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Review article

Chronic Traumatic Encephalopathy: The cellular sequela to repetitive brain injury

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ABSTRACT

This review aims to integrate current literature on the pathogenic mechanisms of Chronic Traumatic Encephalopathy (CTE) to create a multifactorial understanding of the disease. CTE is a progressive neurodegenerative disease, classed as a tauopathy, although it appears the pathogenic mechanisms are more complex than this. It affects those with a history of repetitive mild traumatic brain injury. Currently, there are no treatments for CTE and the disease can only be affirmatively diagnosed in post mortem. Understanding the pathogenesis of the disease will provide an avenue to explore possible treatment and diagnostic modalities. The pathological hallmarks of CTE have been well characterised and have been linked to the pathophysiologic mechanisms in this review. Human studies are limited due to ethical implications of exposing subjects to head trauma. Phosphorylation of tau, microglial activation, TAR DNA-binding protein 43 and diffuse axonal injury have all been implicated in the pathogenesis of CTE. The neuronal loss and axonal dysfunction mediated by these pathognomonic mechanisms lead to the broad psycho-cognitive symptoms seen in CTE.

1. Introduction

Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disease, pathologically marked by tauopathy of the brain. The disease was first described by Martland (1928), who introduced the term "punch drunk" to medical literature to describe a collection of symptoms, including Parkinsonism, mental confusion and psychiatric illness among retired boxers [1]. Epidemiological evidence has established repetitive head trauma as the aetiology of the disease, with the disease most prominent in boxers and American football players [2,3]. Based on a 2013 case series of 68 patients, the largest to date, McKee et.al. established a pathological grading system of I–IV, with this correlating with the severity of symptoms. To summarise macroscopically, milder cases are marked by cavum septum pellucidum and mild enlargement of the frontal and temporal horns of the lateral ventricles, accompanied by microscopic neurofibrillary tangles located perivascular and at the depths of cerebral sulci [2]. These two microscopic findings are what distinguish CTE from other tauopathies [2,4]. Neurofibrillary tangles then spread from the depth of the sulci and perivascular to the adjacent superficial cortical layers. This is accompanied by marked atrophy of the temporal and frontal lobes, diencephalon and brainstem, with depigmentation of the locus coeruleus and substantia nigra [2,5–7]. Axonal pathology in the early stages is defined by distorted axonal varicosities, progressing to axonal loss in the cortex, subcortical white matter, and deep white matter tracts of the diencephalon in later stages [2]. Tar-DNA-binding protein (TDP-43) pathology is seen throughout all stages, though not in all patients, but is universal by stage IV, with 10% of patients also developing a motor neuron disease indistinguishable from Amyotrophic Lateral Sclerosis [2]. Neuronal and axonal loss leads to the symptomatology, shown in Table 1. Despite having characterised the pathological hallmarks of the disease, the pathophysiological events leading to these hallmarks remain poorly understood. This review aims to integrate current understanding of the multiple mechanisms involved in the pathogenesis of CTE to create a multifactorial model of understanding the disease.

2. Pathogenesis of CTE

Much of the information regarding the pathogenesis of CTE has been derived from animal studies. Whilst the pathological hallmarks of the disease have been well characterized in humans, the pathogenesis has been defined to a lesser extent due to the ethical implications of exposing human subjects to head trauma. It is

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Table 1
Symptomatology of CTE [8].

Cognitive features	Behavioural features	Mood features	Motor features
Memory impairment	Physical violence	Depression	Ataxia
Executive dysfunction	Verbal violence	Hopelessness	Dysarthria
Impaired attention	Explosivity	Suicidality	Parkinsonism
Dysgraphia	Loss of control	Anxiety	Gait
Lack of insight	Short fuse	Fearfulness	Tremor
Preservation	Impulsivity	Irritability	Masked facies
Language difficulties	Paranoid delusions	Apathy	Rigidity
Dementia	Aggression	Loss of interest	Weakness
Alogia	Rage	Labile emotions	Spasticity
Visuospatial difficulties	Inappropriate speech	Fatigue	Clonus
Cognitive impairment	Boastfulness	Flat affect	
Reduced intelligence	Childish behaviour	Insomnia	
	Socially inappropriate	Mania	
	Disinhibited behaviour	Euphoria	
	Psychosis	Mood swings	
	Social isolation	Prolix	

not yet clear the degree to which these studies are applicable on humans, but they do provide a model for the disease. Phosphorylated tau deposition, TAR DNA-binding protein 43 (TDP-43), microglial activation and diffuse axonal injury have been implicated in the pathogenesis of CTE.

2.1. Tau phosphorylation

Phosphorylation of tau has been suggested to play a major role in the pathogenesis of CTE. The notion that tau has been implicated as a pathogenic mechanism has arisen in rat studies, in which injection of oligomeric tau into the brains on healthy rats produced measureable behavioural symptoms, likened to that of CTE in humans (Table 1) [9]. It has been hypothesized that the phosphorylated tau found in CTE cause neuronal death in a similar mechanism to those found in Alzheimer's disease (AD), as the tau isoforms found in CTE match those of AD [10,11]. Normal tau is involved in stabilizing microtubule fibrils by binding to tubulin, facilitating neurite outgrowth [12].

Immuunohistochemical studies have ascertained that phosphorylation of tau occurs following mild traumatic brain injury [13]. The phosphorylation of tau arises from an imbalance between kinases and phosphatase activity. The signalling pathways that activate kinases following head trauma are yet to be ascertained, but the levels of active extracellular signal regulated kinases 1 and 2, cycline dependant kinase 5, glycogen synthase kinase 3-beta, protein kinase C, c-jun kinase and Akt are all increased following head trauma [14–19]. One if not multiple are likely are involved in the phosphorylation of tau. Hyperphosphorylation causes dissociation of tau from tubulin, rendering microtubules dysfunctional. This exposes further phosphorylation sites leading to a state of hyperophosphorylation [20]. In this state tau is insoluble, so translocates to the neuron soma [21,22]. Accumulation of insoluble tau leads to the formation of tau oligomers [21,22]. Sequestration of oligomers and post translational modifications lead to neurofibrillary tangle formation (NFT), the pathological hallmark of CTE [22,23].

Whether tau oligomers or NFTs are the source of neurotoxicity is an area of intense research. However, what is clearer is the notion that hyperphosphorylated tau causes neuronal death, as indicated by genetic studies implicating tau as the sole cause of neuronal death in Fronto-temporal dementia and parkinsonism linked to chromosome 17, another tauopathy [24]. Based on the literature, the argument presented in this review is that tau oligomers are the more toxic of the two, yet NFTs represent an adaptive response to prevent the development of toxic oligomers, but ultimately lead to neurodegeneration [22,25]. The aforementioned has been difficult to study given tau does not readily aggregate into filaments within an ideal time frame for culture studies or within an animal's short lifespan, though it is thought that the hyperphosphorylation of tau leads to a toxic gain of function with a loss of function, with this accounting for neuronal death. However, it is not certain whether this toxicity is exerted by NFTs or oligomers [22,25]. Case control studies from the 1970s and 1980s, correlated the severity of cognitive impairments in humans to the extent of NFT formation, which intuitively indicated its role in neurodegeneration [26–28]. This older paradigm has been challenged in a review by Crespo-Biel (2012), which show memory deficits preceding NFT pathology, indicating a toxic intermediate in the tau phosphorylation cascade is likely to blame for neuronal damage [29].

Studies into the mechanism by which these tau oligomers cause cells death are limited. One study has implicated tau oligomers in interfering with anterograde axonal transport system protein kinesin, leading to an inability to maintain axons and axonal degeneration [30]. This would explain the milder cognitive impairments seen early in the disease, without the presence of pathological hallmarks. Neuronal loss can be explained by the resultant deafferentation leading to a lack of survival signalling, known as anterograde transneural degeneration [31]. Some studies have addressed the role of caspase activation in tauopathy, however the findings of these studies are inconsistent. Active caspases have been identified using fluorescent antibody tagging in neurons containing NFT's and shown to cause apoptosis in cultured hippocampal neurons [32–34]. However, other studies have argued against this theory, suggesting apoptosis was not an important contributing factor to neuronal death, rather caspases cleaving tau increases its fibrillogenicity [35,36]. Given either it appears the activation of caspases is pathogenic.

Additionally, other studies have associated tau with increased cell cycle proteins, proposed to cause differentiated neurons to re-enter the cell cycle leading to their death [37,38]. It has also been suggested that tau may lead to membrane permeability changes, leading to mitochondrial dysfunction, raised intracellular Ca2+ and reactive oxygen species production. This idea is based on the propensity for oligomers of beta amyloid and alpha-synuclin to form pores in lipid membranes [39]. Oligomerization is a characteristic shared by tau. There is evidence for mitochondrial dysfunction in tauopathy mice models, indicating this theory may be plausible, but requires more evidence for affirmation [40]. Strongly supported by the evidence presented is the idea that tau effects neurons on two levels – synaptic and axonal dysfunction and neuronal loss, and this is what leads to physco-cognitive symptoms seen in CTE patients [41].

Neurons can survive for decades with NFTs [42]. By forming these large fibrillary aggregates the cell is protected from the immediate cytotoxic effects of oligomers, allowing to the compromised neuron to maintain itself [43]. However, as these NFTs grow, they have been reported to decrease the number of cell organelles, inhibit proteasome activity, and also impair anterograde axonal transport, all of which may negative alter cell homeostasis leading to cell death [44–46].

The progressive neurodegeneration in CTE can be explained by the transmission of tau oligomers between neurons. In rat models where tau is overexpressed, it has been observed to be secreted