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Chronic Traumatic Encephalopathy in Sports Practice: A Literature Review

Encefalopatia traumática crônica na prática de esportes: Uma revisão da literatura

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative syndrome caused by repetitive and cumulative head trauma. Due to the widespread practice of contact and collision sports, a discussion of the long-term repercussions of repeated head trauma is imperative. The present literature review, performed through the SciELO, PUBMED, and BVS-Bireme databases, includes studies conducted since the year 2000, which established the relationship between CTE and the practice of sports. The diagnosis of CTE was notably present in individuals practicing sports that involve repeated traumatic brain injuries. The noticeable changes triggered by CTE include a series of clinical and neuropathological manifestations that can help in the differentiation from other tauopathies.

Keywords
- traumatic brain injuries
- brain concussion
- chronic traumatic encephalopathy
- tauopathies

Resumo

A encefalopatia traumática crônica (ETC) é uma síndrome neurodegenerativa causada por traumatismo craniano repetitivo e cumulativo. Com a prática disseminada de esportes de contato, torna-se importante discutir as repercussões a longo prazo de traumatismos cranianos repetidos. A presente revisão da literatura, executada através das bases de dados SciELO, PUBMED e BVS-Bireme, inclui estudos realizados desde o ano de 2000 que estabeleceram a relação entre a ETC e a prática de esportes. O diagnóstico de ETC esteve notadamente presente em indivíduos praticantes de esportes que envolvem repetidas lesões cerebrais traumáticas. As alterações perceptíveis desencadeadas pela ETC incluem uma série de manifestações clínicas e neuropatológicas, que podem auxiliar na diferenciação de outras tauopatias.

Palavras-chave
- lesões cerebrais traumáticas
- concussão cerebral
- encefalopatia traumática crônica
- tauopatias

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Introduction

Traumatic brain injury is a proven risk factor for neurodegenerative diseases, including chronic traumatic encephalopathy (CTE).[1] Chronic traumatic encephalopathy was first described in boxers under the name "punch-drunk syndrome", in 1928, by the pathologist and examiner Harrison Martland,[2] later renamed as "pugilistic dementia" (Millspaugh, 1937),[3] and, finally, as CTE (Critchley, 1957).[4] It is characterized as a neurodegenerative tauopathy caused by repetitive and cumulative head trauma or traumatic brain injury (TBI).[5–7] Besides the classical description in boxers, other sport activities, such as muay thay, Chinese boxing, mixed martial arts, wrestling, hurdling, lacrosse, rugby, field hockey, and soccer and football, in particular, have been described as potential causes of TBIs and, consequently, risk factors for the development of CTE.[6,8,9]

Epidemiological studies show that trauma is one of the main causes of morbidity and mortality, ranking third in general mortality in Brazil, with greater severity when considering TBI, whether from contact and collision sports or accidents. Traumatic brain injury can be related with intracranial hemorrhages, hematomas, carotid or vertebral dissection, concussions, and diffuse axonal lesions.[10]

Between 1965 and 2019, research from Europe, the United States, New Zealand, and Australia has found that up to one third of all causes of TBI are sport-related. Furthermore, the occurrence of trauma ranged from 3.5 to 31.5 per 100,000 in studies analyzing those individuals who attended hospitals after TBI, whereas, in the community, it ranged 170 per 100,000, according to the population of the countries.[11] In time, it is important to highlight that concussion is very common when related with contact and collision sports, such as in the United States, where 1.6 to 3.8 million sports-related concussions occur annually.[12]

Chronic traumatic encephalopathy is a neurodegenerative syndrome caused by single, episodic, or repetitive blunt force impacts to the head and transfer of acceleration/deceleration forces to the brain. It presents itself clinically as a syndrome composed of mood disorders and behavioral/cognitive impairment, with or without a sensory-motor disease.[13] Furthermore, it is related to the widespread deposition of hyperphosphorylated tau protein (p-tau) in the form of neurofibrillary tangles (NFTs)[14] in the sulci and perivascular spaces[12] with preferential involvement of the superficial cortical layers and a propensity for sulcal depths.[6,15]

The occurrence of CTE has demonstrated significant importance within the scientific context, with regard to its development and specificities inherent to the etiology. In addition, its health implications with differential value to other diseases evoke the need for more thorough studies in this matter.

Therefore, this article aims to clarify, through a literature review, the existing correlation between chronic traumatic encephalopathy and the practice of sports, as well as its main aspects for a differential diagnosis. Additionally, this paper aims to establish a threshold that distinguishes CTE from other pathologies that have similar clinical outcomes.

Material and Methods

This review article was developed based on a data survey found in the literature. The related bibliographic searches were published in the period between 2000 and 2020 in the following scientific databases: SciELO, PUBMED, and BVS-Bireme.

The descriptors used in the medical subject headings (MeSH) and *Descritores em Ciência da Saúde* (DeSC) were: *chronic traumatic encephalopathy*, *traumatic brain injury*, and *trauma in athletes*. Their respective correspondents in Brazilian Portuguese were also consulted. Subsequently, the studies that met the following inclusion criteria were distinguished as such: electronic bibliographies compatible with the descriptors listed above; chronology from the year 2000 on; books; full texts and theses; abstracts; original articles, review articles, and case reports in the aforementioned medical scientific databases. We decided to exclude studies that did not establish a relationship between CTE and the practice of sports, and, in order to guarantee an adequate theoretical basis for the evolution and discussion of the theme, only the studies considered most significant were analyzed.

From this point, 375 manuscripts were found and, after applying the inclusion criteria, 234 were accounted for. By reading the titles and abstracts, 168 texts were eliminated and 66 of them were analyzed and read in their entirety. Thus, 35 references were considered for this review and 8 duplicates were discarded. In the end, 27 sources were included as proper bibliographic references, which present original scientific properties as well as relevance to the approach of this work.

Results and Discussion

Given what was analyzed, there was significant correlation between the diagnosis of CTE and its connection to sports practitioners, or even in cases of repeated traumatic brain injuries.

Thus, from an analysis of postmortem brains donated and obtained from a cohort of 85 individuals with a history of repetitive mild traumatic brain injury, approved by the Boston University School of Medicine, it was found that 80 were athletes, and 22 of these were athletes and military veterans. Of these 85, evidence of CTE was found in 68 individuals. It is worth noting that all (68) those with evidence of CTE were males aged between 17 to 98 years old, 51 (75%) of whom had the confirmed diagnosis and 7 (10.3% of all cases with evidence of CTE) had Alzheimer disease (►**Table 1**), ranging from focal comorbidity in stages I to III to inclusions and generalized neuritis in stage IV[14] (►**Table 2**).

In contrast, in the review study by McKee et al.,[12] it was observed that of 51 neuropathologically confirmed cases of CTE, 46 (90%) occurred in athletes. The first symptoms were noticed between 25 to 76 years old ($M = 42.8$, $SD = 12.7$). One third were symptomatic at the time of retirement from the sport, and half were symptomatic within 4 years of cessation of practice (►**Table 1**).

Table 1 Diagnostic correlation of chronic traumatic encephalopathy with the practice of sports in identified studies

Source	Type of study	N sample	Age group	Diagnosis
McKee et al.[14]	Cohort (autopsy)	80 athletes (22 of whom were also military veterans)	Between 17 and 98 years old (average of 59.5 years old)	Of the 68 cases with evidence of CTE: 51 (75%) - CTE; 8 (12%) - Motor neuron disease; 7 (10.3%) - Alzheimer disease; 11 (16%) - Lewy body disease; 4 (6%) - Frontotemporal lobar degeneration
McKee et al.[12]	Review	51, of whom: 46 (90%) were athletes (39 boxers [85%], 5 football players [11%], 1 professional wrestler and 1 soccer player).	Between 23 and 91 years old	100% - CTE
Montenigro.[16]	Review	202 (141 boxers, 54 football players, 5 ice hockey players and 2 professional wrestlers)		83 - definite CTE, 90 - probable CTE, and 29 - possible CTE.

Table 2 Symptomatology characteristic of chronic traumatic encephalopathy according to stages I to IV of the disease

Stages of CTE	Symptoms
I	Headache, loss of attention and concentration.[14,18]
II	Depression, explosiveness, and short-term memory loss.[14,18]
III	Executive dysfunction and cognitive impairment.[14,18]
IV	Dementia, difficulty finding words, and aggression.[14,18]

Abbreviations: CTE, chronic traumatic encephalopathy.

Table 3 Diagnostic characterization of the pathophysiological impairment of chronic traumatic encephalopathy at the clinical, neuroimaging, and neuropathological levels

Level	Alterations
Clinical	Memory disorders; behavioral and personality changes; parkinsonism; speech and gait abnormalities[6,12,18]
Neuroimaging	Atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem; ventricular dilatation; and a fenestrated septum pellucidum cavum[6,12,18]
Neuropathological	Extensive tau-immunoreactive and astrocytic neurofibrillary tangles; and spindle-shaped neurites throughout the brain[6,12,18]

Similarly, in another review, 202 cases from 20 publication series, 4 books and 1 medical dissertation[16] were analyzed. The Jordan criteria[17] were considered, which are: definite CTE (any neurological process consistent with clinical presentation of CTE in conjunction with pathological confirmation), probable CTE (any neurological process characterized by two or more of the following conditions: cognitive and/or behavioral impairment; cerebellar dysfunction; pyramidal tract disease or extrapyramidal disease; clinically distinguishable from any known disease process consistent with the clinical description of CTE), possible CTE (any neurological process that is consistent with the clinical description of CTE, but can potentially be explained by other known neurological disorders).[17] Thus, in this study, 83 of the cases would have definite CTE; 90, probable CTE, and 29, possible CTE[16] (►**Table 1**).

However, Montenegro et al.[16] point out new diagnostic criteria, such as: a behavioral/mood variant, a cognitive variant, a mixed variant, and dementia (traumatic encephalopathy syndrome). The progressive, stable, and unknown course modifiers are used to describe the clinical course, and if specific motor signs are evident, the modifier with motor characteristics will be added. The selection of the general criteria was based on the literature reviewed by the authors and was designed to favor sensitivity over specificity.[13]

The noticeable changes triggered by CTE involve a series of clinical, encephalic, and microscopic manifestations, which are characteristics that can help in differentiating it from other tauopathies (►**Table 3**).

Pathophysiology

The definitive encephalic lesion, which is established after TBI, is a result of the different densities between the encephalon and the cranial box, thus, when submitted to the same inertial forces, they respond unequally. This mismatch of movements can promote rupture of cerebral veins that flow into the dural sinuses, as well as the impact and laceration of the parenchyma against the rigid structures of the skull. In addition to this mechanism, as the central region of the brain is relatively fixed due to the presence of the brainstem, the peripheral regions of the brain and cerebellum tend to present a greater amplitude of displacement. Therefore, this difference in the extent of movements between the

central and peripheral regions of the brain generates stretching of axons and cerebral blood vessels, which can result in anything from temporary dysfunction to rupture of these structures.[18,19]

The alterations are of macro and microscopic character. Macroscopically, modifications of the septum pellucidum are found, with the presence of fenestrations and a large *cavum*, associated with cerebellar atrophy. On the other hand, microscopically, there is loss of cerebellar Purkinje cells, degeneration, and loss of substantia nigra cells, presence of neurofibrillary tangles (NFTs), which are aggregates of tau polymers, neuropil threads and glial tangles (GTs).[10,12,18]

During a traumatic event, there is a shear deformation in the brain and spinal cord, causing transitory or permanent lengthening of axons. Traumatic axonal injury's outcomes are changes in axonal membrane permeability; ionic changes, including great calcium influx and release of caspases and calpains that can trigger phosphorylation of tau; unfolding; truncation and aggregation, as well as cytoskeletal breakdown with dissolution of microtubules and neurofilaments.[6,20]

Immediately after a biomechanical injury to the brain, there is an abrupt and indiscriminate release of neurotransmitters and uncontrolled ion fluxes. In this regard, the binding of excitatory transmitters, such as glutamate, to the N-methyl-D-aspartate (NMDA) receptor conditions additional neuronal depolarization with potassium efflux and calcium influx. These ionic changes promote acute and subacute changes in cellular physiology.[21]

In the acute deformation, the effort to restore the neuronal membrane potential, the sodium-potassium ($Na+$- $K+$) pump, is beyond normal. Therefore, it requires increasing amounts of adenosine triphosphate (ATP), causing a dramatic jump in glucose metabolism. This "hypermetabolism" occurs in the scenario of decreased cerebral blood flow, and the disparity between glucose supply and demand triggers a cellular energy crisis. The resulting energy shortage is a likely mechanism of post-concussive vulnerability, making the brain less able to respond adequately to a second injury and, thus, leading to prolonged deficits.[21]

After the initial period of accelerated glucose utilization, the affected brain enters a period of depressed metabolism. As such, persistent increases in calcium can impair mitochondrial oxidative metabolism and worsen the energy crisis. In addition, unchecked calcium accumulation can also directly activate pathways leading to cell death, and thus intra-axonal calcium flux disrupts neurofilaments and microtubules, impairing post-traumatic neural connectivity. There are other changes, such as: lactic acid generation, decreased intracellular magnesium, free radical production, inflammatory responses, and altered neurotransmission.[21]

Modifications in neurotransmitters are present in the glutamatergic system through glutamate and NMDA binding, in which long-term potentiation, a measurement of plasticity dependent on this receptor, may be persistently impaired in the hippocampus. Meanwhile, there are impairments to the adrenergic and cholinergic systems, such as early changes in choline acetyltransferase activity and neuronal loss in the forebrain, a triggering factor for learning and memory deficits. The loss of hilar neurons, producers of γ-aminobutyric acid (GABAergic), can compromise the normal inhibition of the hippocampal dentate granule cells. This loss may predispose the traumatized brain to the subsequent development of seizures.[20]

Furthermore, nitric oxide (NO) is produced by the increase in intracellular calcium concentration associated to cellular aggression mechanisms present in trauma. In TBI, its action may be divided into three phases. First, NO seems to act preserving the cerebral blood flow (CBF) in its first 30 minutes. In a second phase, there is a depletion of NO accompanied by a decrease of CBF between 30 minutes and 6 hours. Lastly, NO increases again after 6 hours. In this last phase, the accumulation of this oxide affects the endothelium, causing a potent vasodilation and increase in vascular permeability. The combination of these actions leads to increased CBF, cerebrospinal fluid pressure, and cerebral edema.[22]

Therefore, repeated injuries in collision and contact sport practitioners over a period of time can lead to significant anatomical or behavioral impairment. Traumas can be characterized by concussions, which occasionally lead the brain tissue to a state of progressive deterioration by overstimulation of the injured brain. Thus, the pathophysiology has an impact on the possible apparent signs and symptoms that can lead to CTE.[20]

Clinical Aspects

Individuals with CTE may develop a variety of clinical symptoms and secondary illnesses; and many of these are insidious. These include mood and behavioral impairment, such as the manifestation of depression, anxiety, apathy, paranoia, psychotic symptoms, suicidality, explosiveness, violent amnesia, drowsiness, dizziness, altered level of consciousness, slowness to answer questions or follow directions. There are also changes in cognition, with impaired memory, executive dysfunction, loss of attention, and dementia.[12,16,23,24]

Likewise, some physical or somatic signs and symptoms can be observed, such as: blurred vision, decreased performance, diplopia, fatigue, headache, dizziness, nausea, vomiting, incoordination, tinnitus, seizures, difficulty speaking (incoherence), stray and glassy eyes, seeing bright spots, and vertigo.[12,16,24] Less commonly, eye abnormalities, such as ptosis; and in motor functioning, such as the appearance of Parkinsonism features: ataxia and dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbances, falls, and even Parkinson itself.[12,16,24]

Following a large systematic review of 47 studies, done by McKee AC et al.,[12] that sought to evaluate the long-term effects of sports-related concussion in 46 retired athletes, the mean age of onset was found to be 42.8 years old. Notwithstanding one third of the athletes was symptomatic at that time, the onset roughly occurred around 8 years after retirement. Among the main symptoms noted were major mood disturbances in 30% of the athletes and movement abnormalities (such as Parkinson and slow gait) in 42%.[12]

Therefore, there is social instability, irregular behavior, memory loss, and early symptoms of Parkinson disease in the early affective and psychological disorders. In the later stages, CTE can be clinically confused with Alzheimer disease or frontotemporal lobar degeneration (FTD), as well as general cognitive dysfunction progressing to dementia.[6,14]

Diagnosis Criteria

As previously described, CTE is a progressive neurodegeneration characterized by widespread deposition of hyperphosphorylated tau protein (p-tau) as NFTs, and in late stages it can be clinically confused with other dementia diseases such as Alzheimer disease (AD), frontotemporal lobar degeneration (FTD), and Parkinson disease.[23,24]

Within the vast information present in the literature, it is important to list the topics that guide the laboratory diagnosis of CTE: prominent perivascular distribution of astrocytic tangles (AS) and NFTs; irregular cortical distribution of immunoreactive NFTs to p-tau and AS with a predilection for the depth of the cerebral sulci; subpial and periventricular groups of AS in the cerebral cortex, diencephalon, basal ganglia and brainstem and NFTs located preferentially in superficial layers. Besides the presence of NFTs in the mamillary body, typical of CTE, likewise in the substantia nigra, in a severe stage; and absence of β-amyloid peptide deposits. Regarding macroscopy, there is generalized atrophy of the cerebral cortex, medial temporal lobe, diencephalon and mamillary bodies with enlarged ventricles.[8,25]

Differential Diagnosis

Precisely because it is a dementia, CTE requires differentiation from other syndromes of the same spectrum, as mentioned above: AD, Parkinson disease, and FTD. In order to expose such differences, the following milestones for each pathology are found bellow.

Alzheimer Disease

The criteria for AD were based on the presence of β-amyloid protein plaques and p-tau ENFs. The nature, pattern, and distribution of p-tau neurofibrillary degeneration in CTE are distinct from AD, which denotes diffuse cortical presence of NFTs and absence of pathological perivascular neurofibrillary clustering. Furthermore, there is a widespread cortical distribution of p-tau pathology without accumulation in the sulcal depths, and the subpial region in the depth of the sulcus does not demonstrate AEs positive for p-tau.

Furthermore, there is a notable element of presence of abundant β-amyloid plaques and intercalated NFTs, along with moderate neurofibrillary alteration in the compact substantia nigra typical of severe AD; and absence of AEs or NFTs in the mamillary body in the disease.[14,26]

Parkinson Disease and Lewy Body Dementia

The Parkinsonian diagnosis is made based on the presence of positive Lewy bodies with positive alpha-synuclein predominantly in the brainstem, a laboratory finding absent in CTE. The existence of these bodies may also signal another type of dementia, the Lewy body dementia, which evolves intracytoplasmic aggregation of spherical elements and eosinophilic infiltrate that are, again, elements that are not aggregated to CTE.[14,27]

Frontotemporal Lobar Degeneration

The diagnosis of FTD is based on the predominant involvement of the frontal and temporal cortices and characteristic immunohistochemistry for p-tau and measured by cytoplasmic and intranuclear neuronal inclusions positive for TAR 43 DNA-binding protein, showing some relation with CTE and being presented in the scope of differential diagnoses. Additionally, dystrophic neurites and glial cytoplasmic inclusions are visualized in the superficial layers of the cerebral cortex and dentate gyrus. The differential of FTD includes progressive supranuclear palsy, corticobasal degeneration, and Pick disease, patterns that are absent in CTE.[25,27]

Conclusion

In summary, the relationship established between the genesis of CTE and the practice of sports, especially of contact and collision sports, is clear since repetitive traumas predispose to an array of metabolic, ionic, cellular, and synaptic disorders that may provoke the pathophysiological cascade of CTE. Furthermore, similarities and significant differences have been noted between CTE and other dementia diseases, such as Alzheimer and Parkinson, aiming to present a differential diagnosis.

Conflict of Interests
The authors have no conflict of interests to declare.

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