Review

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Chronic traumatic encephalopathy in athletes, players, boxers and military: systematic review

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Abstract

The objective of the study was to demonstrate whether athletes, players, boxers and military personnel can really be victims of Chronic traumatic encephalopathy (CTE), and to elucidate this pathology. In 53 articles, 14 were selected for qualitative synthesis in the results table that addresses CTE in football, soccer and rugby players, boxers and the military. Neuropathologically, CTE shows cerebral atrophy, a pelvic septum cavity with fenestrations, dense diffuse immunoreactive inclusions and a TDP-43 proteinopathy. Microscopically, there are extensive neurofibrillary tangles and spindle-shaped neurites throughout the brain. Thus, CTE is characterized by being a distinct tauopathy and with a clear environmental etiology. American football players, boxers and the military are more likely to trigger CET, due to the constant mechanical shocks from their heads. The most frequent clinical manifestations were: headache, aggressiveness, dementia, executive dysfunction and suicide. CET is definitely diagnosed only at autopsy, there is no specific treatment for it, but support and safety measures can help the patient. Advances to definitively diagnose CTE in living people and specific treatment for this disease are needed.

Keywords: athletes, boxers, cerebral concussion, chronic traumatic encephalopathy, military

Introduction

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease linked to recurrent head trauma, that may occur during contact sports and military participation[1,2]. This trauma can include mild traumatic brain injury (mTBI), or concussions, as well as subconcussive injuries, that is, mild brain trauma that does not result in the readily observable signs and symptoms of a concussion[1]. The impact of CTE is profound, with a range of potential consequences including executive dysfunction, memory impairment, depression, suicidal tendencies, apathy, and poor impulse control. These effects can eventually lead to dementia. These clinical manifestations not only affect the quality of life of the individuals but also present challenges for healthcare providers in terms of diagnosis and management[1].

HIGHLIGHTS

- The objective of the study was to demonstrate whether athletes, players, boxers and military personnel can really be victims of CTE, and to elucidate this pathology.
- In 53 articles, 14 were selected for qualitative synthesis in the results table that addresses CTE in football, soccer and rugby players, boxers and the military.
- Neuropathologically, CTE shows cerebral atrophy, a pelvic septum cavity with fenestrations, dense diffuse immunoreactive inclusions and a TDP-43 proteinopathy.

Although CTE is associated with a history of reiterative brain trauma, the exact relationship between acute traumatic injury and CTE is unclear. It has been hypothesized that a neurodegenerative cascade is triggered by repetitive axonal stretching and deformation induced by trauma, particularly in individuals with previous unresolved concussive and/or subconcussive injuries[3].

Over the last several decades, clinical and neuropathologic evidence of CTE has emerged in association with various sports, military service and many other activities associated with repetitive mild head trauma[3,4]. The manifold impairments of CTE substantially impact the health of affected individuals, constituting an important disorder that needs to be highlighted.

The focus of this study is on athletes, players, boxers, and military personnel due to their increased exposure to repetitive head trauma, which is recognized as the primary environmental factor leading to CTE. Contact sports, involve repeated concussive impacts to the head. Military personnel are frequently exposed to blast injuries and other traumatic brain injuries in combat or training. These high-risk groups are particularly susceptible to the neuropathological alterations characteristic of

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CTE, rendering them optimal populations for investigating the clinical, diagnostic, and therapeutic aspects of the disease. By concentrating on these groups, this study strives to corroborate evidence from environments where repetitive head trauma is pervasive, thereby advancing a more comprehensive understanding of CTE and its ramifications.

Given the considerable impact of chronic traumatic encephalopathy (CTE) on at-risk populations, the present study aims to consolidate existing scientific evidence and investigate the clinical, neuropathological, and therapeutic characteristics of this condition through a systematic review of the existing literature, with a particular focus on CTE among athletes such as football players, boxers, and military personnel. The aim of this approach is to identify and examine the main clinical, neuropathological, epidemiological, diagnostic, and therapeutic characteristics of this pathological process.

Material and methods

Ethical standards

The present study was based on previously published studies and no ethical approval or informed consent was required.

Study design and identification

This is a systematic review, based on the preferred reporting item guidelines for systematic reviews and meta-analyses (PRISMA)[5–7], being a literature review with a synthesis of the scientific evidence found (Fig. 1). Based on the guiding question: "athletes, players, boxers and military personnel can really be victims of CTE, and what are the main scientific evidences about this pathology, with emphasis on pathophysiology, diagnosis and treatment?". A systematic and comprehensive review of the literature was carried out from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science and SciELO, using the following keywords: "chronic traumatic encephalopathy", "brain concussion", "players", "boxers", "athletes" and "military". These are in combination with the Boolean operators: "AND" and "OR". The keywords were searched in the modality "all fields". Each article and its respective references were obtained in full and carefully analyzed.

Eligibility criteria

Inclusion criteria were articles that presented scientific evidence about CET in players, athletes, boxers and/or military personnel

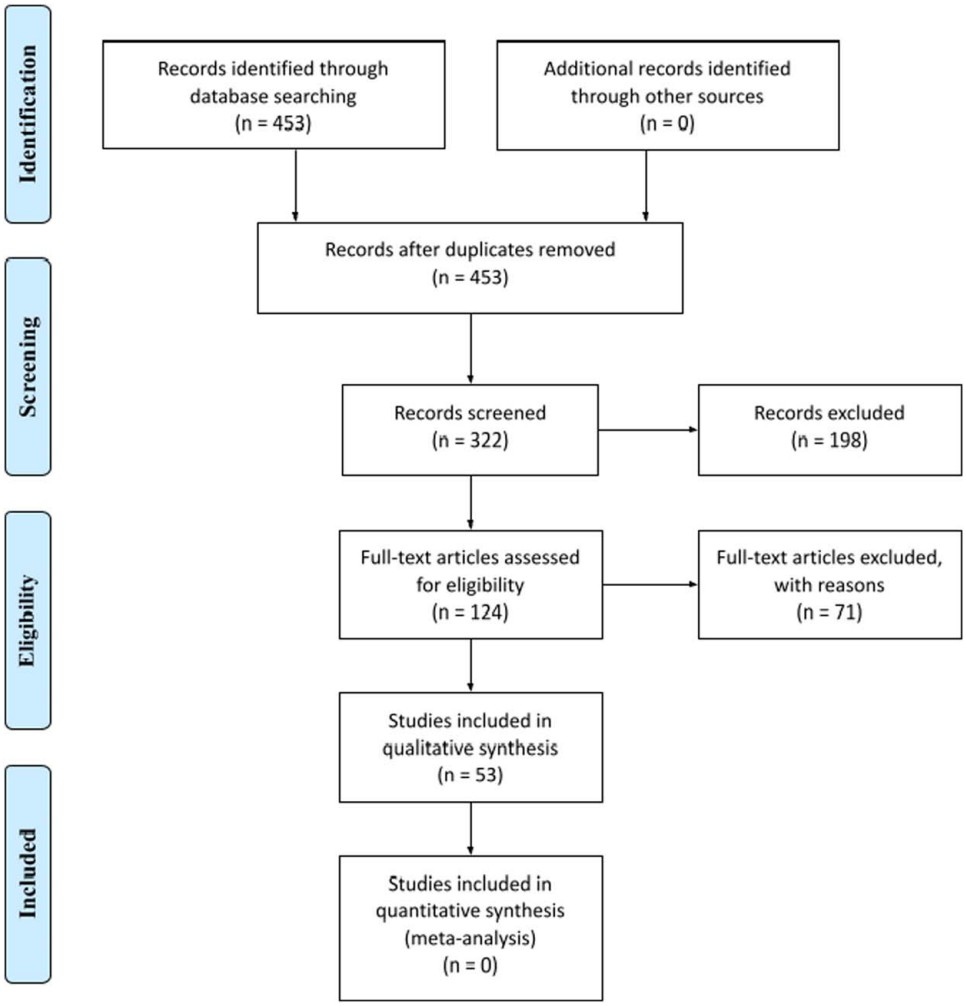

Figure 1. Flowchart: Represent identification, screening, eligibility and Inclusion and exclusion criteria of this systematic review.

(Table 1). Only studies that clearly presented the diagnosis of chronic traumatic encephalopathy in players, athletes, boxers and/or military personnel. In addition to presenting a description of the clinical conditions and evolution of these individuals, which are well done methodologically and adequately developed, they were included in this study. And also studies that showed the main news and updates in medical literature on the subject, in prestigious journals.

Furthermore, other inclusion criteria were to select qualitative and quantitative primary research (such as randomized controlled trials and observational studies) and secondary research (such as meta-analyses and patient review reports), which were available online in full as an article in the languages: English, Spanish or Portuguese. Free text words and controlled vocabulary/MeSH terms were combined without any limitation in the search period. MEDLINE search terms were adapted for each database.

Additional relevant studies were identified in the references section of the included articles and conducting a manual search ("snowball" method) in order to also include relevant and reliable gray literature, applying the same selection criteria described above. Narrative and integrative review articles, monographs, letters to the editor, and any studies with animal models were excluded. Moreover, methodologically poorly carried out works from small journals, with low scientific evidence and studies that lacked details about the patient's clinical conditions, evolution and clear diagnosis were also excluded.

Population data

The population selection was based on articles that addressed CET in athletes, players, boxers and/or military personnel. No restrictions on age, sex, race, color or socioeconomic status were imposed.

Mapping, analysis, validation and data extraction process

Following PRISMA guidelines and the Population, Intervention, Comparison and Result (PICO) structure[8], two individuals independently examined the titles and abstracts identified in the research. Articles considered relevant were selected and downloaded for full-text review. Two researchers independently reviewed the full texts and selected the articles to be included in the review based on inclusion and exclusion criteria.

Relevant study characteristics, including study type/design, sample size, individual profile (whether military, athlete, boxer or player), clinical conditions and patient outcomes, were collected, analyzed and later extracted. Disagreements in data collection were discussed with the third researcher until a consensus was

Table 1

The study presented the main scientific evidence about CTE.

Author	Type of study	Country	Total no. cases reviewed	Chronic traumatic encephalopathy	Deaths of chronic traumatic encephalopathy	Clinical condition	Perfil analyzed
McKee *et al.*,[13]	CS	USA	12	12	12	Motor neuron sympstoms, dementia	Boxers, football player, Professional hockey
Omalu *et al.*,[14]	CR	USA	1	1	1	Depression, suicidal tendency	American football players
Gavett *et al.*,[4]	RS	USA	321	12	12	Irritable, angry, apathetic or as having a shorter fuse, cognitive difficulties	American football players
Omalu *et al.*,[15]	CR	USA	1	1	1	Dizziness, irritation, anhedonia symptons	Military Veterans
Omalu *et al.*,[16]	RCS	USA	17	11	0	Composite syndrome of mood disorders and neuropsychiatric and cognitive impairment	Footbal player, wrestler, boxer
Goldstein *et al.*,[17]	RCT	USA	12	8	NR	Progressive affective lability, irritability, distractability, executive dysfunction, memory disturbances, suicidal ideation, and in advanced cases, cognitive deficits and dementia	Military Veterans, American football players
McKee *et al.*,[18]	RCS	USA	85	68	43	Irritability, impulsivity, aggression, depression, short-term memory loss and heightened suicidality	Military Veterans, Athletes
Stern *et al.*,[19]	RS	USA	81	36	36	Behavior, mood and cognitive variant	American football players. Hockey players, football player
Stein *et al.*,[20]	RS	USA	100	68	68	Mild cognitive and behavioral symptoms	Military Veterans, Athletes
Bieniek *et al.*,[21]	RS	USA	1721	21	21	Headaches, loss of attention and short-term memory loss, behavioral changes, rage, dyscontrol, depression, suicidal tendency, dementia, and gait abnormalities	Footbal player, baseball, basketball, wrestler, boxer, rugby
Mez *et al.*,[2]	CS	USA	202	177	138	Behavior, mood, cognitive symptoms and dementia	American football players
Bonfante *et al.*,[22]	CS	USA	85	68	68	Altered mood and behavior, cognitive impairment, depression	American football player, boxers, military veterans

CR, case report; CS, cohort study; CTE, Chronic traumatic encephalopathy; RCS, retrospective cohort study; RCT, randomized clinical trial; RS, retrospective study.

reached. Finally, a third independent researcher checked the extracted data in order to resolve disagreements and verify consistency. When the relevant data available was limited, an attempt was made to contact the authors of the respective article in order to obtain the necessary additional data, information and clarification.

The quality of each article was evaluated and the level of evidence was qualified according to the classification of the Oxford Center for Evidence-Based Medicine[9].

Bias risk assessment

The risk of bias assessment of each study was performed according to the following criteria: selection bias (random sequence generation, allocation concealment); performance bias (blind process for participants and research staff); detection bias (blind outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); and others[10]. As per the Cochrane database, the risk of bias can be categorized into high, low and uncertain, with a high risk of bias being determined when jobs do not meet any of the assessment criteria described above. The risk of bias was rated as low when these criteria were properly determined. In contrast, the risk of bias was classified as uncertain when the information available was insufficient to categorize the risk of bias for each item as low or high, or it was not correctly described in the article[11,12].

In order to assess the risk of bias, an approach based on the Cochrane criteria was employed. These criteria encompass five domains: selection, performance, detection, attrition, and reporting bias. Although tools such as QUADAS-2, ROBINS, and NOS are widely used, our analysis focused on criteria that best suited the included studies, considering the diversity of study designs. Studies with a high risk of bias were carefully considered and, when included, it was due to their unique contribution to the understanding of CTE. Case reports, due to their specific nature, were assessed with adapted criteria to ensure the inclusion of relevant data.

Results

Through a systematic literature review of 53 articles included in the qualitative synthesis, which met all eligibility and quality criteria, 12 articles were found with clear and confirmed diagnostic results of chronic traumatic encephalopathy present mainly in soccer players, boxers, football players, rugby players and war veterans. The studies analyzed are of American origin and are of the randomized clinical trial, retrospective cohort study, cohort study, retrospective study and case report type.

Encephalopathy was confirmed postmortem through autopsy and pathological and micropathological examinations of brains donated for encephalopathy research. The symptoms presented are generally associated with behavioral changes, psychological disorders, dementia, cognitive symptoms, tendencies to violence, exacerbated irritation and, in many cases, suicidal tendency.

Discussion

Historical retrospective

CTE was formerly termed dementia pugilistica or "punch-drunk" when thought limited to boxers[13–19]. In 1928, Harrison Stanford Martland, a forensic pathologist and medical examiner, introduced the term 'punch-drunk' to describe the clinical features of a distinct neuropsychiatric syndrome that affected boxers; a condition that later came to be known as 'dementia pugilistica[16,20–23]. From the 1940s onward, the broader designation "chronic traumatic encephalopathy" or "CTE", introduced by Critchley in 1949, was in common use, recognizing that the condition could arise from brain trauma from a variety of sources in addition to boxing, and therefore CTE became the preferred designation for the condition[23,24].

Seventy-four years later, Dr Bennet Omalu, another forensic pathologist and medical examiner in Allegheny County, Pittsburgh, Pennsylvania, recognized CTE in football players[16]. In 2005, Omalu and colleagues described the first case of neuropathologically confirmed CTE in an American football player. Since that time, there has been increasing public attention to this disease. Dr Omalu, the Brain Injury Research Institute, and other researchers have identified and described CTE in numerous football players, wrestlers, boxers, and ice hockey players, which have been reported in the literature[15,25].

Epidemiology

The incidence and prevalence of CTE are unknown, although the number potentially affected could be quite large. Every year, between 1.6 and 3.8 million individuals in the US experience a sports-related concussion, and the number of youth sports-related concussions has grown in recent years[25]. CTE has been found most often in professional athletes involved in contact sports (such as boxing, ice hockey, martial arts, American football, soccer, rugby and wrestling) who have been subjected to repetitive head blows resulting in concussive and subconcussive trauma[14,25,26]. CTE pathology has also been documented in soldiers exposed to explosive blasts, during military training and combat, and others subjected to repetitive brain trauma (RBT)[19,21,26].

CTE neuropathology

Through electrophysiological studies it was already possible to identify that cerebral concussion results in an active response on the part of the central nervous system. This active response constitutes the synaptic release of many neurotransmitters[27]. Through fluid percussion, the glutamate of excitatory amino acids revealed itself as a final space in the massive flow of ions and also showed impairment in neuronal functioning that led to energy deficits and vulnerability[28,29]. In addition, it was possible to observe an increase in extracellular potassium induced by concussion, which through induced synaptic activity caused the hippocampus to release a certain amount of potassium.

Using microdialysis, the researchers were able to determine that blocking synaptic activity had no effect on "supra-physiological" levels. In view of the repertoire of calcium acting on the pathophysiology of cerebral ischemia, the researchers determined that calcium was involved in traumatic brain injury, even in mild brain trauma, calcium accumulates in tissues that would not necessarily die, differently from what was reported for potassium. However, the extracellular increase in potassium causes cells to seek energy to activate the sodium-potassium pump that is financed by ATP, and the intracellular increase in calcium can buffer mitochondria, resulting in a reduction of this organelle in producing ATP through oxidative metabolism[30,31].

Since 1940, researchers have suspected that human cerebral concussion was due to the compression and displacement of the nutritive cerebrospinal fluid that deprived neurons of glucose and, as a result, there would be a transient interruption of brain function. As a result of the increase in extracellular potassium that was induced by fluid percussion, there is a need to metabolize glucose to activate the sodium and potassium pump. To prove this logic, the researchers used 2-dioxide-Glucose autoradiography, which assesses the regional use of glucose in brain metabolism and, thus, the expectations were confirmed. With that, the researchers suggested that this could be the cause of the unconsciousness that occurs after the concussion[28,29].

According to related studies, it has been determined that after traumatic injury there is an increase in brain lactate, which is the by-product of anaerobic glycolysis. These results were interpreted as a confirmation that the accumulation of lactate after the traumatic injury is the result of increased glycolysis to help ion pumping mechanisms. In addition, the researchers determined that a second concussion during the recovery period of the first injury produces a longer period of cell dysfunction and even cell death[32]. As an example, athletes who participate in exhaustive activity right after the injury exhibited worse neurocognitive performance than those who were more rested. However, there is also evidence that controlled exercise can be beneficial. The concussion brain temporarily loses its cerebral blood flow for neuronal activation coupling, the combination of these studies points to the effect of an energy crisis after concussion which, if not properly recognized and managed, can result in permanent damage[33].

Neuropathologically, CTE is marked by widespread accumulation of hyperphosphorylated tau (p-tau) in neurons and astrocytes in a pattern that is unique from that of other tauopathies, including Alzheimer's disease (AD) and frontotemporal lobar degeneration[19,25]. The p-tau deposition initially occurs focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci. It spreads to involve superficial layers of the adjacent cortex, eventually resulting in widespread degeneration of the medial temporal lobes, frontal lobes, diencephalon, and brainstem[28]. Grossly identifiable changes in the brain are unusual in early or mild CTE; in intermediate and advanced CTE, macroscopic changes include a reduction in brain weight, gray and white matter atrophy (typically most severe in the frontal and anterior temporal lobes), enlargement of the lateral and third ventricles, cavum septum pellucidum, septal fenestrations, atrophy of the thalamus, hypothalamus and mammillary bodies, thinning of the isthmus of the septum corpus callosum and depigmentation of the locus coeruleus and substantia nigra[24]. A staging scheme has been proposed, with cortical pathology in Stages I and II, and more extensive subcortical pathology in Stages III and IV[21].

CTE is divided into four stages, briefly stage I is characterized by 1–2 lesions of isolated perivascular epicenter that affects the frontal cerebral sulcus and temporal or parietal cortex, in stage II it is delimited in 3 or more lesions that reach multiple cortical regions and superficial, in stage III there are several superficial and diffuse cortical lesions with neurofibrillary degeneration of the entorhinal and perirrinal cortices, tonsils and hippocampus, in stage IV the lesions of CTE are distributed throughout the cerebral cortex, diencephalon and brainstem with neuronal and gliosis. Stages I and II are considered mild and stages III and IV are considered severe. Therefore, understanding the responses of basic cell lines to this injury must be explored in relation to the severity and degree of concussion so that management and treatment can be used appropriately[2,4].

Clinicopathological considerations

The early scope of amygdalo-hippocampal-septum-hypothalamic-mesencephalic continuum by the tau protein, in an abnormal way, can be the axis of many of the early behavioral symptoms, involving predisposition to emotional lability, violent outbursts and aggression. The symptomatic frequency of episodic memory disorder may be due to the early involvement of the hippocampus, entorhinal cortex and medial thalamus[4,34–36].

Probably the disexecutive symptoms occur due to neurofibrillary degeneration of the frontal cortex and the underlying white matter. On the other hand, cases of visuospatial difficulties can happen due to neurofibrillary degeneration in the dorsolateral parietal, posterior temporal and occipital cortexes; however, this is much less frequent and also less severe[18,34,35].

In one study, they noticed that 41.1% of the analyzed CTE cases had parkinsonian peculiarities, and these are probably the result of the degeneration of the substantia nigra pars compacta. In cases of gait disorders, whether staggered, delayed, scrambled or frankly ataxic, they may be the consequences of an association of cortical and subcortical frontal damage, degeneration of the cerebellar tracts in the brainstem, direct cerebellar injury. Furthermore, in the reported cases of speech disorders, for example slow and slurred speech, they probably occur due to multiregional degeneration. Degeneration of the brainstem nuclei, such as the hypoglossal and oculomotor nuclei, is probably the cause of the symptoms of dysarthria, dysphagia and ocular abnormalities[18,34,35].

General clinical symptoms

Clinical symptoms of CTE include progressive affective lability, irritability, distractability, executive dysfunction, memory disturbances, suicidal ideation, and in advanced cases, cognitive deficits and dementia (Table 2)[17]. These neuropsychiatric symptoms usually occur 8–10 years after exposure to repetitive brain injury and embrace headaches, mood disorder (mainly depression), paranoia, agitation, social withdrawal, poor judgement and aggression. Cognitive impairment tends to emerge later and typically includes impairment across the domains of orientation, memory, language, attention, information processing speed and executive functioning[21,37].

CTE in players and boxers

Even at the beginning of the 20th century, it was already possible to observe players and boxers exhibiting cognition, behavior or motor abnormalities that were well known by physitions, sports communities and even laypeople. These abnormalities were referred to by a variety of terms, such as "punch-drunk", "goofy" and "injured madman"[4,38,39]. Therefore, in order to give medical validity to the condition, a more formal term - pugilistic dementia - was introduced. Faced with these abnormalities, medical researchers sought an explanation[4].

Through the sample of deceased football players who donated their brains for research, the researchers observed a high proportion presented neuropathological evidence for CTE[2]. In view of this, the researchers found that CTE occurs after one or more

Table 2

Most common clinical picture of each stage of CTE.

Author	Type of study	Country	CET stage classification	Total no. cases reviewed	Clinical condition	No. cases	Perfil analyzed
McKee *et al.*,[18]	RCS	USA	I	7	Asymptomatic; headache, loss of attention and concentration; short-term memory difficulties, aggressive predispositions and depression; executive dysfunction and explosiveness; post-traumatic stress disorder;	1 4 3 2 2	Military Veterans, Athletes
McKee *et al.*,[18]	RCS	USA	II	14	Asymptomatic; depression or mood swings, headaches, short-term memory loss, executive dysfunction, impulsivity, suicide and language difficulties;	3 11	Military Veterans, Athletes
McKee *et al.*,[18]	RCS	USA	III	12	Asymptomatic; loss of memory, depression or mood changes, explosiveness, executive dysfunction, difficulty in attention and concentration, cognitive impairment, visuospatial difficulties, aggression, apathy, headaches, impulsiveness and suicide;	1 11	Military Veterans, Athletes
McKee *et al.*,[18]	RCS	USA	IV	13	Asymptomatic; executive dysfunction, memory loss, excessive loss of attention and concentration, language difficulties, explosiveness, aggressive tendencies, paranoia, depression, gait and visuospatial difficulties, all of whom evolved with severe loss of memory and dementia, impulsivity, dysarthria, parkinsonism, suicide;	0 13	Military Veterans, Athletes

CTE, Chronic traumatic encephalopathy; RCS, retrospective cohort study.

causes of repeated head trauma, suggesting that any repeated blows to the head, such as those that occur due to football, hockey, soccer, professional wrestling and physical abuse, may also lead to neurodegenerative diseases[4,13].

These diseases are generally spread throughout the cerebral cortex in an irregular and superficial distribution, with focal epicenters in the depths of the grooves and around the cerebral vasculature that include changes such as cerebral atrophy, diffuse axonal injury, peltid septum cavity with fenestrations, shrinkage of the nipple bodies, dense immunoreactive inclusions of tau and, in some cases, a TDP-43 proteinopathy[2,4,13]. In association with these pathological changes, affected individuals usually exhibit disordered memory and executive functioning, personality and behavioral disorders (apathy, depression, irritability, impulsivity, suicide), parkinsonism and, occasionally, motor neuron disease[4].

Although the incidence and prevalence of CTE is not so clear at the moment, it is already possible to note that some factors can influence the risk of CTE that probably varies according to sport, position, duration of exposure and age at the time of initial or subsequent head trauma, as well as with additional variables, such as genetic predisposition[2,4,13]. In addition, it is possible to observe that behavior, mood and cognitive symptoms are common among those with mild and severe CTE pathology and signs of dementia are common among those with severe CTE pathology[4]. In addition, CTE usually manifests in middle age[4,13].

Corsellis *et al.* (1973) studied the brains of 15 retired boxers and verified that a single punch or many punches eventually will initiate the destruction of cerebral tissue, and this is usually slight enough in the early stages to be undetectable, but if the boxing continues, it may escalate until it becomes clinically detectable. Since the destroyed cerebral tissue can never be replaced, it could already be too late when the damage becomes apparent, because the process of degeneration continues even after the boxing has stopped[40].

CTE in military

Exposure to explosive explosions affects combatants and civilians in conflict regions around the world[17]. This exposure is associated with traumatic brain injury (TBI), with part of the military showing neuropsychiatric symptoms and long-term cognitive impairment. Thus, a series of postmortem brain cases of US military veterans exposed to explosion and/or injury was analyzed in order to find traces of the concussion. Therefore, the researchers found evidence of chronic traumatic encephalopathy, which was similar to the CTE neuropathology observed in young amateur football players and a professional fighter with a history of concussion injuries[17]. Soon, the researchers exposed mice to explosions and, through kinematics, it was found that the head oscillation induced by explosion culminates in accelerations that are sufficient to cause brain damage[17].

In addition, it should be noted that the military is not at risk for concussive TBI only during combat, but also performing training exercises and recreational activities[20]. To analyze all this risk that the military is exposed to, in 2008, the Center for the Study of Traumatic Encephalopathy (CEET) at Boston University School of Medicine established the CEET brain bank to analyze the brain

and spinal cord after death of military veterans who have suffered a slight recurrence of head trauma. As a result, it was possible to comprehensively analyze the brain and spinal cord of 85 donors for evidence of CTE[18]. Thus, traces of the CTE were found in 21 veteran soldiers who presented mild repetition of head trauma. Many of those with CTE participated in the Iraq and Afghanistan conflict or the Gulf War or World War II. However, part of the military that showed evidence of the CTE was not present in combat. In view of this, it is notable that the military is not subject to developing TBI only in conflicts, but also in internal activities[18].

Faced with such a situation, individuals exposed to the explosion have an increased risk of traumatic brain injury (TBI), which is often reported as mild. Explosion-related TBI represents a neuropsychiatric spectrum disorder that clinically overlaps with chronic traumatic encephalopathy[18,20]. The neuropathological characteristics of CTE in military veterans provide mechanistic evidence linking the explosion to persistent deficiencies in neurophysiological function, learning and memory[17], including, also, widespread cortical foci of perivascular pathology, disseminated microgliosis and astrocytosis, myelinated axonopathy and progressive neurodegeneration[20]. Finally, it should be noted that CTE in military personnel can trigger molecular changes that result in the overproduction of proteins such as TDP-43, amyloid-beta and alpha-synuclein, for example, in addition to presenting an accumulation of hyperphosphorylated tau (p-tau) in perivascular aggregates in neurons[18,20,41]. In view of this, these cellular changes can cause damage to the blood-brain barrier, impair the activation of neuroinflammation and damage neurons at synapses[17,41].

CTE diagnosis

The clinical diagnosis of CTE is difficult because, currently, there is no consensus on the diagnostic criteria, large-scale longitudinal clinical-pathological correlation studies or effective and consolidated biomarkers[4,35]. However, it is believed that several biomarkers have the potential to contribute to the identification of CTE in living people. As an example, changes in the integrity of the white matter caused by repeated head trauma may be detectable using magnetic resonance imaging[23]. This through spectroscopy may also be able to detect changes in glutamate/glutamine, N-acetyl aspartate and myo-inositol, molecular abnormalities that can serve as markers of brain damage caused by head injuries. Besides that, measuring tau and phospho-tau in cerebrospinal fluid can produce diagnostic markers useful CTE[4].

Other potential biomarkers for CTE comprehend neuroimaging techniques, for instance volumetric magnetic resonance imaging (MRI)[42], functional MRI measuring specific patterns of connectivity[42], MRI detection of specific structural abnormalities common in CTE (e.g. cavum septum pellucidum[43,44]), magnetic resonance spectroscopy[45], and diffusion tensor imaging[46]. However, these techniques would probably operate as proxy biomarkers, rather than specific markers of the underlying p-tau pathology[47]. Another emerging approach to detect and measure brain p-tau directly involves positron emission tomography (PET) radioligands that are specific for the paired helical filament tau (PHF-tau)[48–50].

Recently, Stern and colleagues developed a case-control study approaching plasma exosomal tau levels between former NFL players and a control group of non-contact sport athletes without any history of concussion or other mTBI. The NFL group had significantly higher plasma exosomal tau than the Control group ($P < 0.0001$), and the number of tau-positive plasma exosomes was significantly correlated with neuropsychological test performance—worst performance in the areas of memory ($P = 0.0126$) and psychomotor speed ($P = 0.0126$); there was no significant correlation with behavior and mood. The study verified exosomal tau discriminated between the groups, with 82% sensitivity, 100% specificity, 100% positive predictive value, and 53% negative predictive value, which suggests that plasma exosomal tau may be a non-invasive and accurate biomarker for CTE[47].

Although the neuropathological characteristics of CTE seem to be different from other neurodegenerative diseases, the differential diagnosis of CTE often includes Alzheimer's disease (AD) and frontotemporal dementia (DF), depending on the age of onset and the problem presented[4,35]. Older individuals with memory difficulties may appear to have AD and, in fact, may have evidence of AD and CTE neuropathologically. When the patient's age is between 40 and 60 years and he has behavioral dysregulation or apathy, it can be difficult to rule out DF. Although the history of remote traumatic brain injury may be suggestive of CTE, head trauma has been implicated as a risk factor for neurodegenerative diseases such as AD, Parkinson's disease (PD), for example[4].

The same way PET could be a possible biomarker for CTE, it could also be an important imaging approach in AD. Since the degree of cognitive impairment in AD is linked to aggregates of hyperphosphorylated tau (PHF-tau), PET provides a non-invasive detection and a quantification of proteins linked to disease, allowing an early and differential diagnosis of AD and non-AD tauopathies[48,50]. A reliable diagnostic tool for PHF-tau could enable the diagnosis of AD years prior to symptom presentation, objectively quantify disease progression, and accelerate the discovery of effective treatments[48].

Thus, currently, neuropathological examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression, and to develop therapies to delay or reverse its course[4,18].

Guidelines for prevention and treatment (Figs. 2 and 3)

Clearly, the easiest way to decrease the incidence of CTE is, in theory, to decrease the number of concussions or mild traumatic brain injuries[35]. In athletes, this is sought by limiting exposure to trauma, for example by penalizing intentional blows to the head (as is happening in football and hockey), in addition to game referees always paralyzing the game in situations of head shock between players[4]. However, in some sports, such as boxing and football, it can be almost impossible to avoid repetitive head injuries, especially repeated subconcussive blows[4,35].

In sports in which repeated blows to the head are unavoidable, proper assessment and management of concussion can be instrumental in preventing long-term consequences. At the moment, it is not known, with any certainty, that returning to play while symptomatic of a previous concussion, or sustaining a second concussion while symptomatic, is a risk factor for the development of CTE, since, all confirmed cases CTE patients so far have a history of multiple head injuries[4,51], in addition to experimental evidence in animals suggests that there is expansion

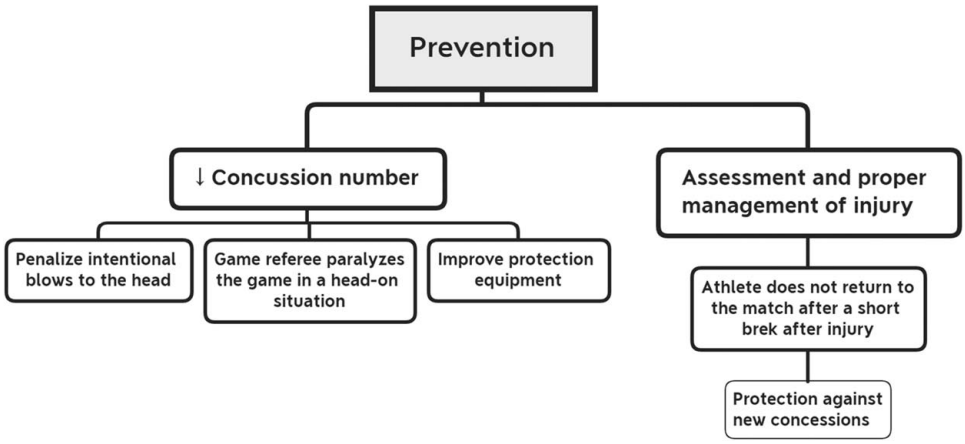

Figure 2. Flowchart: Ways of preventing cerebral concussion by reducing the number of concussions and the appropriate management of injuries. The decrease must occur through penalties applied by the referees and also by improving the equipment. In addition, it is essential to observe the athlete after the head shock, given that the inadequate management of the concussion can lead to worsening of the clinical picture[3,4,35,51,52].

of brain injury and inhibition of functional recovery if the animal is subjected to hyperactivity in the first week after the first injury[35]. Also, other strategies to reduce the number and severity of head trauma are possible, such as limiting contact practices and improving protective equipment, for example[52].

Still, neuropsychological tests are also helping to provide estimates of the appropriate time for athletes to return to training and games after a concussion. These studies indicate that guidelines for a safe return to gambling may require at least a month to facilitate a more complete recovery and to protect against new injuries, as a second concussion occurs much more frequently in the immediate period after a concussion[4,35].

In addition, many studies support some forms of treatment that have shown considerable anecdotal success, such as using natural anti-inflammatory with diets and supplements with omega-3 fatty acids (fish oil) and / or vitamin D3 for their anti-inflammatory effect, in order to decrease inflammatory prostaglandins and neuroinflammation[51–53]. Bearing in mind that no reliable or specific measure of neurological dysfunction after concussion currently exists, most medical recommendations are focused on the resolution of acute symptoms, such as headache, confusion, sensitivity to light and others[35]. It is also worth noting that the research being conducted has profound implications for the current practice of medical professionals, sports coaches and military specialists, in addition to the results being policymakers in government and sports organizations to provide adequate guidance on the prevention and treatment of brain trauma at all levels of athletic as well as military involvement[3,4].

In light of the mounting evidence linking repetitive head trauma to chronic traumatic encephalopathy (CTE), this systematic review highlights the urgent need for the development of early detection and prevention strategies for at-risk populations,

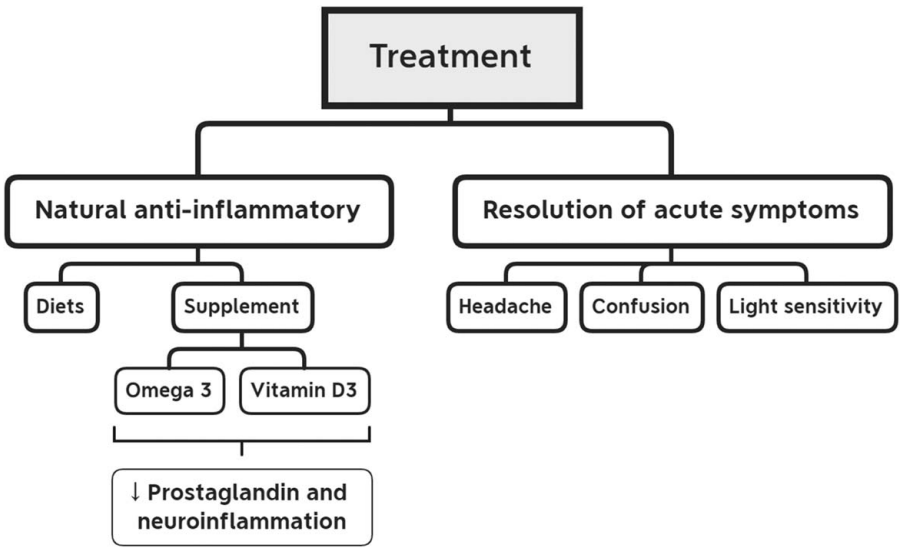

Figure 3. Flowchart: Treatment for chronic traumatic encephalopathy is performed through the use of natural anti-inflammatory drugs through diets and supplements of fatty acids and D3 vitamins, with the aim of reducing neuroinflammation. In addition, treatment requires the resolution of specific complaints[3,4,35,51,52].

including athletes and military personnel. The review identifies current deficiencies in longitudinal studies and diagnostic tools, emphasizing the necessity of advancing diagnostic techniques and therapeutic interventions. To advance this field, a collaborative effort is required to enhance understanding of the long-term effects of repetitive brain trauma and to develop strategies to mitigate the associated neurodegenerative outcomes.

This systematic review has several limitations, particularly regarding the heterogeneity of the included studies. Variations in study methodology, sample size, and diagnostic criteria for chronic traumatic encephalopathy (CTE) contribute to the challenge of synthesizing consistent conclusions. In addition, the lack of large-scale longitudinal studies makes it difficult to identify long-term trends in CTE progression, limiting our ability to predict the course of this disease in different populations. Another limitation is the geographic bias of the studies, as most of the research has been conducted in the United States. This regional focus may limit the generalizability of the findings to other populations and cultural contexts, where different patterns of exposure to TBI may exist.

Despite these limitations, this systematic review has important strengths. It presents a comprehensive analysis of high-quality studies addressing CTE in athletes, boxers, and military personnel, providing a valuable synthesis of the current state of knowledge in this area. The rigorous methodology, based on the PRISMA guidelines, ensures that the included studies adhered to robust selection criteria, thereby enhancing the reliability and validity of the results. In addition, the review's inclusion of multiple databases, such as MEDLINE, EMBASE, and Cochrane, broadens the scope of the findings and ensures a more thorough and comprehensive examination of the existing literature on CTE. These methodological strengths reinforce the contribution of this review to the ongoing discourse on CTE, despite the limitations noted.

Conclusion

This systematic study highlighted the alarming prevalence of CTE in at-risk populations and elucidated its clinical and neuropathological manifestations. The most common clinical manifestations were: headache, loss of attention and concentration, short-term memory, depression, executive dysfunction, stress disorder, impulsivity, suicide, visuospatial difficulties, dementia and language difficulties. Advances to definitively diagnose CTE in living people and specific treatment for this disease are needed.

Ethical approval

Ethics approval was not required for this review.

Consent

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