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Proteinopathies and Neurotrauma: Update on Degenerative Cascades

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Abstract

Neurotrauma, especially repetitive neurotrauma, is associated with the development of progressive neurodegeneration leading to chronic traumatic encephalopathy (CTE). Exposure to neurotrauma regularly occurs during sports and military service, often not requiring medical care. However, exposure to severe and/or repeated sub-clinical neurotrauma has been shown cause physical and psychological disability, leading to reduce life expectancy. Misfolding of proteins, or proteinopathy, is a pathological hallmark of CTE, in which chronic injury leads to local and diffuse protein aggregates. These aggregates are an overlapping feature of many neurodegenerative diseases such as CTE, Alzheimer's Disease, Parkinson's disease. Neurotrauma is also a significant risk factor for the development of these diseases, however the mechanism's underlying this association are not well understood. While phosphorylated tau aggregates are the primary feature of CTE, amyloid-beta, Transactive response DNA-binding protein 43 (TDP-43), and alpha-synuclein (αSyn) are also well documented. Aberrant misfolding of these proteins has been shown to disrupt brain homeostasis leading to neurodegeneration in a disease dependent manor. In CTE, the interaction between proteinopathies and their associated neurodegeneration is a current area of study. Here we provide an update on current literature surrounding the prevalence, characteristics, and pathogenesis of proteinopathies in CTE.

ABBREVIATIONS

Aβ: Amyloid-beta; APOE4: Apolipoprotein E 4; CTE: Chronic Traumatic Encephalopathy; MSA: Multiple Systems atrophy; NFT: Neurofibrillary tangles; NVU: Neurovascular Unit; DLB: Dementia with Lewy bodies; PD: Parkinson's Disease; PDD: Parkinson's Disease with Dementia; SNpc: Substantia Nigra pars compacta; ASyn: Alpha-synuclein; TBI: Traumatic Brain Injury; TDP-43: Transactive response DNA-binding protein 43

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of mortality and disability throughout the world [1,2]. Over the past thirty years, the prevalence of TBI have increased by over 8% and in 2016 alone, there were over 27 million new cases of TBI [1]. The heterogeneous nature of TBI and its downstream pathology are significant barriers to its management. As reviewed in Pierre et al 2021, management of TBI is multifaceted, encompassing use of medications for "off-label" treatment of symptomology and non-pharmaceutical modalities such as cognitive behavioral therapy, motor therapy, diet, and aerobic exercise [3].While increased adherence to newer TBI guidelines has been shown to significantly reduce mortality in trauma care, there is little data showing improvements in long term outcomes to severe TBI over recent decades [4-6]. Studies suggest that life expectancy beyond the acute insult, are predicted by patient demographics and health behaviors rather than severity of TBI alone [7,8]. Life expectancy following acute recovery from TBI is significantly shorter than that of the general population, and growing evidence suggest that a progressive neurodegenerative process underlines this difference [9-12]. Additionally, patients afflicted with TBI often suffer from cognitive and behavioral dysfunction, seizures, and subsequent socioeconomic burdens as a result (cite review). The chronic changes following neurotrauma have been especially highlighted by studies of repetitive brain trauma leading to chronic traumatic encephalopathy (CTE) [13]. CTE is a condition that results from regular successive mild traumatic brain injury like those seen in the context of contact sports and blast exposure during military combat [14,15]. A majority of brain injuries sustained in these contexts are sub-acute and clinical presentation after long term exposure may include behavioral and mood disturbances in younger patients and cognitive impairment in older patients [16,17]. TBI has long been thought of as a confirmed risk factor for the development of all-cause dementia, however limitations of previous studies make it difficult to draw a causal link between the two broadly defined conditions [18,19]. Still, the reported abnormalities of proteins such as tau, Transactive response DNA-binding protein 43 (TDP-43), amyloid-beta (Aβ), and αSyn suggest mechanistic overlap between post-neurotrauma pathology and neurodegeneration seen in other neurodegenerative proteinopathies which are themselves defined by dysfunction of these proteins [10,20-22]. Acute traumatic brain injury and mild traumatic brain injury disrupts homeostatic mechanisms locally which is thought to

lead to diffuse changes in brain function [11]. Understanding the significance and mechanisms of overlapping pathophysiology may provide insight into therapeutic targets and disease susceptibility. Herein, we explore the current literature on neurotrauma as it relates to tau, TDP, Aβ, and αSyn proteinopathies, respectively.

Tau

Tau is an axonal protein encoded by the MAPT gene with the primary physiologic function of promoting microtubule assembly; misfolding of tau and subsequent inclusion formation is implicated in a number of neurodegenerative disorders termed tauopathies [23]. Accumulation of hyperphosphorylated tau (p-tau), most commonly detected using the AT-8 epitope, is the hallmark neuropathologic feature in CTE [24]. The standard pathological grading schema for CTE developed by Mckee has 4 stages, ranging from stage 1 defined by limited p-tau within sulcal depths mostly in temporal regions to stage 4 with widespread severe p-tau pathology throughout the cortex [25]. Although p-tau forms inclusions in CTE, there are marked differences from tau in other tauopathies in terms of spatial distribution, inclusion morphology, and even in the biochemical structure of the misfolded tau aggregates [24,26], these differences likely reflect the varied mechanisms of tau misfolding and accumulation across the spectrum of tauopathies and may govern the unique natural history of each disease.

The most common tauopathies, neurodegenerative disorders characterized by inclusions of misfolded p-tau, include Alzheimer's disease (AD), progressive supranuclear palsy (PSP), Pick's disease, corticobasal degeneration (CBD), and CTE [27]. The clinical characteristics have been previously reviewed [27], however neuropathological differences in the unique features of tau amongst these diseases can be challenging due to comorbidity of multiple neurodegenerative conditions such as CTE with AD [24]. The first broad distinction amongst tauopathies is apparent when examining the ratio of the 3R vs 4R isoform of tau present in respective inclusions, where PSP and CBD are 4R predominant, Pick's disease is 3R predominant, and AD and CTE have mixed 3R/4R pathology [28,29]. Secondly, these diseases are often distinguished based on cellular elements involved with unique morphology, with AD characterized mainly by intra-neuronal neurofibrillary tangles (NFTs), PSP and CBD more-so with glial pathology such as "tufted" astrocytic p-tau, astrocytic plaques, and oligodendroglial coiled bodies, and Pick's disease with neuronal rounded pick bodies of p-tau [29]. CTE is cellularly and morphologically similar to AD as CTE has NFTs, however some studies suggesting that astrocytic tangles seen in higher McKee stages are a distinguishing feature of CTE [30,24]. This distinguishment is obscured by the presence of age-related tau astrogliopathy in older adults, calling into question the mechanism of association between astrocytic tauopathy and CTE independent of age [31]. Thirdly, the spatial distribution of p-tau throughout the neuroaxis is a distinguishing feature amongst tauopathies [27] that is particularly important in distinguishing AD and CTE given the histologic similarities. In CTE, NFTs are primarily located in perivascular foci at sulcal depths, most prominent in cortical layers II and III [24]. Of note, p-tau pathology in CTE has been identified to have a predilection for the dorsolateral frontal cortex (DLF), superior temporal lobe, amygdala, entorhinal cortex and locus coeruleus (LC) with earliest pathology being restricted to the DLF and LC [32]. In contrast, NFTs in AD are postulated to first originate in medial temporal regions with stereotyped progression at higher stages to broadly involve the neocortex without restriction to sulcal depths and NFTs more widespread throughout cytoarchitectural layers [33]. Overall, CTE has unique histological features compared with other tauopathies, with the most similar being AD. From a mechanistic and biochemical perspective, although p-tau accumulates in all of these diseases, there are profound differences that may be important in therapeutic development. PSP, CBD, and Pick's disease are thought to accumulate p-tau through direct genetic predisposition in MAPT or other genes without other inciting pathology, as MAPT mutations are often identified in these diseases and there is no preceding accumulation of Aβ such as in AD [23]. In contrast, in AD the NFT pathology is always preceded by Aβ accumulation, with no identified MAPT mutations being causative in AD [23,34]. Additionally, in the aforementioned tauopathies it is thought that misfolded p-tau may have prion-like properties inducing physiologic tau to itself misfold and form inclusions throughout the neuroaxis in stereotyped patterns driven by neuronal connectivity and other cellular predisposing elements such as lysosomal failure in handling NFTs [34]. In CTE, the mechanisms of p-tau accumulation are less well understood, particularly with regards to any prion-like progression of pathology vs the NFT burden being directly proportion to physical trauma throughout the lifespan. Although AD is histologically similar and Aβ is present in many older individuals with CTE, only a small portion of young CTE patients display Aβ plaques demonstrating the differing temporal development of Aβ pathology between these diseases [24]. Indeed, in CTE the initial misfolding of tau is linked to axonal damage as a consequence of shearing and stretching forces in trauma, which has been demonstrated in pre-clinical models to induce tau disassociation from microtubules and subsequent phosphorylation and misfolding [Figure 2] [24]. Continued progression of CTE pathology and symptoms through prion-like spread requires further study, particularly with respect to the biochemical structure and post-translational modifications of tau in CTE compared with other tauopathies, as differences in these elements are thought to underlie why tau has a disease dependent "strain"-like behavior in prion-like disease models [26]. Indeed, electron microscopy of tau aggregates from CTE have suggested fundamental differences in the structure of misfolded tau in this disease compared with other tauopathies [26]. As with other tauopathies, development of therapies targeted at preventing further tau accumulation and toxic sequelae may be key at halting disease progression, and this will only be accomplished with more complete understanding of the unique biochemical signature of misfolded p-tau in each respective disease.

Aβ

Like Tau, Aβ deposition has long been thought to be associated with traumatic brain injury. However, as previously mentioned, the temporal distribution of Aβ plaque formation in relation to tau, differs from that seen in AD, with plaques being associated with more advanced disease [35]. Indeed, clinical and pathological progression were strongly associated with Aβ

burden which was present in more than half of CTE patients [35]. While CTE stage is associated with age, it remains strongly associated with neuritic plaque burden when age is controlled for [35],[25]. In a cohort of 85 subjects with a history of mild TBI, only one third of donor brains with Aβ burden had pure CTE, with others having concomitant AD or Lewy body pathology [25]. Aβ burden, defined as the percentage of cortical coverage by Aβ1–40 or Aβ1–42 plaques, was seen to be higher in AD subjects than those with both AD and CTE [25]. While plaque distribution in AD was evenly distributed between sulsi and gyri, the spatial distribution of Aβ plaques in CTE-AD is shown predominantly in the sulci [25,35]. Aβ1–42 plaque burden was similar among AD and CTE-AD subject, with a significant reduction in Aβ1–40 plaques over all [25]. Aside from cortical pathology, cerebral vascular Aβ deposition resulting in neurodegeneration is also seen in AD and CTE [36,37]. A study on the association of CTE and this pathology, termed Cerebral Aβ Angiopathy, revealed that it is more severe in the frontal leptomenigeal vesicles of subjects with CTE and was an independent predictor of dementia development [37].

Acutely, early reports have demonstrated elevated expression of Aβ precursor protein (APP) localized within swollen axons, dystrophic neurites and neuronal perikarya following ischemic insults and stab injury [38,39]. Contrary to these focal alterations in APP levels seen in regions surrounding the injury, Murakami et al.[40], has shown increased expression of APP in both the cerebral cortex and hippocampus, away from the site of injury. APP was preferentially localized within hippocampal CA3 neurons one day post-injury and was followed by pyknotic nuclei evident 3 days post-injury and decreased CA3 cell density 7 days post-injury. This pattern of APP overexpression was the first to suggest AD-like neurodegeneration following neurotrauma.

Recent studies have tried to elucidate the mechanism underlying APP upregulation-mediated neurodegeneration. Some groups have focused on the APP intracellular domain (AICD), a known derivative of APP with pro-apoptotic and transcription factor activity [41-43]. Liu et al., observed elevations in APP and AICD following optic nerve axotomy (ONA) in a mouse model [44]. This was associated with JNK3 upregulation and retinal ganglion cell (RGC) death [44]. APP knockout and gamma-secretase inhibitors that reduce AICD levels were both associated with JNK3 downregulation and reduced ONA-induced RGC death [44]. This not only supports the role of Aβ in neurotrauma-associated neurodegeneration, but also provides a therapeutic target.

Mechanistically, Aβ is thought to dysregulate neuronal and cerebrovascular homeostasis in multiple ways that ultimately lead to neurodegeneration. Disruption of calcium (Ca2+) – a key intracellular signaling molecule – constitutes one proposed mechanism by which Aβ is neurotoxic. Recent thinking has shifted from Aβ plaques to Aβ oligomers as the disease-causing agent in AD [45]. These Aβ oligomers have been shown to induce Ca2+ entry via NMDA receptors and induce cell cycle reentry [46], which ultimately leads to neuronal death [47]. The mitochondria is a key regulator of calcium and, when overloaded with Ca2+, is thought to become indiscriminately permeable, resulting in mitochondrial swelling followed by eventual cell death [48,49]. Urolithin A has emerged recently as a promising therapy in targeting this mechanism, reducing Aβ-mediated Ca2+ entry as well as ROS species in mitochondria [50]. Further evidence has pointed towards a synergistic mechanism by which Ca2+ dysregulation is both induced by Aβ and contributes to it [51,52], producing a vicious, unregulated cycle. Ultimately, this calcium dysregulation puts neurons at risk for excitotoxicity and oxidative damage, further compounding the chance of damage occurring [53]. While largely studied in the context of AD, similar neuroinflammatory cascade and Aβ accumulation has been studied in the acute and chronic neuropathology following neurotrauma. Rodent models supporting this association have shown elevation of inflammatory cytokines IL-1a and IL-b along with Aβ precursor protein within hours of TBI [54,55]. Proinflammatory calcium binding protein S100A9 is also implicated in this Aβ-neuroinflammation cascade leading to neuronal cell death [56]. In this mechanism, brain injury induces rapid production of S100A9, which induces Aβ plaque formation and subsequent BAX activation and apoptosis [56]. An elevated oxidative state is also one of the key mediators in the neuroinflammatory pathway which occurs after trauma. For one, metal ions are thought to coordinate with Aβ and lead to reactive oxygen species (ROS) production [57]. These ROS in turn increase blood-brain barrier (BBB) permeability by decreasing the selectivity of the barrier through tight junctions [58] – specialized protein complexes which regulate the entrance of hydrophilic and large molecules into the brain – and permitting the entrance of peripheral immune cells [59], compounding the neuroinflammatory effect. A prolonged neuroinflammatory state can, in turn, produce activated microglia which induce neuronal death [60,61]. The clinical associations, post-mortem data, and mechanistic plausibility described here, suggest that Aβ contributes to neurodegeneration in many cases of CTE both acutely and chronically.

TDP-43

TDP-43 is a transcriptional repressor that regulates the expression of hundreds of genes through RNA binding, splicing, and alternative polyadenylation [62,63]. Wood et al., revealed the maintenance function of TDP-43 in promoting genomic integrity and cell viability. It was found that in human cells without TDP-43, there is increased histone phosphorylation and double-stranded DNA breaks [64]. However, the pathology of neurodegenerative conditions such as CTE, AD, amyotrophic lateral sclerosis, and frontotemporal lobar degeneration have been increasingly characterized by a distinctive accumulation of TDP-43 [63,65,66]. In these disorders translocate of TDP-43 from the nucleus to the cytoplasm is thought to cause a toxic increase or decrease in TDP-43 function, contributing to gradual neurodegeneration [63]. Like tau pathology seen across tauopathies, TDP-43 proteinopathy has is heterogenous in its cell type and spatial distribution that's associated with distinctive clinical presentation [67]. More recently, the aggregation of TDP-43 is being studied as a potential indicator of neurodegeneration following trauma. The relationship between TDP-43 and other deposited proteins like hyperphosphorylated tau (p-tau), while not fully understood, plays a role in the staging of CTE with p-tau. The greater the staging of CTE, the more severe and abundant TDP-43 becomes within the neural tissue. In grave cases of CTE, dense accumulation of TDP-43 is noted in a similar distribution

pattern as that seen in frontotemporal lobar degeneration with TDP-43[24,68]. Regarding neurodegeneration in relation to CTE, ALS, AD, and PD have been linked to repetitive CNS trauma. McKee et al., evaluated 12 athletes with pathologically consistent CTE and extensive TDP-43 proteinopathy was found in greater than 80% of subjects, linking the widespread damage to symptoms of neurodegeneration and proteinopathy [69].

The same cytoplasmic translocation of TDP-43 protein seen in other neurodegeneration disorders was noted by Kahriman et al., in mice following a closed head injury [70]. In an earlier study also based on a mouse model, Tan XL et al. found increased levels of multiple TDP-43 protein fragments in both the nucleus and cytoplasm of neurons. The mice with the most intense TDP-43 abnormalities simultaneously experienced the greatest behavioral deficits and overall cell death [63]. An earlier study from Huang et al., proposes that TDP-43 accumulation in astrocytes is associated with neuronal loss and astrogliosis, an abnormal increase in astrocytes. However, the motor dysfunction associated with these signs of neuroinflammation was reduced when TDP-43 proteolysis was prevented [71]. Another TBI rodent model showed that accelerated TDP-43 proteolysis led to symptoms of frontotemporal dementia [72]. Together, these findings indicate that TDP-43 fragments are cytotoxic in neuronal or glial cells following neurotrauma [63,71,72].

The previously outlined clinical and animal studies indicate that TDP-43 proteinopathy plays a detrimental role in neurodegeneration following repetitive neurotrauma. Its relationship with hyperphosphorylated tau protein that is also present in neurodegenerative diseases is ambiguous and calls for further investigation [66]. Additionally, there is need for further investigation into the pathophysiological pathways and genetic predispositions that serve as the basis for TDP-43 proteinopathy and neurodegeneration following repetitive neurotrauma. Given these abnormalities and findings following injury, TDP-43 may be an important target for future neurotrauma therapeutics.

Synuclein

Sports and Synucleinopathies: Synucleinopathies are a spectrum of neurodegenerative diseases which share the common feature of progressive misfolding and accumulation of αSyn, an intrinsically disordered protein which associates with presynaptic vesicles in neurons [73]. The main synucleinopathies are Parkinson's disease (PD), PD with Dementia (PDD), Dementia with Lewy bodies (DLB) and Multiple Systems atrophy (MSA) [74], and while they share a common pathological protein, they exhibit great heterogeneity in presenting clinical features.

The relationship between impact-induced neurotrauma and synucleinopathies is uncertain. Due to the relationship between contact sports, like American football, boxing or hockey, and parkinsonism[75], αSyn has been a keen focus of neurotrauma research as αSyn is frequently reported to be upregulated in the CSF after traumatic brain injury (TBI) [76-78], in TBI with loss of consciousness (LOC) before the age of [79], and it is positively associated with cortical Lewy body pathology [80]. Studies assessing other synucleinopathies such as MSA, PDD and DLB found no association between TBI and incidence of disease [81]. This suggests that the relationship between molecular accumulation and spread of αSyn and neurotrauma may be incidental, and possibly due to bias in data collection, for example, meta-analyses that rely on assessment of TBI in PD patients.

Neurotrauma induced synucleinopathies: PD is clinically characterized by movement deficits such as resting tremor, rigidity, bradykinesia and postural instability, and eventual dementia [82,83], resulting from the progressive loss of A9 dopaminergic neurons in the Substantia Nigra pars compacta (SNpc)[84]. Many clinical studies have demonstrated the increased risk of PD-like symptoms after concussion [22,86,87], with TBI being a major non-genetic risk factor for PD [80,88].

PD and neurotrauma induced pathophysiology share many common features including progressive degeneration of neurons, permeabilized blood brain barrier and microgliosis, including the infiltration of peripheral macrophages [60,78,89-91], however, these pathologies are common across other neurodegenerative disease and not unique to PD, and therefore is not strong evidence for a causal link. However, it may be suggestive of exacerbation of underlying concomitant disease, whether that be Aβ plaque pathology, tauopathy or αSyn inclusions, especially as these pathologies and associated clinical symptoms are commonly seen in association with neurotrauma.

The molecular consequences of neurotrauma may provide clues to the molecular mechanisms leading to parkinsonism. Mechanical force from repeated TBI or one serious impact to the head may lead to a cascade of harmful inflammatory responses [Figure 1]. For example, following a single moderate to severe TBI, several neuronal assaults take place including hypoxic-ischemic injury, axonal injury and initiation of inflammatory cascades, lipid peroxidation and oxidative stress [92,93]. Unsurprisingly, these events are associated with neuronal loss, particularly in the hippocampus and SN, and while features histologically reminiscent of PD, such as pale regions in the SN, have been observed in patients with CTE, it is notable that classical Lewy bodies in these cases are rare [24].

However, studies have used in vivo models to connect TBI induced lipid peroxidation with αSyn oligomerization, dopaminergic dysregulation, and neuronal death [93,94], and while these provide potential molecular mechanisms, further investigation is needed to demonstrate parallel processes occurring in TBI patients. αSyn in particular has also been shown to activate mitochondrial fragmentation an event that greatly increases αSyn-induced mitochondrial loss, and it is expectedly shown that aggregate αSyn also induces excessive mitophagy via inhibition of complex I which leads to further neuronal death [79,95]. Furthermore, as previously alluded to, mitochondria play a crucial role in cell apoptosis through release of cytochrome c and subsequent activation of protease activating factor-1 (APAF1), caspase-9 and caspase-3 [96]. Though mutated versions of αSyn such as A53T αSyn have been noted to have a direct impact on complex 1 deficiency [97], further studies are needed to understand the mechanisms of αSyn mediated mitochondrial pathology in the context of synucleinopathies [98]. The differential effect of mutant αSyn on disease pathogenesis may explain heterogeneity in data which attempts to link TBI to PD, as the association may depend on underlying susceptibility [75,81]. This is supported by findings that TBI was only on

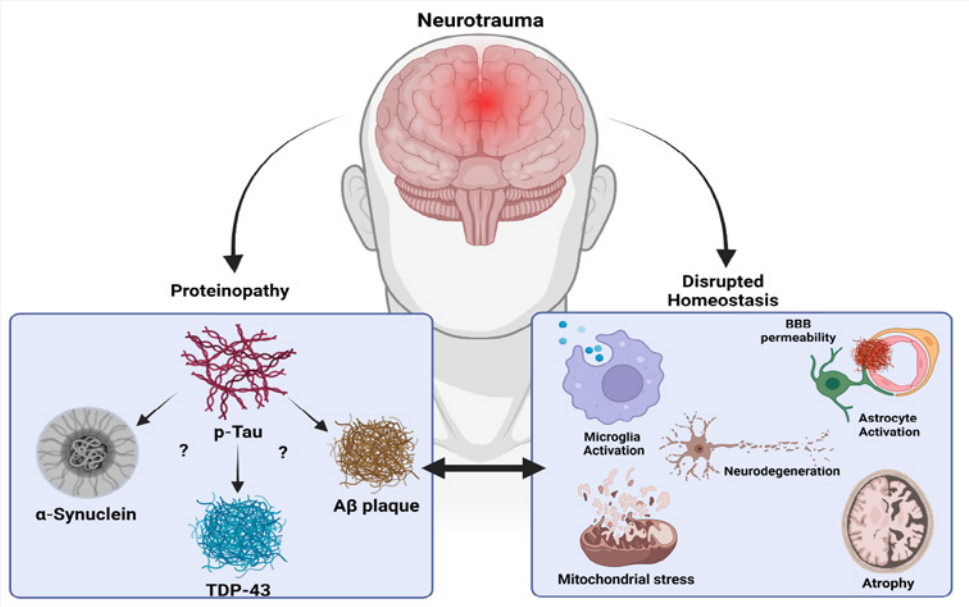

Figure 1 Abstract.

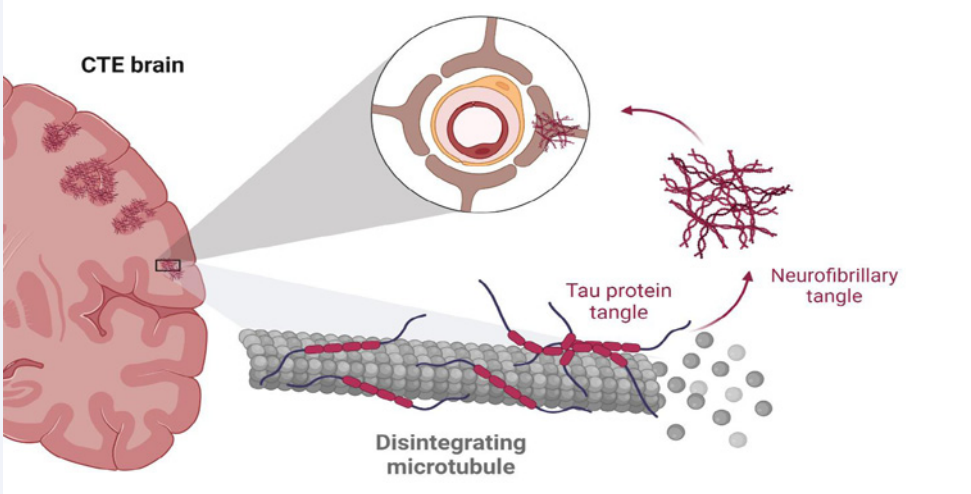

Figure 2 Neurotrauma induced axonal damage induces tau disassociation from microtubules leading to aggregation to perivascular foci at sulcal depths.

associated with PD among individuals with an expansion of Rep1, a polymorphic mixed-dinucleotide repeat in the SNCA promoter region, which results in increased αSyn expression [22].

Importantly, parkinsonism, as a dysfunctional movement symptom, does not require αSyn inclusion pathology and may simply be the result of neuronal loss in motor control regions of the brain, such as the basal ganglia. In fact, the vulnerability of dopaminergic neurons in the basal ganglia have been well documented, specifically the selective loss of A9 and sparing of adjacent A10 neurons in PD [78]. While the biological mechanism is not fully understood, one hypothesis is that A9 neurons are larger, more metabolically demanding and express higher levels of mitochondria, leaving them vulnerable to environmentally induced stressors such as neurotrauma. Therefore, the association of neurotrauma with parkinsonism and PD-like features may likely occur due to loss of vulnerable neurons in the basal ganglia rather than driven by a specific proteinopathy.

CONCLUSION

As outlined here, current research indicates that the clinical presentation and progression of CTE is the result of underlying proteinopathies, with tauopathy as the universal and clinically diagnostic finding. While there is significant overlap between CTE and development of other proteinopathies, CTE has important distinctions in temporal and spatial distribution of pathology. The implicated sequence of pathology following TBI that leads to chronic pathology involves direct neuronal damage, disrupted cerebrovasculature, with chronic glial

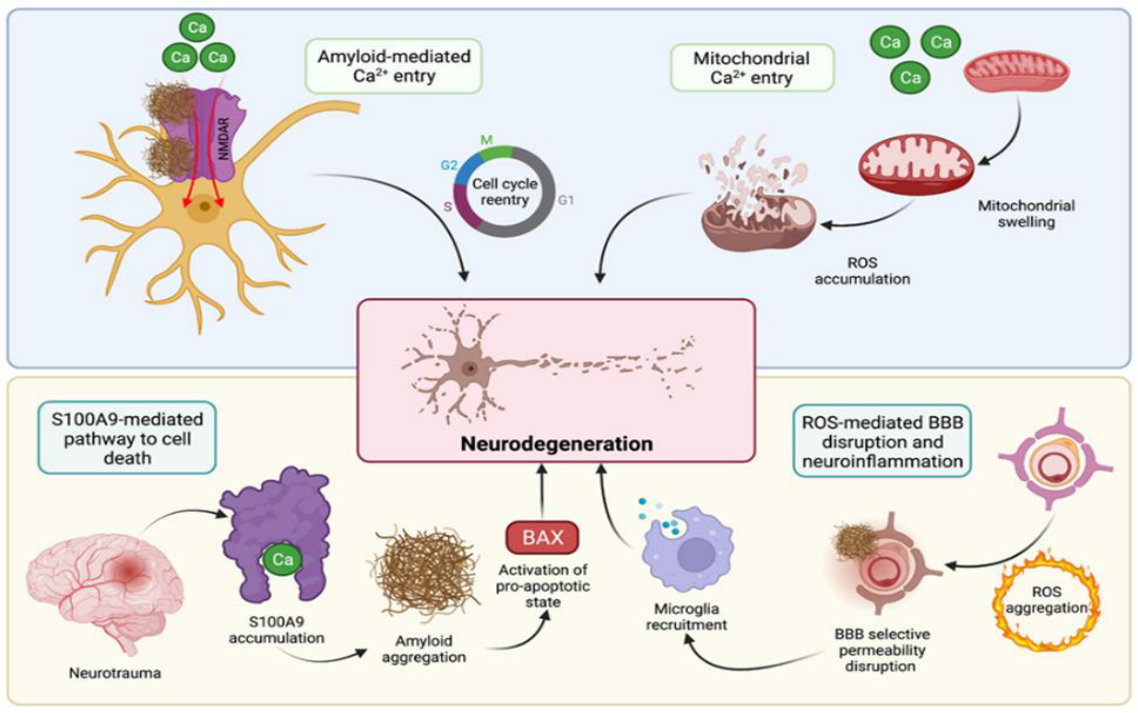

Figure 3 Overview of calcium-mediated and neuroinflammatory pathways leading to neurodegeneration following neurotrauma. Created with BioRender.com.

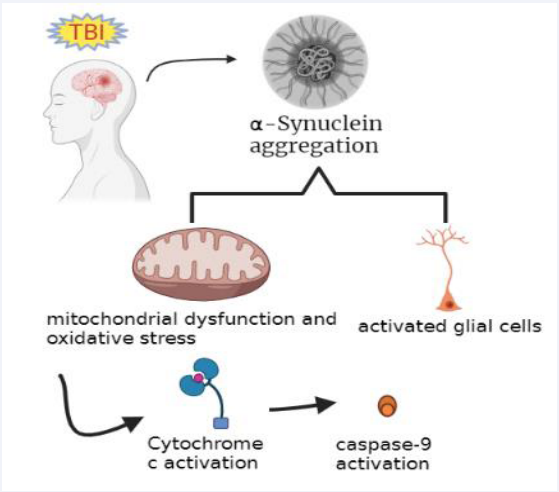

Figure 4 Injury to the head can result in a cascade of deleterious effects. Oligomerized α Syn aggregates cause further molecular alterations which result in the ultimate release of caspase-9 that inhibits complex I.

and peripheral immune mediated inflammation [99]. These disruptions in each component of the neurovascular unit (NVU) leads to perivascular Tau, Aβ, TDP-43 and αSyn aggregation (24). Additionally, each of these disordered proteins has been shown to disrupt components of the NVU in models of acute injury and chronic neurodegenerative diseases [100-104]. Perivascular tau inclusions are the most notable indicator of impaired glymphatic function in CTE. Despite the limited presence of other types of disordered protein inclusions, this does not rule out their role in the pathogenesis of TBI and CTE [102], [25]. In fact, evidence from AD research supports Aβ oligomers, rather than inclusions, as a primary neuropathologic mediator and in CTE a reduction of Aβ42 in the CSF is a clinically significant biomarker of disease severity, potentially indicating reduced glymphatic clearance[105-107]. TDP-43 accumulation is more strongly associated with models of axonal injury, as it is acutely upregulated following axonal injury and intrinsically prone to aggregation [108]. Conversely tau is seen to be elevated in the cerebrospinal fluid in patients presumably due to continued neurodegeneration. Consistent with impaired glymphatic flow as an underlying mechanism precipitating proteinopathy, following mild repeated TBI in mice, perivascular flow has been shown to be altered [109]. Future mechanistic and biochemical studies are necessary to unravel potential molecular interactions among different disordered protein inclusions following TBI and to determine if there is a compounding effect of one proteinopathy interacting with and even amplifying another proteinopathy in a biologically and clinically meaningful manner. Further, the heterogeneity in presentation and progression of CTE-proteinopathy is likely due to variability in exposure, environmental, and genetic susceptibility. There have been several genes thought to influence functional out-comes following TBI and progression of CTE [110]. Apolipoprotein E 4(APOE4) genotype is a notable genetic risk factor for poor long-term outcomes following CTE [111] and Aβ deposition has been significantly associated with APOE4 genotype in CTE [35]. Larger population-based prospective studies need to be implemented to confirm the genetics associated with CTE development and severity. Additionally, studies on the influence of health behaviors on CTE development are warranted. As

previously stated, outcomes one year following severe TBI have been associated with environmental factors which influence health behaviors [18,112]. In fact, disease severity including tauopathy is significantly attenuated via dietary modifications in a mouse model of repetitive mild TBI [113]. Neurotrauma represents an identifiable exposure that induces a distinct pathology leading to CTE, that may also exacerbate age-related or concomitant non-CTE neurodegenerative proteinopathies. Future treatments may involve preventative measures for those with identifiable risk factors and targeted therapies for those with significant exposure. While these proteinopathies differ in distribution and biochemical characteristics among diseases, therapies that target the pathogenic players covered here may have broad applications. Given that individuals can be identified from the military and sports populations that have a high degree of neurotrauma exposure, there is an opportunity for population based prospective studies which may clarify the complex interaction between genetics, environment, and neurotrauma as they relate to proteinopathies.

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