

Mini-Review

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Brain and Spinal Cord Trauma as a Risk Factor for Amyotrophic Lateral Sclerosis: A Mini-Review

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ABSTRACT

Trauma to the central nervous system (CNS) has been investigated as a risk factor for amyotrophic lateral sclerosis (ALS) despite conflicting epidemiological reports. Studies have suggested a link between ALS and traumatic axonal injury which complements the "dying back" theory of ALS. The theory suggests that neuronal dysfunction first occurs at the neuromuscular junction, and subsequent axonal impairment leads to dysfunction of the cell body. A pathological link has been shown between CNS trauma and ALS, further supporting this relationship. Another proposed hypothesis is that differences in "molecular thresholds" based on individual genetic backgrounds could explain some individuals developing ALS or ALS-like pathology subsequent to trauma, as well as elucidate the seemingly increased risk for ALS associated with multiple traumas. However, it is still unclear how trauma to the CNS might directly or indirectly trigger ALS. The current mini-review re-examines the relationship between CNS trauma and risk of developing ALS or an ALS-like pathology, and explores potential explanations for discrepant study results.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons, characterized by progressive muscle atrophy, paralysis and death. ALS is the most common motor neuron disease [1] affecting approximately 0.8-8.5 people per 100,000 worldwide [2]. While approximately 5% of cases are genetically linked (familial ALS), the majority of cases, 95%, are sporadic ALS with

poorly understood etiologies. However, clinical presentation and pathology of sporadic and familial ALS are similar. The major risk factor for ALS is age, with the typical onset between 40 and 60 years of age [1]. Another risk factor of recent interest is trauma, specifically trauma to the brain and spinal cord. Epidemiological literature has reported a link between repeated head trauma and increased risk of ALS. Further, epidemiological

research has identified an increased risk of ALS in individuals likely to suffer head trauma, such as soccer players [3], football players [4, 5], and military veterans [6-10]. Several case studies also suggest a relationship between axonal trauma and increased risk of ALS, which meshes with the “dying back” hypothesis [11] of motor neuron degeneration in ALS. Finally, a pathologic link has been shown between ALS and cerebral trauma, which have several common pathways. The current mini-review explores the relationship between trauma and ALS.

EPIDEMIOLOGY

Numerous epidemiological studies suggest a link between ALS and trauma; however, there is conflicting evidence for this connection. Studies examining single incidences of trauma [12] show tenuous or non-existent relationships between trauma and ALS. Conversely, studies in which the participants suffered multiple traumas seem to show a stronger relationship between trauma and risk of developing ALS [4, 12]. Additionally, this relationship has been investigated in high risk sports such as American football with similarly inconclusive results. A study by Savica et al. [5] investigated risk of ALS in men who played high school football prior to helmet protection. These men had the same risk for developing ALS as a control group of individuals from the same high school who participated in band, glee club, or choir. Conversely, Lehman et al. [4] found a significantly increased risk of ALS in a group of professional football players who played between 1959 and 1988. These differing results could be explained by the increased likelihood of severe and/or repeated trauma in professional football.

Several studies have also reported a relationship between risk of ALS and military service [6-10], another occupation carrying an increased risk of trauma to the central nervous system (CNS). Two studies in 2003 first investigated this relationship. Haley [10] compared observed and expected incidence rates of ALS in Gulf War veterans from 1991 through 1998. Results showed that over the 8 year observation period the expected incidence of ALS increased by 0.93 cases/year to 1.57 (due to increased age of subjects); however, the observed incidence of ALS increased from 1 to 5 cases during the same time period. Further, although

during the first four years after the Gulf War the number of new cases was only 0.94 times the expected value, during the next four years the observed incidence rose to 2.27 times and, during the 8th year after the Gulf War, peaked at 3.19 times the expected incidence. These results may suggest a latency period between encountering a risk factor and developing ALS or could indicate involvement of additional hazards such as chemical exposure. Similar results were found by Horner et al. [7] in a nationwide study using case ascertainment, with deployed military personnel at significantly higher risk of ALS than non-deployed military personnel. These results were expanded upon by Schmidt et al. [13] who conducted a logistic regression and reported that military veterans experiencing head injuries were 2.33 times more likely to develop ALS compared to other military veterans. These results provide support for the hypothesis that head injury increases risk of ALS.

Further, the effect of trauma on risk of ALS may be minor. A meta-analysis by Chen et al. [14] showed a significant relationship between trauma and risk of ALS, however, this relationship was not identified by the individual studies. A very large sample size was needed to confirm this relationship.

There are limitations to the existing epidemiological literature. Many of the reviewed studies had very small group sizes, increasing the likelihood of a type 1 error. Moreover, in several of the studies the incidences of trauma were self-reported, which is prone to inaccuracy and recall bias. Further, studies of hospital data fail to capture less severe but more common traumas. Also, knowledge of trauma type and post-traumatic consequences might be important in understanding any link to ALS. Finally, epidemiological studies can only identify correlations between trauma and occurrence of ALS; these studies cannot determine causation, which requires additional investigation.

CASE STUDIES OF ALS AND TRAUMATIC AXONOPATHY

Case studies can provide an additional avenue of exploratory investigation. Riggs [15-18] describes numerous case studies of patients suffering traumatic axonopathy to the lower

motor neurons who later developed ALS. Traumatic axonopathy is damage to the axon caused by trauma, and may represent the instigating trauma factor leading to ALS or ALS-like symptoms. The majority of patients developed ALS when relatively young, 28-43 years old. ALS is much more common in older individuals, who are less likely to suffer trauma [15]. As such, Riggs suggests that it would take an astronomical amount of patients to see a relationship between trauma and ALS [18]. The types of trauma in the cases described included radiculopathy, brachial plexopathy, and compression of the spinal nerve roots, among others. Further, the intervals between trauma and ALS diagnosis ranged from 5 to 42 months. Riggs also investigated traumatic axonal injury as a risk factor of ALS in a slightly different way. The author [19] conducted a reverse probability analysis to provide a range of risk ratios depending on the respective incidence of ALS and traumatic axonal injury to motor neurons in the population. Results indicated that if the incidence of traumatic motor axon injury associated with ALS is low (9 men between the ages 28-43 years old diagnosed over a 14 year period), and the incidence of trauma in a well-matched control population was above 0.52%, then there would be no association between traumatic axon injury and ALS. However, if there were a higher incidence of trauma associated with ALS (90 men between the ages 28-43 years old diagnosed over a 14 year period), and the incidence of trauma in a well-matched control population was below 7%, then injury to motor axons would be a significant risk factor for ALS. These results provide an interesting framework for including trauma as a risk factor for ALS.

Riggs also provides several hypothetical mechanisms that could explain traumatic axonopathy increasing the risk of ALS. The author [16] suggested that traumatic axonal injury may induce apoptosis in motor neurons, particularly in people with an underlying genetic predisposition to difficulty with apoptosis regulation. It was also suggested that people with a genetic predisposition to neurotrophin deficiency may show increased vulnerability of motor neurons after trauma and consequently increased risk of ALS [17]. Both of these hypotheses have some support from research involving the overarching “dying back” hypothesis.

THE DYING BACK HYPOTHESIS

Two opposing hypotheses have been proposed to explain the motor neuron degeneration in ALS, the dying forward and the dying back hypotheses. In brief, the dying forward hypothesis suggests that the initial dysfunction in ALS occurs in the corticomotor neurons. These corticomotor neurons then cause glutamate excitotoxicity in the lower motor neurons leading to degeneration [20]. Conversely, proponents of the dying back hypothesis believe that initial ALS dysfunction occurs at the neuromuscular junction. According to this theory, in healthy neurons trophic factors are released by the post-synaptic membrane and are transported via retrograde transport to the cell body; however, in ALS dysfunction of the lower motor neurons prevents this transport. The disrupted retrograde transport of trophic factors is hypothesized to be the initiating factor in ALS by the “dying-back” hypothesis.

There are several pathologic mechanisms that could underlie the dying back hypothesis. The two most pertinent to trauma are motor neuron dysfunction and axonal transport disruption, particularly alteration of retrograde transport [11]. A sublethal insult to the cell body could interrupt nutrient flow to the distal axon, primarily affecting the largest and most metabolically active nerve fibers (e.g. large motor neurons) as they are the most vulnerable to deprivation. Trauma could potentially have this effect upon the cell body, either via primary insult or by a secondary mechanism such as inflammation [21]. Abnormal neurofilament accumulation might also disrupt axonal transport, leading to degeneration in nerve fibers, possibly by preventing delivery of neurotrophic factors to the cell body [11]. Trauma could increase abnormal protein accumulation [11] and/or initiate damage to the axon itself with the same effect of disrupting axonal transport.

TRAUMATIC AXONAL INJURY AND MECHANISMS OF ALS

Trauma to the spinal cord or peripheral nerves could disrupt axonal transport and might initiate many mechanisms believed to underlie ALS. Studies investigating traumatic axonal injury (TAI) have noted several links between TAI and

ALS. Pathologic mechanisms that underlie TAI [22] such as the caspase death cascade, impaired axonal transport, impairment of retrograde transport, and the separation of the axon from its target have also been identified in ALS [23]. A review by Vickers et al. [24] related axonopathy and cytoskeleton disruption to various CNS degenerative diseases, including ALS. Lower motor neurons in ALS show axonal swelling and protein aggregates relatively early in disease progression. The authors suggested accumulation of neurofilaments and disruption of retrograde transport as potential mechanisms initiating ALS. Axonal changes may be one of the earliest pathologies in ALS [24, 25].

CHRONIC TRAUMATIC ENCEPHALOPATHY AND ALS

Recently, a link has been made between chronic traumatic encephalopathy (CTE), a disorder associated with trauma to the CNS, and ALS [26]. CTE is caused by repeated trauma to the head, and is common in boxing [27]. The mechanisms suspected to underlie CTE are axonal stretching and deformation [28]. The pathology typically includes general brain atrophy and decreased brain mass, particularly in the frontal and temporal lobes, as well as reductions in the hypothalamic floor, hippocampus, entorhinal cortex and amygdala, neurofibrillary tangles, neuropil neuritis, and pathological white matter [28]. The intracellular TDP-43 aggregates, discovered in the degenerating cells in ALS [29-31], have also been implicated in CTE proteinopathy [26]. In CTE, TDP-43 aggregation is primarily found in the brainstem, frontal and temporal cortices, hippocampus, and amygdala. Further, in some individuals TDP-43 pathology extends into the spinal cord, manifesting clinically as an ALS-like motor neuron disease. The authors propose a common mechanism for the pathogenesis of both diseases via traumatic axonal injury. While a subset of the CTE population express a clinical manifestation similar to ALS, and a subset of ALS patients have had trauma to the CNS, CTE and ALS seem to be separate diseases which in some cases may share a common mechanism. Interestingly, a single traumatic brain injury can be followed by increased cytoplasmic levels of TDP-43 [32] suggesting initial involvement of the CNS injury in

abnormal protein aggregation. Additionally, the combination of trauma with environmental stressors such as toxins might trigger early TDP-43 aggregation [33-35].

DOES CNS TRAUMA INDUCE ACTUAL ALS?

ALS is a progressive neurodegenerative disease with a complexity of clinical manifestations. Although numerous hypotheses have been proposed regarding ALS etiopathology [23, 36, 37], the causes of motor neuron degeneration and pathogenic mechanisms are still uncertain. The criteria for a definite ALS diagnosis include lower and upper motor neuron degeneration as evidenced by clinical, electrophysiological, or neuropathic examination followed by progressive spread of symptoms indicating the involvement of diffuse motor neuron degeneration within the CNS [38]. The confirmation of ALS diagnosis is also based on criteria excluding other neurodegenerative diseases. Some ALS symptoms can occur due to non-ALS-related pathogenic processes such as post-poliomyelitis, multifocal neuropathy with or without conduction block, endocrinopathies, lead intoxication, or paraneoplastic syndromes.

However, similarities in pathological processes underlying trauma to the CNS and ALS discussed above may suggest that trauma associated with ALS does not lead to a disorder mimicking ALS, but instead creates an environment more favorable to ALS development. Perhaps it is not the trauma itself, but instead axonal damage due to CNS trauma, which initiates ALS symptoms. As mentioned above [16, 17], in a person with genetic vulnerabilities, such as dysfunctional apoptosis or a propensity for neurotrophin deficiency, traumatic axonal injury could lead to CNS degeneration similar to a motor neuron disease like ALS. This scenario could also account for the epidemiological evidence suggesting that professional athletes have greater risk than amateurs. Also, multiple injuries and/or their severity could increase vulnerability to axonal damage and to developing an ALS-like pathology more so than a single injury. Further, perhaps motor neurons are more vulnerable to damage resulting from trauma than sensory neurons because of their higher energy requirements [11, 25]. This greater susceptibility

of motor neurons could explain how trauma might increase the risk of motor neuron dysfunction but leave sensory neuron function intact, creating an ALS-like pathology.

Yip and Malaspina [21] propose a “molecular threshold” for injury to the spinal cord. The authors posit that each of us has a molecular threshold, and if a response to a spinal cord injury or to an accumulation of injuries surpasses the individual’s molecular threshold, progressive tissue and functional losses are triggered. In a person with vulnerabilities, particularly in large motor neurons that are the most metabolically active, a clinical manifestation of ALS or ALS-like symptoms could be initiated.

Injury to the CNS causes a variety of changes in molecular processes such as increases in oxidative stress, inflammation, apoptosis, and protein cleavage along with decreases in axonal function, energy metabolism, and lipid metabolism [21]. Numerous genetic factors such as mutant SOD1, mutant APP, and APOE4 are also known to affect these molecular processes [21], and there are likely numerous undiscovered relevant genetic factors. Individual differences in these genetic factors may account for ALS-like pathology and symptomology in only a subset of CNS trauma sufferers. Individual differences could also account for discrepant epidemiological evidence between professional athletes compared to amateurs, as well as the increased effect of multiple injuries versus a single injury. Professional athletes and individuals with multiple injuries generally incur more cumulative damage and are more likely to exceed their molecular threshold than amateur athletes or individuals with single incidents of trauma.

Individual differences in molecular thresholds may also account for the minimal effect size seen in the epidemiological literature.

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CONCLUSIONS AND FUTURE DIRECTIONS

From the current research results, it is possible that trauma to the CNS in some individuals initiates mechanisms and patterns of protein aggregation similar to those seen in ALS, and results in ALS-like symptoms. However, due to the poorly understood etiopathology of ALS and its link to CNS trauma, it is premature to conclude that trauma may cause ALS. Epidemiologic studies, while beneficial in identifying potential risk factors of disease, are insufficient to determine causation. Post-traumatic ALS-like symptoms are likely a type of axonopathy but this possibility needs to be confirmed by further research. In order to better understand the etiology of ALS, further research to explore the relationship between genetic variability and risk of ALS may be an important area of interest. Further research might identify specific genes that reflect a propensity for apoptosis dysfunction or vulnerable motor neurons, and potentially identify individuals at an increased risk of developing ALS or an ALS mimic after CNS trauma.

LIST OF ABBREVIATIONS

- ALS – amyotrophic lateral sclerosis
 CNS – central nervous system
 CTE – chronic traumatic encephalopathy
 TAI – traumatic axonal injury

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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