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Traumatic brain injury (TBI) in collision sports: Possible mechanisms of transformation into chronic traumatic encephalopathy (CTE)

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and disability, contributing to ~30% of all injury-related deaths in the US. TBI occurs when a force transmitted to the head causes neuropathologic damage and impairment of brain function. TBI doubles risk of suicide and is the major determinant of acquired seizure disorders. TBI arising from closed head trauma (CHT) significantly increases the risk of developing Alzheimer's disease (AD), Parkinson's disease (PD) and chronic traumatic encephalopathy (CTE). Evidence for a possible role of TBI as a risk factor for sporadic amyotrophic lateral sclerosis (sALS) has been provided by studies of professional players of European football. Depending on age, genetic make-up (in particular, being a carrier of one or two *ApoE4* alleles), the number of TBIs sustained, their severity, the time periods involved, and many other factors that affect vulnerability, decades may pass after occurrence of one or more TBIs before sequelae such as AD, PD, sALS or CTE become clinically evident. Among college and professional football players who experience repeated concussions and sub-concussive blows to the head, the risk of developing CTE increases with the number of years actively devoted to the sport, and the degree of exposure to physical impacts inherent in the position played. Following a moderate or severe concussion, or a series of mild blows to the head, the brain may undergo subtle pathophysiological changes that are unlikely to be detected with confidence using available diagnostic methods. Biomarkers are being sought that can help the attending physician infer the likely presence of an ongoing occult neurodegenerative process. One example of the adverse effect of collision on the brain is "heading" the soccer ball—a feat that, repeated over years of competition, has been found to produce severe brain damage in veteran players. CTE has attracted increasing national attention because of its devastating effects in a high proportion of retired professional players of American football. In a study of brains from deceased former football players, contributed mostly by family members, CTE was neuropathologically diagnosed in 110 of 111 of National Football League (NFL) veterans. In the CTE-positive subjects, the authors observed extensive brain atrophy, astrogliosis, myelinated axonopathy, microvascular injury, perivascular neuroinflammation, and phosphorylated tau protein pathology. CTE's neuropathology has been formally defined as a *tauopathy* characterized by a distinct perivascular accumulation of hyperphosphorylated tau in neurons and astrocytes within cerebral sulci. Although the mechanism that underlies the unforeseen emergence of CTE long after the occurrence of one or more closed head traumas is unknown, an explanation proposed by Albayram and associates is persuasive. They discovered TBI-induced neuronal production of the toxic compound *cis* P-tau, an abnormal and destructive isomer of the normal and benign *trans* P-tau, in mouse models of CTE. *Cis* P-tau produced a CTE-like syndrome via a process they termed *cistauosis*. Cistauosis can be blocked in laboratory animals by *cis* P-tau monoclonal antibody, which prevents later development of tau tangles, brain atrophy and virtual CTE. In a subsequent study, the same group found in human samples obtained post-TBI from a variety of causes, that *cis* P-tau is induced in cortical axons and cerebrospinal fluid and positively correlates with axonal injury and clinical outcome. Thus, *cis* P-tau appears to contribute to short-term and long-term sequelae after TBI, but may be subject to neutralization by *cis*-antibody treatment.

1. Introduction

Traumatic brain injury (TBI)—particularly the form resulting from closed head trauma (CHT)—is a consequential clinical and public health problem which, inter alia, significantly increases the risk of developing Alzheimer's disease (AD) [1], Parkinson's disease (PD) [2],

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and chronic traumatic encephalopathy (CTE) [3]. Recently, it has been reported that sALS incidence was uncommonly high among professional football (America "soccer") players in Italy [4–6]. In their study population, Chen et al. [4] found that "physical injuries of other body parts ... including trunk, arms, or legs, were not related to ALS risk". These data provide support for the belief that head injury (presumably from "heading" the ball) may increase the risk of sALS.

Depending on the patient's age, genetic make-up, general health status, and other factors that affect vulnerability, it may take decades after the occurrence of one or more TBIs before the neurodegenerative disease in question becomes clinically manifest. This review is primarily concerned with TBI as a risk factor for CTE.

During the years that follow a moderate or severe concussion or, in some cases, a series of mild blows to the head, the brain may undergo pathophysiologic changes that are difficult—often impossible—to detect with certainty in living subjects by means of currently available diagnostic methods [1]. Nevertheless, progress continues to be made in the identification of putative biomarkers that may help the attending physician infer the presence of an ongoing occult neurodegenerative process [3].

2. Scope of review

This review embodies: (i) definitions of TBI and CTE; (ii) an explanation of the risks of experiencing repetitive TBIs that result from participation in amateur and professional collision sports, including the practice of 'heading' the ball in international 'football' (American soccer); (iii) an account of the technical obstacles that complicate efforts to uncover the presence of a TBI-generated chronic occult process at work in the brain—a process of the kind that eventually gives rise to the widespread neurodegenerative damage that underlies the behavioral changes and progressive impairment of cognitive function that characterize CTE; (iv) an authoritative description of the unique neuropathology of CTE, based on many careful analyses of post-mortem studies of victims' brains [7].

In contrast, consensus with respect to the mechanism(s) responsible for the evolution of CTE from TBI has yet to be achieved. Some of the more persuasive explanations of why and how TBIs might trigger the TBI → CTE process are considered in the latter part of the review.

3. Clinical signs and neuropathology of traumatic brain injury (TBI)

Common types of (usually) "mild" TBI include contact sports-related concussions and 'subconcussions'. "Concussions and 'subconcussions' are produced by acceleration and deceleration forces on the brain, which may be linear or rotational" [8]. It is evident that collision sports like American football, soccer, and ice hockey can create conditions that favor concussion. Moreover, among soccer players, "heading" the soccer ball is a maneuver that, repeated over years of competition, has been reported to produce severe brain damage [9].

The forces involved in the very rough contact that frequently occurs in American football can subject neurons and other brain structures to excessive physical stress. These circumstances may give rise to such secondary effects as central nervous system (CNS) vascular injury, with hemorrhage, hypoxia and ischemia, impairment of mitochondrial function, insulin resistance, hypometabolism, neuroinflammation, and brain swelling [7].

In 2015, McKee and Daneshvar [10] reviewed the symptoms, signs, and neuropathology of TBI. They also considered the conditions under which TBI can evolve into chronic traumatic encephalopathy (CTE). They introduced their overall analysis with a broad definition which stated that "TBI occurs when a force transmitted to the head or body results in neuropathologic damage and dysfunction". This definition was derived from a more detailed description of TBI developed by the U.S. Department of Veterans Affairs (VA) and the Department of Defense (DoD), which specified "new onset or worsening of at least one of the following clinical signs immediately following the event: any period of loss or a decreased level of consciousness (LOC), any loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA]), any alteration in mental state at the time of the injury (confusion, disorientation, slow thinking, etc.), neurological deficits (weakness, loss of balance, change in vision, praxis, -paresis/-plegia, sensory loss, aphasia, etc.) that may or may not be transient, or an intracranial lesion."

4. The search for biomarkers

The daunting obstacles to a definitive diagnosis of preclinical CTE while it is evolving have stimulated an extensive search for relevant biomarkers to help physicians identify patients who are in the process of (or are at high risk of) developing this TBI complication.

During the last half-dozen years, these efforts have begun to bear fruit [7]. Early on, six imaging modalities were listed by Turner et al. [3] as providing potential insight into the development or tracking of CTE. Examples included diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS).

Pioneering studies directed at finding reliable biomarkers for TBI and/or CTE in the circulating blood, blood components, or cerebrospinal fluid, have been reported by Mondello et al. [11], Pasinetti et al. [12], and Oliver et al. [13].

Between Dec. 6, 2012 and March 20, 2014, 1977 patients were studied in cooperating hospital emergency departments in the attempt to validate a blood test—one that combined ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acidic protein (GFAP)—to predict the presence or absence of traumatic intracranial injuries measured by CT head scan acutely after TBI. For detection of intracranial injury, the test had a sensitivity of 0.976 (95% CI 0.931−0.995), and a negative predictive value (NPV) of 0.987−0.999. The CT scan was positive when the blood test was negative in <1% of patients [14].

5. Proportion of sports-related TBI victims who later develop CTE

The proportion of sports-related TBI victims in whom CTE emerges as a sequela is not known. However, among college and professional football players who have experienced repeated concussions and sub-concussive blows to the head, the risk of developing CTE is substantial, increasing with the number of years actively devoted to the sport, and the degree of exposure to physical impacts inherent in the position played (i.e. offensive lineman, wide receiver, and running and defensive backs) [15].

In addition to American football and boxing [16], other contact sports known to be associated with an increased risk of developing CTE include ice hockey, professional wrestling, soccer, rugby, and baseball [17]. CTE is a condition that significantly shortens the life span, some victims committing suicide as brain function becomes progressively and (seemingly) hopelessly impaired [18].

6. Chronic traumatic encephalopathy (CTE) in athletes: a sequela of TBI

Because so many members of the public follow professional football on television, national attention has also been directed to the devastating and often lethal chronic traumatic encephalopathy (CTE) found among a significant proportion of retired professional football players and others with a history of concussions who died prematurely because of worsening brain damage, and suicide.

The average age at death among one sample of 80 CTE victims ((which included 58 who played American football as their primary sport), was 54 ± 23 (mean ± SD) years).

A control group of 18 cognitively intact subjects without known history of repetitive mild TBI had a life-span of 62 ± 17 years [19].

In contemplating the causes of CTE, note should be taken of recent evidence derived from studies in laboratory animals and clinicopathologic observations in teen-age athletes who died unexpectedly. Pathologic examinations of the brains of these individuals have shown that TBI and CTE can be generated by repetitive 'hits to the head' that, considered as individual events, do not result in any obvious disturbances of cerebral function (see section on neuropathologic considerations, below) [20].

7. Neuropathologic considerations

In 2008, medical scientists at Boston University (BU) formed a brain bank to collect relevant brain samples from deceased U.S. football players and other individuals whose brains were likely to have been damaged by various forms of repetitive head trauma. The brain specimens acquired by the 'bank' were contributed mostly by family members and were the basis of a series of neuropathologic studies published by members of the BU group who participated in the TBI-CTE research program.

Using specimens from the brain bank, J. Mez and colleagues from Boston University's (BU's) neuropathology service and department of neurology published the results of an extensive clinicopathological evaluation of chronic traumatic encephalopathy (CTE) in players of American football [21]. The focus of their report was on the findings in the brains of 202 deceased former football players whose median age at death was 67 years. Of this group, 111 were veterans of the National Football League (NFL). Of these 111, CTE was neuropathologically diagnosed in 110 (99%).

Neuropathological severity of CTE in the entire group was distributed as follows: Among 14 former high-school players 3 (21%) had mild pathology. Fifty-six percent of former college and semiprofessional players, and 86% of professional players (including some who played in the Canadian Football League) had severe CTE pathology.

In 2018, the findings of a multicenter study of concussion, microvascular injury and early tauopathy in young athletes were published by a large group of investigators representing various medical schools and hospitals in different parts of the US [20]. Included in the study was post-mortem examination of brains from teen-age athletes who died unexpectedly during the acute-subacute period after mild closed-head impact injuries sustained during football games and/or practice sessions.

In these cases, [the authors] found "astrogliosis, myelinated axonopathy, microvascular injury, perivascular neuroinflammation, and phosphorylated tau protein pathology."

To gain more detailed information about causal mechanisms, the study's investigators developed a mouse model of "lateral closed-head impact injury" that used "momentum transfer" to induce "traumatic head acceleration." They observed that this impact injury was associated with "axonopathy, blood-brain barrier (BBB) disruption, astrocytosis, microgliosis, …. monocyte infiltration, and phosphorylated tauopathy in cerebral cortex ipsilateral and subjacent to impact."

However, to the authors' surprise, "acute neurobehavioral deficits at the time of injury did not correlate with BBB disruption, microgliosis, neuroinflammation, phosphorylated tauopathy, or electrophysiological dysfunction. … Concussion-like deficits were observed after impact injury, but not after blast exposure under experimental conditions." The investigators concluded that "… closed-head impact injuries, independent of concussive signs, can induce traumatic brain injury as well as early pathologies and functional sequelae associated with beginning CTE." A senior member of the investigative group, Lee Goldstein, was quoted as saying, "The same brain pathology that we observed in teenagers after head injury was also present in head-injured mice. We were surprised that the brain pathology was unrelated to signs of concussion, including altered arousal and impaired balance, among others. Our findings provide strong causal evidence linking head impact to TBI and early CTE, independent of concussion. … The results may explain why approximately 20 percent of athletes with CTE never suffered a diagnosed concussion." [22].

8. Chronic traumatic encephalopathy (CTE)

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease usually caused by repetitive head trauma. On occasion, CTE can occur after a single moderate or severe TBI which, for reasons that remain to be clarified, progresses gradually to dementia.

The condition, now known as CTE, was first described medically in 1928 in boxers who were described as being "punch drunk"—a term that was later replaced by "dementia pugilistica" (DP) [23]. Subsequently it became evident that athletes in other sports were developing similar dementias, and DP was renamed "chronic traumatic encephalopathy" (CTE) in the 1960s.

According to Mckee and Daneshvar [10], CTE's gross pathologic features include generalized cerebral atrophy involving the frontal and temporal lobes. Other areas subject to atrophy encompass the thalamus and hypothalamus and the mammillary bodies—the latter being involved in recollective memory. There is also enlargement of the lateral and third ventricles and thinning of the corpus callosum. In these cases, the substantia nigra and locus coeruleus take on a pallid appearance.

In 2016, a consensus meeting was held to develop neuropathologic criteria for the diagnosis of chronic traumatic neuropathy (CTE). In the report on the meeting's conclusions, prepared by McKee et al. [24], CTE was defined as a neurodegeneration characterized by the abnormal accumulation of hyperphosphorylated tau protein within the brain. It was acknowledged that, "at present, CTE can only be definitively diagnosed by post-mortem examination of brain tissue." The pathognomonic lesion of CTE was defined as an accumulation of abnormally hyperphosphorylated tau (p-tau) in neurons and astroglia distributed around small blood vessels at the depth of cortical sulci and in an irregular pattern. Supportive but non-specific p-tau immunoreactive features of CTE were defined as pre-tangles and neurofibrillary tangles (NFTs) affecting superficial layers of cerebral cortex; pre-tangles, NFTs or extracellular tangles in CA2; and pre-tangles and proximal dendritic swellings in CA4 of the hippocampus. According to Perl [25], tau is the primary constituent of the neurofibrillary tangle. Other proteins found in the NFT include ubiquitin, cholinesterases, and amyloid-beta 4 (Aβ4); however, tau is the key constituent.

In a recent review of neurodegenerative diseases associated with tau, Josephs [26] introduces the subject with a discussion of tau biology. He reminds us that tau is a microtubule-associated protein which is responsible for the stabilization and assembly of microtubules. Microtubules are essential to proper axonal transport. In the mature brain, tau is situated within neurons and, for the most part, within axons. As pointed out by Josephs, the tau amino acid sequence can be divided into 4 compartments or domains: (i) the N-terminal domain; (ii) a proline-rich domain; (iii) a microtubule-binding domain; and (iv) the C-terminal domain. "In its normal form, tau is unfolded and phosphorylated, whereas its abnormal form, found in the brains of patients with primary tauopathies, is characterized by hyperphosphorylated and aggregated tau. The binding of tau to microtubules is regulated by the phosphorylation/dephosphorylation equilibrium of tau." The problem with hyperphosphory-lated tau may result from an increase in the proportion of tau sequences that are phosphorylated, outweighing an increase in the number of phosphorylated epitopes per sequence.

Josephs [26] describes CTE as a "primary tauopathy consisting of mixed 3 and 4 repeat tau isoforms." In his words, "There are 6 isoforms of tau that are expressed in the adult brain. They are derived from the alternative splicing of 3 N-terminal exons in the tau gene: exon 2, exon 3, and exon 10. The healthy human brain consists of equal amounts of tau with 3 and 4 repeated microtubule domains. However, some tauopathies have a *predominance* of isoforms with 3 or 4 repeated microtubule-binding domains (3R or 4R tauopathies).

Other tauopathies (CTE being one example) are characterized by a predominance of an approximately equal mix of isoforms with 3 and 4 repeated microtubule-binding domains (3R+4R tauopathies)."

9. Clinical and pathologic transition from traumatic brain injury to CTE: stages of CTE

In the experience of McKee et al. [19], early-stage CTE (Stage I) is frequently asymptomatic. Symptoms that may be present such as headache, attentional impairment, inability to focus, depression, and irritability are not definitive. Patients in Stage II CTE may manifest short-term memory deficits, aggressive behavior, explosivity, mood swings, and problems with planning and organization. Stage II disease is also associated with paranoia and suicidality (27%). As CTE victims progress to Stages III and IV, cognitive impairment and memory loss become evident. By Stage IV, dementia is virtually inevitable. At this point it may become clinically difficult to distinguish between the presence of CTE dementia and the clinical pictures associated with AD and frontotemporal dementia. The pathology of CTE was described by McKee and associates as "…. characterized by a distinctive pattern of progressive brain atrophy and accumulation of hyperphosphorylated tau neurofibrillary and glial tangles, dystrophic neurites, 43 kDa TAR DNA-binding protein (TPD-43), neuronal and glial aggregates, microvasculopathy, myelinated axonopathy, neuroinflammation, and white matter degeneration."

Clinical features include behavioral changes and insidious, slow progression—over decades in some cases—of cognitive impairment. More data, including accurate timetables of key events, are needed that record the incidence and prevalence of PTSD and CTE, genetic risk factors, and the age of occurrence, circumstances, and nature of the head trauma experienced in the past by CTE victims.

10. Possible mechanisms whereby TBI is transformed into CTE

Of the many challenges associated with TBI, none seems more urgent than the need to discover why, in some cases, an acute TBI later evolves into chronic traumatic encephalopathy (CTE). To understand this transition to chronicity it is necessary to identify the steps in the sequence of events that transform an acute to a chronic condition. To come to grips with the disheartening transformation from TBI to CTE, Table 1 was assembled in the hope that the tabular configuration would facilitate an analytic comparison of certain trauma-induced perturbations thought by various investigators to be potentially responsible for the TBI → CTE process.

Given that CTE is a tauopathy with a neuropathology that has been formally defined as displaying "a distinct perivascular accumulation of hyperphosphorylated tau in neurons and astrocytes within cerebral sulci", it is reasonable to focus initially on proposed mechanisms that give rise to the unforeseen emergence of CTE after one or more closed head traumas. Some of the more persuasive explicative concepts of this subcategory of TBI's, shown in Table 1, are briefly discussed below:

11. Adverse effect of TBI on the brain's energy metabolism

At the present time, the mechanism(s) responsible for transition from the clinical effects of a single concussion or a repetitive series of "mild" TBIs, to the devastating chronic condition known as CTE, is poorly understood [27]. Veech et al. [28] have proposed that "TBI involves

Table 1
Comparison of certain mechanisms thought to be involved in the transition from TBI to CTE.

Title	Initial ('key') response to TBI	→Next in response chain	→Next in response chain	→Next in response chain	Comments
Adverse effect of TBI on the brain's energy metabolism R.L. Veech et al. [28]	→ a) opening of the mitochondrial permeability transition pore (MPTP) → b) insulin resistance↑	→ a) sets into motion the complex series of acute and chronic pathologies associated with TBI → b) reduction in PDH complex activity	→ b) reduced Krebs cycle energy production	→ b) CNS hypometabolism	Cyclosporine has been found to bind specifically to mitochondrial cyclophilin-D and thereby close the MPTP. Ketone ester administration also can close the pore and should be tested as a possible treatment of TBI-caused opening of the MPTP.
Reduced TBI-induced phosphatase activity is associated with increases in phosphorylated proteins J-S Seo et al. [30]	→ Reduced phosphatase activity	→ Abnormally phosphorylated proteins↑	→ Damage to brain parenchyma	→ Tauopathy spreads with age and CTE worsening → widespread CNS degeneration	"Neuropathology of CTE is defined by the distinct perivascular accumulation of hyperphosphorylated tau in neurons and astrocytes at the depths of cerebral sulci."
TBI-generated neuroinflammation → Tau hyperphosphorylation → brain damage L.E. Collins-Praino & F. Corrigan [31]	→ Axonal injury	→ Triggers dissociation of tau from microtubules	→ Tau becomes abnormally phosphorylated	→ Formation of NFT aggregates→ damage to synaptic function→ dementia	Pathologic studies have found a close association between axonal disruption and tau pathology. Recent research suggests that TBI-induced tau phosphorylation is linked to cellular prion protein (PrP^{C}).
Microglial activation and inflammatory response to TBI C.K. Donat et al. [33]	→ Microglial activation (acute→ chronic)	→ Classic activation phenotype formed with release of pro-inflammatory molecules → further tissue damage	→ Activated microglia initiate and are potentiated by inflammatory responses (reactive microgliosis)	→ Microglial activation can occur at a distance from the site of the original local injury	'Vicious circle' established with TBI → microglial activation→ release of pro-inflammatory cytokines→ tissue damage→ continuing microglial activation.
Cis-P tau is induced in clinical and preclinical TBI and contributes to development of CTE O. Albayram et al. [35]	→ In human samples obtained post TBI cis P-tau (not *trans* P-tau) is induced in cortical axons and CSF	→ These effects show a positive correlation with axonal injury and clinical outcome	→ Within hours after closed head injury in mouse models, neurons produce *cis* P-tau prior to tau oligomerization and aggregation which causes and spreads axonal pathology by a process called *cistauosis*	→ In mouse models of severe repetitive TBI, *cis* P-tau elimination with neutralizing antibody attenuates development of neuropathology and brain dysfunction, including CTE-like changes	*Cistauosis* is effectively blocked in vitro and in vivo by *cis* P-tau monoclonal antibody (*cis* mAB), which prevents later development of tau tangles and brain atrophy. *Cis* mAB may prevent CTE and AD later in life in humans

impairment of both cerebral blood flow and metabolism, with decreased cerebral O_2 uptake, increased lactate production and depletion of brain high-energy phosphate stores." Indeed, as reported by T.C. Glenn et al. [29], "... the magnitude of the deficit in cerebral energy metabolism after TBI has been shown to be the best predictor of outcome."

Veech et al. [Ibid] call attention to the observation that cyclosporine A (an early immunosuppressive drug) mitigates TBI's adverse effects in man and in animal models of TBI. They suggest that "because cyclosporine has been found to bind specifically to mitochondrial cyclophilin-D and thereby close the mitochondrial permeability transition pore (mPTP) ... this observation, together with other information about MPTP's role in mitochondrial metabolism strongly suggests that opening of the pore sets into motion the complex series of acute and chronic pathologies associated with TBI." In addition, TBI gives rise to insulin resistance [28,29], which results in reduction in the activity of pyruvate dehydrogenase, a rate-limiting step in the conversion of pyruvate into acetyl CoA. This process is needed for proper operation of the Krebs cycle. The Cycle produces the reducing power required by the electron transport chain for synthesis of ATP. By attenuating the Krebs cycle's efficiency, TBI-induced insulin resistance contributes to CNS hypometabolism.

12. Alterations in protein phosphatase expression associated with tauopathy

Analysis of post-mortem CTE brain tissue shows that reduced phosphatase activity in such samples is directly associated with increases in phosphorylated (P)-tau proteins.

Seo et al. [30] cite evidence that "the neuropathology of CTE is defined by the distinct perivascular accumulation of *hyperphosphorylated* tau in neurons and astrocytes at the depths of cerebral sulci." They also refer to findings showing that "the tauopathy spreads with age and the increasing severity of CTE to involve widespread regions of the brain." They state that the tauopathy observed in CTE involves pathological mechanisms similar to AD and note that the reduced phosphatase activity resulting from TBI is directly associated with increases in aberrantly phosphorylated (p)-tau proteins. These findings suggest that TBI-induced reduction in (PPP3CA/PP2B) phosphatase activity plays a causative role in the neurodegeneration that occurs in CTE.

13. Does TBI-generated neuroinflammation drive the relationship between tau hyperphosphorylation and development of dementia?

Collins-Praino and Corrigan [31] have addressed the relationship between TBI and increased risk for the later development of dementias; notably, Alzheimer's disease (AD) and CTE. Both AD and CTE are distinguished by an accumulation of hyperphosphorylated (p-tau) aggregates thought to contribute to the developing neurodegeneration that gives rise to dementia. It has been suggested that TBI-induced axonal injury triggers dissociation of tau from microtubules, promoting its abnormal phosphorylation and aggregation. L. Holleran et al. [32] have found that axonal disruption and tau pathology are closely associated. The intracellular neurofibrillary tangles (NFTs) that ensue appear to have a damaging effect on synaptic function and other neuronal activities that mediate memory and cognition.

Following TBI there may develop a chronic inflammatory response that increases the pace of neurodegeneration. Also, TBI-associated immune activation, exemplified by increased production of pro-inflammatory cytokines such as IL-1β, may prolong the tau hyperphosphorylation process with its progressively destructive consequences.

14. Microglial activation and inflammatory response in traumatic brain injury

C.K. Donat et al. [33] emphasize the importance of microglial activation in response to CNS damage. "... early microglial activation following TBI may contribute to the restoration of homeostasis in the brain. On the other hand, if they remain chronically activated, the microglial cells display a classically activation phenotype, releasing pro-inflammatory molecules that can produce further tissue damage—a vicious circle. The authors describe investigations involving the *in vivo* imaging of microglia ... showing that microglial activation can occur in regions far remote from sites of local injuries .... A common feature of the pathologies developing as a consequence of TBI is that they initiate and are potentiated by an inflammatory response."

Kumar and associates [34] investigated the role of microparticles (MPs), members of the extracellular vesicle family. MPs appear to enable the exchange of pro-inflammatory molecules between brain immune cells and thereby function as key pathways of inflammation propagation following brain trauma.

The authors subjected adult male C57BL/6 mice to controlled experimental TBI for 24 h, after which 'trauma-enriched' MPs were isolated from the blood at the same time neuroinflammation status was assessed in the animals' cerebral cortex. Based on studies involving stereotaxically-injected MPs into the cortex of uninjured mice, the authors were able to assess MP-related seeding of neuroinflammation in vivo. They observed that, as the neuroinflammatory response is in the process of developing in the post-TBI brain, microglial-derived MPs are released into the circulation.

Treatment of uninjured 'control' mice with MPs from the TBI animals is able to activate naïve microglia (in this context, 'naïve' means 'derived from an uninjured animal') in vitro. Lipopolysaccharide (LPS) stimulation was found to increase MP release from microglia in vitro and to enhance their content of pro-inflammatory mediators such as interleukin-1β and microRNA-155. Thus, the authors found that enriched MPs from activated microglia in vitro or CD11b-isolated microglia/macrophages from the TBI brain ex vivo were sufficient to produce neuroinflammation after they were injected in the cortex of naïve control animals.

15. *Cis* Phosphorylated-tau (*Cis* P-tau) is induced in clinical and preclinical TBI and contributes to development of CTE

Given that CTE is a tauopathy and that CTE's neuropathology has been formally defined as displaying "a distinct perivascular accumulation of hyperphosphorylated tau in neurons and astrocytes within cerebral sulci", it is reasonable to focus initially on proposed mechanisms that give phosphorylated tau (p-tau) a prominent role in CTE's etiology. In Table 1, two different processes involving increased production of abnormally phosphorylated proteins are described in victims of TBI: (i) reduced phosphatase activity causing an increased production of abnormally phosphorylated proteins; and (ii) axonal injury triggering dissociation of tau from microtubules, causing the tau to become abnormally phosphorylated, with the disposition of the resulting neurofibrillary tangles (NFTs) to aggregate, further damage brain parenchyma, and promote widespread CNS degeneration.

Two additional potential mechanisms are described in the table, in which chronic neuroinflammation appears to be an important contributor to the CNS damage that occurs in CTE: (i) One that is especially persuasive is TBI-induced neuronal production in mouse models of CTE of the toxic compound *cis* P-tau, an abnormal and destructive isomer of the normal and benign *trans* P-tau. Albayram et al. [35] found *cis* P-tau to produce a CTE-like syndrome via a process they termed *cistauosis*. Cistauosis is blocked by *cis* P-tau monoclonal antibody, which prevents later development of tau tangles, brain atrophy and virtual CTE in laboratory animals. (ii) Another possible mechanism is TBI-caused microglial activation, with the associated formation and release from microglia of pro-inflammatory molecules that cause further tissue damage [CK Donat et al., ibid]. Because activated microglia initiate and are potentiated by inflammatory responses, a 'vicious circle' may become established in which the tissue damage caused by inflammatory cytokines, in its turn, tends to perpetuate microglial activation and the activation-associated

pro-inflammatory cytokine secretion. TBI-generated neuroinflammation also activates formation of microglia-derived microparticles (MPs). The MPs carry pro-inflammatory molecules which are released into the parenchyma and the local circulation. They are believed to be involved in the propagation of neuroinflammation in the post-TBI brain.

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Declaration of Competing Interest

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