Presence of this allele is also linked to larger intracerebral haematomas.¹⁹ When the brain experiences traumatic injury, it becomes especially sensitive to ischaemia; additional head injury are therefore associated with a poorer prognosis. Different studies show that carriers of the ApoE $\epsilon 4$ allele experiencing TBI have poorer prognoses.^{18,20} In a study of professional boxers, Jordan et al.²¹ demonstrated that the individuals with poorer scores on neurocognitive tests had at least one ApoE $\epsilon 4$ allele. These authors concluded that the ApoE $\epsilon 4$ allele is linked to increased severity of chronic neurological deficits in high-exposure boxers.

Histopathology

The main findings in patients with CTE are reactive astrocytes, dot-like spindle-shaped neuropil neurites, and a band-shaped or flame-shaped accumulation of small and large globose neurofibrillary tangles which are immunoreactive to phosphorylated tau protein.^{22,23} Other less consistent, non-specific findings of the disease include amyloid- β deposits, which are present in about 50% of patients with CTE compared to nearly all patients with AD.⁷ Another difference between these 2 entities is the distribution of neurofibrillary tangles; whereas in AD they distribute homogeneously, in CTE they show an irregular pattern: they are typically perivascular and most dense at the depths of cortical sulci.²⁴ In CTE, these changes are especially evident in the dorsolateral frontal, subcallosal, insular, temporal, dorsolateral parietal, and inferior occipital cortices.²³ Furthermore, hippocampal involvement is scarce in CTE but constitutes a nearly constant early finding in AD.²⁵ Another difference between CTE and AD is abnormal accumulation of TDP-43 protein, which is associated with phosphorylated tau protein, in patients with CTE (>85% of patients). This proteinopathy is also found in some variants of amyotrophic lateral sclerosis; it has therefore been suggested that certain subtypes of the disease may be associated with repeated mild TBI.²⁶

Pathophysiological correlations

According to Omalu et al.,²⁷ CTE is a progressive neurodegenerative syndrome which develops as a result of episodic, repeated head trauma that damages the brain due to rapid acceleration and deceleration forces.

In the last decade, researchers have expressed a growing interest in analysing the effect that repeated head trauma may have on different neurological functions.^{28,29} Likewise, a study conducted by Kanayama et al.³⁰ shows that repeated mild TBI, unlike a single TBI, leads to alterations in cytoskeletal proteins in the cortex and hippocampus. Laurer et al.¹¹ concluded that the brain's vulnerability to head trauma increases when a second episode occurs within 24 hours. Another study by the same research group suggests that short- and long-term lesions are more severe when further injuries takes place within an even shorter time period.³¹

Axonal damage was initially thought to be a mechanical injury due to the effect of shearing forces on axonal membranes.¹³ The theory of immunotoxicity^{23,32} suggests that small defects or local changes in the blood-brain barrier promote the entry of proteins which act as mediators of the enzyme cascade initiating during inflammation and repair. However, when a stimulus remains active in time (for example, in the case of a second TBI) it induces immunotoxicity and changes in axolemma membranes and in the microtubules making up axons and neurons,^{33,34} thus leading to protein tau deposition; this protein has been suggested as the main trigger factor of neural impairment.³⁵

The first studies of the biophysics of head trauma and concussion, conducted in primates, concluded that brain injury was essentially due to angular acceleration impacts and shearing forces rather than to the coup/contre-coup phenomenon.^{36,37} Although injury modelled in primates was similar to concussion in humans, the results of these studies cannot be extrapolated due to their small sample sizes. Recent advances are based on telemetry data obtained from sensors placed in the helmets of athletes playing contact sports at the university and professional levels.^{38,39} According to these studies, the larger part of the force of the impact reached the region corresponding to the diencephalon and telencephalon⁴⁰; forces applied to such structures as the midbrain (ascending reticular formation), corpus callosum, and fornix are responsible for the episodes of loss of consciousness, amnesia, and cognitive dysfunction.^{7,40} Crisco et al.⁹ found that impacts to the top of the helmet generated the lowest peak rotational acceleration magnitudes but the greatest peak linear acceleration magnitudes, and they were associated with neck fractures. On the other hand, impacts to the side of the helmet caused great peak rotational acceleration, which resulted in brain injury and loss of consciousness.

According to the 'cognitive reserve hypothesis', the nervous system may develop alternative systems or pathways to compensate for initial deficits.⁴¹ The presence of certain degenerative mechanisms (age, toxic agents, trauma, etc.) is enough to overpower cognitive abilities by making compensatory mechanisms insufficient; this situation decreases neurocognitive function.

Clinical presentation

Concussion is the manifestation of a temporary state of axonal and neuronal deterioration, whereas CTE is a neurodegenerative disease occurring years or decades after

recovery from acute and subacute symptoms of head trauma. Although symptoms associated with post-concussion syndrome may remain for long periods of time, they usually resolve within the first 3 months.¹³ In contrast, CTE symptoms are degenerative, progressing over time. CTE symptoms usually appear in middle age, typically after retirement, although some athletes may experience early-onset cognitive symptoms. Such neurocognitive symptoms as memory and attention deficits and frontal and executive function deficits are the first to appear in these patients, and almost all patients will exhibit them in early stages of the disorder.⁷ Neuropsychological symptoms will appear at later stages, although some of these manifestations may also be present in the initial stages. They tend to go undetected since they are frequently difficult to differentiate from premorbid personality traits.⁵ More specifically, mood and behavioural changes, described by family and friends as apathy, aggressiveness, irritability, and unexplained anger, have been reported in nearly a third of all patients with symptoms compatible with CTE.⁷ Neuropsychological tests are especially useful for early diagnosis of CTE and for follow-up on athletes who play contact sports: psychocognitive changes tend to remain even when the neurological motor symptoms manifesting after concussion have disappeared, and neuropsychological tests may determine how to manage the patient and if he/she is fit to return to the sport when psychological and behavioural symptoms persist.⁴² Similarly, motor symptoms may appear in up to 40% of individuals with CTE, according to the study by McKee et al.⁷ Early motor symptoms include mild dysarthria and instability, which can be diagnosed using the Romberg test.⁵ As symptoms progress, patients develop ataxia, altered motor coordination, spasticity, and parkinsonism.⁴³ Patients with CTE rarely develop dementia.¹³ This may be due to early mortality associated with suicide, although this relationship has not been clearly established in the literature.⁴⁴

Diagnosis

Neuropsychological and neurophysiological tests

Although most cognitive and motor changes are initially asymptomatic, after a short post-concussion period⁴⁵ these athletes are more likely to score lower on neuropsychological and motor tests as age increases.⁴⁶ In recent years, multiple neurophysiological tests have been developed to detect subclinical electrophysiological changes in response to stimuli in young athletes. According to these studies, electrophysiological changes vary according to the number of concussions.⁴⁷ Young athletes exhibiting obvious changes in this neurophysiological pattern during the initial stages of their career are more likely to display neurocognitive dysfunction that can be detected by conventional tests.⁴⁶ However, motor tests evaluating stability are not sensitive enough to detect evident alterations in early stages of the disease.^{48,49} On the other hand, transcranial magnetic stimulation shows an association between different responses to these stimuli and the number of concussions. In any case, these conclusions are based on preliminary studies; it remains to be seen whether altered transcranial magnetic

stimulation readings are early markers of the disease.⁵⁰ We are currently unable to determine whether these subclinical early-onset alterations result from repeated head trauma rather than appearing as a premorbid characteristic in athletes who are at risk for a concussion.⁵¹ Prevention and treatment strategies should aim to maintain the athlete's functional reserve as long as possible and to achieve the closest possible recovery to the baseline state.

Magnetic resonance imaging

Conventional MRI has a limited role in preventing the negative effects of head trauma. Conventional MRI sequences display non-specific changes in patients with CTE. However, these changes occur once there is structural damage to the brain parenchyma, which will inevitably lead to CTE (if it is not already present). Likewise, gradient echo sequences have been proven to be useful for detecting microhaemorrhages associated with diffuse axonal damage. However, even when conventional MRI techniques detect focal structural lesions, the prognostic value of this finding is unclear.^{52,53} Research with animal models has shown diffusion tensor imaging to be useful and sensitive for detecting ultrastructural changes. Mac Donald et al.⁵⁴ found a positive correlation between anisotropy and density of APP-stained axons, which indicates that diffusion tensor imaging is sensitive enough to detect very subtle ultrastructural changes. The mechanism responsible for these changes in anisotropy is unknown, although it has been hypothesised that the loss of white matter microstructural integrity may alter values of fractional anisotropy (FA).⁵⁵ However, whether or not this is useful for predicting CTE has yet to be clarified. Mounting evidence suggests that individual differences in white matter microstructural integrity are responsible for the variations in performance in certain cognitive domains.⁵⁶ Thus, individuals with a history of concussion show a correlation between memory impairment and high values of FA in the frontoparietal white matter, whereas individuals with high anisotropy values in the frontostriatal white matter tend to display attention deficits.^{57,58} Recognising specific lesion patterns in CTE may be helpful for early detection of the athletes at the greatest risk for developing the disease.

Nuclear medicine: positron-emission tomography-computed tomography

Brain glucose metabolism can be estimated using 18F-fluorodeoxyglucose.⁵⁹ Functional neuroimaging techniques are highly sensitive to alterations after TBI and offer a good anatomical-clinical correlation.⁶⁰ In one animal model,⁶¹ those individuals subjected to head trauma displayed a triphasic pattern in cerebral glucose metabolism. A short period of hyperglycolysis as the initial response was followed by a relatively long period of metabolic depression associated with neurological impairment, and a third period in which metabolic recovery occurred in the most relevant areas. A similar triphasic pattern has been found in humans.^{62,63} Several studies have shown that patients with good neurological recovery display a higher cerebral glucose metabolism.^{63,64} However, studies with single-photon emission computed tomography (SPECT) show dissimilar

results.⁶⁵ Although the usefulness of these imaging techniques is controversial, it seems that these tools may help identify athletes at a greater risk of developing CTE/DM.

New trends in prevention and treatment

Few treatments have been proven to slow CTE progression; current treatment approaches aim to minimise or alleviate the presence of motor, neuropsychological, and cognitive symptoms. Selegiline has been proposed by Colosimo and Albanese⁶⁶ to slow disease progression in boxers, although its use is limited. Empirical treatment with antiparkinsonian drugs (levodopa) is recommended for patients with disabling motor symptoms.⁵ It is unclear whether cholinergic treatment halts or improves cognitive symptoms.^{67,68}

Most preventive strategies focus on avoiding prolonged exposure to contact sports and detecting those individuals most at risk of developing CTE.⁵ To this end, genetic tests which detect the presence of the ApoE ϵ 4 allele are crucial. The use of suitable neuropsychological tests helps clinicians detect those individuals with early symptoms, guiding patient management and the decision to resume play.⁶⁹

Conclusion

CTE is a syndrome of neurological impairment associated with phosphorylated tau protein deposition resulting from repeated head trauma. Given that some findings and clinical progression patterns in CTE are similar to those of other neurodegenerative diseases such as AD, final diagnosis can only be established by autopsy.

Neuropsychological tests seem to be the most sensitive tools for detecting early symptoms of CTE and they are helpful for setting up patient management protocols that will shed light on when to resume play. Although they hold promise, new MRI sequences (gradient echo, diffusion) and nuclear medicine are not currently used for diagnosing this disease. Since no specific therapeutic targets have been established, the most widely-used approach to CTE is based on prevention: avoiding prolonged exposure to contact sports and identifying individuals with a higher level of risk (through genetic studies to detect the ApoE ϵ 4 allele).

Conflict of interest

The authors have no conflict of interest to declare. No funding was received for this study. This study has not been presented at any congress nor has it been published in any journal.

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