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Many roads to Parkinson's disease neurodegeneration: Head trauma- A road more traveled than we know?

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The precise etiology for idiopathic Parkinson's disease (PD) is currently unknown; however several lines of converging evidence exist to suggest a central role of pathologic aggregation of alpha-synuclein as a driving force underlying mechanisms of PD neurodegeneration. First, pathogenic missense mutations¹ or gene multiplications² of the alpha-synuclein gene (*SCNA*) result in an increased propensity for alpha-synuclein to fibrillize *in vitro*³ and clinically manifest as early-onset PD with typical Lewy pathology (LP) composed chiefly of insoluble amyloid fibrils formed by pathologically altered alpha-synuclein proteins at autopsy.⁴ Comparisons of large numbers of PD cases at autopsy demonstrate a sequential non-random progression of LP from the lower brainstem into limbic and neocortical regions in the majority of PD patients.⁵ This progression of LP into neocortical areas appears to be the strongest neuropathological correlate of dementia in PD,^{6–8} further reinforcing the importance of alpha-synuclein misfolding and aggregation into LP in the neurodegenerative process. Finally, recent work in cell^{9, 10} and animal^{11, 12} models of PD demonstrated that pathological alpha-synuclein proteins may spread from neuron-to-neuron to induce LP as well as neurodegeneration. Furthermore, in animal models, this process recapitulates clinical and pathological phenotypes of PD, thereby mirroring the proposed staging systems^{5, 13} of LP in human disease. Indeed, alpha-synuclein fibrils alone, appear to be capable of transmission of LP within an animal.^{11, 12} Despite these similarities to PrP^{Sc} neuron-to-neuron transmission in the spongiform encephalopathies,¹⁴ there is currently no data to suggest humans¹⁵ or non-human-primates¹⁶ exposed to pathogenic alpha-synuclein from brain tissue of PD patients develop clinical PD. Thus, the apparent lack of transmission between individuals is in sharp contrast to human prion disease.

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There are many potential triggers for this pathological cascade of misfolding and aggregation of alpha-synuclein into LP within individuals with sporadic PD. LP contains alpha-synuclein proteins that are altered by several pathological modifications, including phosphorylation,¹⁷ ubiquitination, oxidation, nitration, and conformational changes.^{18, 19} Furthermore, multiple cellular factors may be involved in the pathologic accumulation of alpha-synuclein, including mitochondrial dysfunction and oxidative stress, excitotoxicity, deficits in protein degradation pathways, and disruption of axonal transport.²⁰ Epidemiological investigations have linked several environmental exposures, including pesticides that may alter mitochondrial function and induce oxidative stress, as potential risk factors for developing PD which could be modified by genetic factors in some individuals.²¹

Here, in the current issue of *Movement Disorders*, Jafari and colleagues perform a careful and detailed meta-analysis of previous studies examining the risk of PD in individuals with a history of significant head injury.²² This study addresses the important issue of inconsistencies in the previous literature on the association of PD and head injury. The authors thoughtfully control for several potential confounding factors in their results, including heterogeneity between studies, effects of adjustment or matching of patients, and quality of studies. In so doing, their meta-analysis convincingly demonstrated a significantly increased risk of PD in individuals with a history of head trauma that results in a loss of consciousness (OR 1.57, 95% CI 1.35–1.83) based on 18,344 cases and 79,028 controls from 22 studies world-wide.²² In addition, a sub-analysis including only studies that adjusted for potential confounding variables, finds a stronger association of head trauma and PD; Thus, these findings further reinforce their conclusions linking traumatic brain injury (TBI) to increased risk for PD. This is important work that identifies head trauma as potential modifiable environmental risk factor in PD.

TBI has also been implicated as a risk factor for other neurodegenerative diseases such as Alzheimer's disease (AD)²³ and frontotemporal lobar degeneration.²⁴ Furthermore, there is a considerably large body of evidence at a basic science level to support the association of a history of head trauma and neurodegenerative disease, including PD. TBI generally refers to any external traumatic force applied to the head causing altered brain function, and may result in focal injuries, such as cerebral hemorrhages (i.e. contusions, epidural, subdural, intracerebral or intraventricular hemorrhages) and diffuse injuries, including hypoxia/ ischemia and diffuse axonal injury. This heterogeneity in traumatic insults and resultant injuries poses a significant challenge for study. Jafari et al,²² identified head trauma in this study as injury resulting in loss of consciousness, hospitalization, seizure, intracranial hemorrhage, concussion or post-concussive syndrome (as defined by the presence of amnesia, prolonged headache or vestibular, motor, sensory or visual symptoms). Thus, this definition may have excluded cases of repetitive TBI which has been linked to chronic traumatic encephalopathy (CTE), a neurodegenerative condition consisting of abnormal tau and TDP-43 inclusions.²⁵

As reviewed recently Smith and colleagues,²⁶ acute TBI resulting in diffuse axonal injury can be considered a neuroinflammatory and neurodegenerative disorder, with similarities to age-associated neurodegenerative diseases (i.e. AD, PD). These include the presence of abnormal protein aggregations²³ of tau, A β , and alpha-synuclein with long-term

neuropathological^{27, 28} and clinical sequelae.²⁷ Axonal injury results in accumulation of amyloid-precursor protein (APP) within hours in terminal axonal retraction bulbs, accompanied with the end-product protein, A β , and enzymes responsible for APP cleavage into A β .^{23, 29, 30} This accumulation of APP and proteolytic enzymes in axonal retraction bulbs is a potential substrate for A β plaque accumulation in the brain in TBI, and could potentially explain the epidemiological association of head injury and AD.²³ Indeed, a significant subset of TBI patients display diffuse A β plaque pathology at autopsy in proximity to APP-laden axonal bulbs.^{29, 31, 32} This suggests that A β aggregations in axonal bulbs could leak into the extracellular matrix to form plaques. A subset of patients also shows tau accumulation in glial cells^{30, 33} and axonal bulbs.³⁰ Similar findings have been noted in a porcine model of diffuse axonal injury, and also include tau reactivity in the perikarya of neurons resembling “pre-tangle” neurofibrillary pathology in AD.³⁴ Furthermore, tau inclusions in professional boxers who sustained repetitive TBI have similar tau isoform composition and tau epitopes to neurofibrillary pathology in AD.³⁵ Interestingly, long term survivors of acute TBI have similar APP-positive axonal bulbs but minimal plaques compared to TBI patients with a shorter survival, which may be mediated by a catabolic process for A β deposits by microglia over time.³² This suggests that A β plaque formation induced by TBI may be a dynamic process.

Abnormal accumulations of alpha-synuclein have also been described in acute axonal injury associated with TBI.^{30, 36} These aggregations have pathogenic modifications seen in PD, including nitration, ubiquitination, and conformational changes.^{30, 36} Indeed, TBI can lead to oxidative stress and inflammation,³⁷ thought to play a role in alpha-synuclein aggregation in PD.²⁰ Additionally, LP in PD is thought to arise in the axonal compartment in Lewy neurites (LN) and coalesce into Lewy bodies in the cell soma,³⁸ as also seen in cell culture models of alpha-synuclein transmission.¹⁰ Indeed, a large degree of axonal LN from projecting nigral cells are found in the striatum of PD patients¹⁹ and brainstem LN may be one of the earliest site of LP in PD.⁵ Thus, altered axonal transport in TBI could feasibly contribute to the initiation and spread of LP within an individual. Indeed, in a rat model of TBI there is a transient increase in abnormally modified alpha-synuclein in the cortex and striatum.³⁹ In addition, CSF alpha-synuclein levels also increase following acute TBI,⁴⁰ suggesting pathological conformers of alpha-synuclein are released into the brain interstitium which could lead to seeding of inclusions in neighboring cells.

One major caveat to the interpretation of these data is that not all TBI patients are destined to develop PD or AD. Many factors may contribute to the varying expression of cognitive and motor deficits after TBI, including the heterogeneity of TBI, cognitive reserve and genetic factors that may alter the balance between anabolic and catabolic processes for pathogenic protein aggregations. Indeed, a recent study found that expansion of a dinucleotide repeat in the promotor region in *SNCA* known to increase alpha-synuclein expression (i.e. Rep-1) was associated with an increased risk of developing PD in patients with a history of head trauma,⁴¹ suggesting genetic factors could modify the risk of TBI induced PD. Furthermore, APOE genotype may influence the progression of TBI induced plaque formation, as TBI patients found with A β plaque pathology at autopsy are more

likely to carry the APOE ϵ 4 risk allele⁴² and the APOE ϵ 4 genotype may confer a worse prognosis in TBI.⁴²

The current work by Jafari and colleagues helps to reconcile previous discrepancies in the literature on TBI and risk for PD, as well as bring attention to the observation that TBI (including non-life threatening concussions which commonly occur in many athletic activities) can possibly result in neurodegenerative disease decades later. Limitations of a retrospective meta-analysis, such as recall bias and publication bias, are thoughtfully addressed. Additionally, the authors include a sensitivity analysis which further bolsters their observation. These limitations notwithstanding, this study provides convincing evidence of an association of head injury and clinical PD; however, despite the careful clinical criteria for PD employed in the study, conclusions on a direct relationship between TBI and alpha-synuclein are limited due to the lack of autopsy confirmation, which is not feasible for a meta-analysis. Further work in animal models and prospective series followed to autopsy will be crucial in determining the causal nature of this association with alpha-synuclein mediated PD and the factors that may modify the development of clinical symptoms. It will also be crucial to further clarify the effects of specific forms of TBI on PD risk and underlying neuropathology. Furthermore, TBI patients provide a potential pre-clinical at-risk population to study biomarkers of progression and interventions for prevention of PD, AD and other neurodegenerative conditions.

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