FOCUSED ULTRASOUND IN MODERN NEUROSURGERY: SURGERY WITHOUT A SCALPEL

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Abstract

Diffuse Axonal Injury (DAI) is a pervasive and debilitating consequence of traumatic brain injury (TBI), representing a primary determinant of mortality and long-term neurological disability. Historically conceptualized as immediate mechanical tearing of axons, DAI is now understood as a progressive pathophysiological process initiated by rotational and acceleration-deceleration forces, leading to widespread white matter disruption. Gross pathology may reveal subtle hemorrhages in the corpus callosum and brainstem, while microscopic examination identifies axonal swelling, retraction bulbs, and eventual secondary axotomy. Molecular mechanisms include calcium influx, calpain-mediated cytoskeletal degradation, mitochondrial dysfunction, and Wallerian degeneration. Immunohistochemical markers, such as Amyloid Precursor Protein (APP), facilitate early detection, and advanced neuroimaging modalities—including Diffusion Tensor Imaging (DTI)—enable in vivo assessment of axonal integrity. Chronic changes involve

demyelination, gliosis, and neuroinflammation, with long-term functional outcomes determined by network disconnection and residual neuronal reserve. Understanding DAI's pathological anatomy is essential for prognostication, clinical management, and development of neuroprotective interventions.

Keywords: Diffuse Axonal Injury, Traumatic Brain Injury, Axonal Swelling, Secondary Axotomy, Amyloid Precursor Protein, Neuroimaging, Diffusion Tensor Imaging, Cytoskeletal Disruption, Wallerian Degeneration, Neuroinflammation

Introduction and Clinical Significance of Diffuse Axonal Injury

Diffuse axonal injury (DAI) represents one of the most pervasive and debilitating pathological features of traumatic brain injury (TBI), serving as a primary determinant of mortality and long-term morbidity in patients who sustain closed head trauma. Historically termed "shearing injury" or "diffuse degeneration of white matter" by Strich in landmark neuropathological studies conducted in the mid-20th century, the condition was initially conceptualized as the immediate physical tearing of nerve fibers due to mechanical forces [1].

However, decades of advanced research have radically transformed this understanding, redefining DAI not merely as a primary mechanical event but as a complex, progressive pathophysiological process initiated by trauma that unfolds over hours, days, and even weeks. Epidemiological data suggest that DAI is present in approximately 40% to 50% of patients admitted to hospitals with severe TBI and is the underlying pathology in nearly one-third of all TBI deaths [2]. Furthermore, it is the leading cause of persistent vegetative state and severe disability in survivors, highlighting a profound clinical significance that necessitates a rigorous examination of its pathological anatomy. The disconnect between the often subtle macroscopic findings and the devastating clinical outcomes, such as deep coma without mass lesions, constitutes a hallmark "clinical-radiological dissociation" that challenges clinicians and underscores the necessity of microscopic and molecular interrogation of the tissue [3].

Biomechanical Mechanisms of Diffuse Axonal Injury

The biomechanical genesis of diffuse axonal injury is distinct from focal injuries such as contusions or hematomas, which typically result from direct contact forces and skull deformation. DAI is fundamentally the result of inertial loading, specifically rotational acceleration and deceleration forces applied to the head [4]. The brain is a viscoelastic structure, enclosed within the rigid cranial vault and tethered by dural folds and vascular structures. When the head undergoes rapid rotation, the varying specific gravities and consistencies of the gray and white matter facilitate differential movement between these tissue layers. This discordance generates significant shear strains—forces that slide tissue planes against one another—and tensile strains that stretch the neuronal axons [5].

Holbourn's seminal work on the mechanics of head injury established that shear strain is the most damaging force to the brain's internal architecture, as brain tissue is relatively incompressible but highly deformable [6]. The distribution of these forces is not uniform; the greatest shear strains typically occur at the junctions between tissues of differing density, such as the gray-white matter interface, and in central brain structures where rotational forces are amplified. Experimental models, particularly those utilizing non-impact rotational acceleration in primates, have demonstrated that the direction, magnitude, and duration of the acceleration are critical variables; coronal (lateral) head motion tends to produce more severe and deeper lesions than sagittal (front-to-back) motion, likely due to the limited damping provided by the falx cerebri against lateral movement [7].

Gross Pathology of Diffuse Axonal Injury

Gross pathological examination of a brain affected by DAI may be deceptively normal, particularly in the acute phase or in cases of lesser severity. Unlike the expansive hemorrhage of a contusion, the macroscopic hallmarks of DAI are often subtle and require meticulous inspection. In fatal cases, the classic triad of lesions described by Adams and colleagues includes hemorrhagic lesions in the corpus callosum, hemorrhagic lesions in the dorsolateral quadrant of the rostral brainstem, and microscopic evidence of diffuse damage to white matter axons [8]. The corpus callosum, particularly the splenium and the undersurface of the posterior body, is a site of predilection due to its susceptibility to the

falx cerebri causing direct trauma during brain lag, as well as the high density of transversely oriented fibers subjected to shear. Similarly, the brainstem lesions are typically located in the superior cerebellar peduncles or the region of the decussation, reflecting the extreme tension placed on the brainstem as it acts as a fulcrum during rotational acceleration [9]. It is critical to note, however, that macroscopic hemorrhages are not the injury itself but rather markers of severe tissue shear that has disrupted local vasculature; the true axonal pathology extends far beyond these visible punctate bleeds. Over time, in patients who survive for months or years, the gross pathology evolves into a generalized atrophy. This is characterized by ventriculomegaly—often termed hydrocephalus ex vacuo—resulting from the loss of white matter bulk, thinning of the corpus callosum, and widening of the sulci, reflecting the massive, cumulative loss of axons and subsequent myelin degradation [10].

Microscopic Pathology and Axonal Changes in DAI

The microscopic pathology of DAI provides the definitive diagnosis and reveals the temporal evolution of the injury, which is critical for understanding the potential therapeutic window. The classical histological marker of DAI is the "axonal bulb" or "retraction ball," a profound swelling of the axon that Strich originally attributed to the elastic recoil of a severed nerve fiber [1]. While true primary axotomy—the immediate tearing of the axon at the moment of impact—does occur, particularly in severe injuries and typically involving large-caliber fibers, modern ultrastructural studies have demonstrated that the vast majority of axonal pathology in DAI is a phenomenon of "secondary axotomy" or delayed disconnection [11].

In this scenario, the mechanical force renders the axolemma (cell membrane) momentarily porous or disrupts the internal cytoskeleton without severing the axon entirely. This perturbation triggers a catastrophic disruption of fast axonal transport. Anterogradely transported organelles, vesicles, and proteins, continuing their journey from the soma, encounter a blockade at the site of cytoskeletal damage, where they accumulate and cause the axon to swell locally [12]. This evolving pathology explains why axonal bulbs are not immediately visible upon death in hyper-acute cases (those dying within

minutes); they require a period of survival, typically 12 to 24 hours, to develop sufficiently for detection by standard silver stains or hematoxylin and eosin (H&E) [13].

Molecular and Cellular Mechanisms of Secondary Axotomy in DAI

The molecular and cellular mechanisms underpinning this delayed disconnection are complex and offer potential targets for neuroprotective intervention. The initial mechanical strain causes a conformational change in the sodium channels and arguably more importantly, mechanically sensitive voltage-gated calcium channels, leading to a massive, unregulated influx of extracellular calcium into the axoplasm [14]. This calcium surge activates a host of calcium-dependent proteases, most notably calpains. Activated calpains aggressively degrade key structural proteins of the axonal cytoskeleton, such as the spectrin-fodrin network and neurofilaments, and initiate the proteolysis of microtubules [15]. The breakdown of the sub-axolemmal spectrin meshwork compromises the structural integrity of the membrane, while the dissolution of microtubules directly halts axonal transport. Concurrently, the calcium overload creates a "mitochondrial permeability transition," leading to mitochondrial swelling, loss of membrane potential, and the release of cytochrome c, which further drives apoptotic cascades and energy failure within the axon [16]. This process culminates in the physical separation of the distal and proximal axon segments—secondary axotomy—usually occurring 12 to 72 hours post-injury. Once separation is complete, the distal segment undergoes Wallerian degeneration, a process of active disintegration involving the fragmentation of the axon and myelin sheath, while the proximal segment may either regenerate or, more commonly in the CNS, die back to the cell body, triggering chromatolysis and potentially neuronal apoptosis [17].

Immunohistochemical Detection and Biomarkers of Axonal Injury in DAI

Immunohistochemistry has revolutionized the detection of DAI, allowing pathologists to identify axonal injury much earlier and with greater sensitivity than traditional silver impregnation techniques. The gold standard in modern neuropathology involves antibodies against Amyloid Precursor Protein (APP). APP is a ubiquitously expressed transmembrane protein that is carried via fast axonal transport. Under normal conditions, it is barely detectable in axons due to its rapid transit; however, in the event of

cytoskeletal disruption, APP accumulates rapidly at the site of injury [18]. Positive APP staining can visualize axonal injury in as little as 1.5 to 3 hours post-trauma, appearing as varicosities or beaded swellings along the white matter tracts. This technique has revealed that the extent of axonal injury is often far greater than suggested by conventional histology, uncovering a "pervasive" pattern of damage even in mild TBI models [19]. Other markers, such as antibodies against non-phosphorylated neurofilaments (e.g., SMI-32) and spectrin breakdown products, provide complementary information regarding the integrity of the cytoskeleton and the activity of proteolytic enzymes, offering a window into the specific molecular stage of the injury process [20].

Chronic Pathology of DAI: Degeneration, Gliosis, and Neuroinflammation

In the chronic phase of DAI, the pathological landscape shifts from axonal swelling to degeneration and gliosis. Following the disconnection and subsequent Wallerian degeneration, the brain mounts a neuroinflammatory response. Microglia, the resident immune cells of the central nervous system, proliferate and migrate to the sites of injury to scavenge myelin debris and axonal fragments. These clusters of activated microglia are sometimes referred to as "microglial stars" and can persist for months [21]. Astrocytes also respond by undergoing hypertrophy and hyperplasia, forming a glial scar (astrogliosis) that replaces the lost white matter tracts. This scarring, combined with the loss of myelin lipids, results in the firmness and reduced volume of the white matter seen grossly in long-term survivors. The demyelination is not merely a passive consequence of axonal loss; evidence suggests that the oligodendrocyte-myelin unit may also be directly susceptible to mechanical trauma and excitotoxicity, contributing to the overall pathology and hindering potential remyelination efforts [22].

Classification and Grading of Diffuse Axonal Injury

The classification and grading of DAI have traditionally relied on the seminal work of Adams and colleagues, who proposed a three-tiered grading system based on the anatomical distribution of lesions observed at autopsy. Grade 1 DAI is defined by histological evidence of axonal injury in the white matter of the cerebral hemispheres (cortex, subcortical white matter, corpus callosum) without focal lesions in the corpus

callosum or brainstem. Grade 2 requires the presence of a focal hemorrhagic lesion in the corpus callosum, in addition to diffuse white matter injury. Grade 3, the most severe form, involves a focal lesion in the rostral brainstem, usually in addition to the findings of Grades 1 and 2 [8]. This grading system has proven robust in predicting clinical severity and outcome in fatal cases, with Grade 3 correlating with the deepest coma and worst prognosis. However, its reliance on macroscopic hemorrhagic markers is a limitation, as it may underestimate severe diffuse microscopic injury that occurs without vascular disruption. Furthermore, the Adams grading is a pathological tool and is difficult to apply strictly in a clinical setting, although modern neuroimaging seeks to approximate it [23].

Neuroimaging Correlates of Diffuse Axonal Injury

The correlation between pathological anatomy and neuroimaging is a critical area of translational research, as accurate in vivo diagnosis remains challenging. Computed Tomography (CT), the workhorse of acute trauma triage, is notoriously insensitive to DAI, often missing non-hemorrhagic lesions entirely. Magnetic Resonance Imaging (MRI) is far superior, particularly sequences sensitive to blood breakdown products and water diffusion. T2*-weighted Gradient Echo (GRE) and Susceptibility Weighted Imaging (SWI) exploit the paramagnetic properties of hemosiderin and deoxyhemoglobin to visualize the microscopic hemorrhages associated with shearing injury, serving as a surrogate marker for the adjacent axonal damage [24]. These sequences frequently reveal multiple hypointense foci at the gray-white matter interface, corpus callosum, and brainstem, aligning with the pathological distribution described by Adams. However, the most significant advance in imaging the pathological anatomy of DAI is Diffusion Tensor Imaging (DTI). DTI measures the directionality (anisotropy) of water diffusion in tissues; in healthy white matter, water diffuses preferentially along the axis of the axons (high fractional anisotropy). In DAI, the disruption of the axonal membrane and cytoskeleton allows water to diffuse more randomly (reduced fractional anisotropy) or increases diffusivity perpendicular to the tract. DTI has demonstrated the ability to detect white matter tract integrity issues in patients with normal conventional MRI scans, providing an in vivo correlate to the "disconnection" seen under the microscope [25].

Clinical Implications and Functional Outcomes of DAI

The clinical relevance of these pathological findings is inextricably linked to the patient's functional outcome. The cumulative load of damaged axons results in the disconnection of neural networks essential for arousal, awareness, and higher cognitive functions. Damage to the ascending reticular activating system in the brainstem, often seen in Grade 3 DAI, is a primary driver of coma. Meanwhile, diffuse cortical and subcortical disconnection contributes to the cognitive slowing, executive dysfunction, and memory deficits observed in survivors [26]. The variability in outcome—why some patients with apparent heavy lesion loads recover while others do not—may be explained by the concept of "functional reserve" and the microscopic heterogeneity of the injury; not all swollen axons proceed to disconnection, and some may recover transport function if the cytoskeleton is repaired before critical failure occurs [27].

Despite significant progress, limitations in our understanding remain. Much of the pathological data is derived from fatal cases, which inherently biases the understanding toward the most severe spectrum of the disease. The pathological anatomy of "mild" DAI, such as that occurring in concussion, is less well-characterized in humans due to the lack of autopsy material, though animal models suggest a continuum of pathology where sparse axonal varicosities exist without overt cell death [28]. Furthermore, the precise temporal window for therapeutic intervention remains elusive; while the concept of delayed axotomy provides a theoretical window for neuroprotection (e.g., calpain inhibitors or membrane sealants), clinical trials have largely failed to translate these findings into successful treatments. This failure suggests that the pathological cascade may be more multifactorial than currently modeled, perhaps involving parallel pathways of inflammation, oxidative stress, and tau pathology that are not fully captured by the single-mechanism focus of previous studies [29].

Future Directions and Biomarkers in DAI Research

Future research directions in the pathological anatomy of DAI are increasingly focused on the chronic sequelae of the injury, particularly the link between a single moderate-severe TBI and the later development of neurodegenerative diseases. There is

growing evidence that the axonal pathology of DAI may seed the accumulation of abnormal proteins, such as hyperphosphorylated tau and amyloid-beta, potentially triggering a self-propagating neurodegenerative process similar to Alzheimer's disease or Chronic Traumatic Encephalopathy (CTE) [30]. Understanding the molecular intersection between the acute cytoskeletal shattering of DAI and the chronic protein misfolding of neurodegeneration is the next frontier. Additionally, the development of fluid biomarkers, such as Neurofilament Light Chain (NfL) in blood, acts as a "liquid biopsy" of ongoing axonal breakdown, promising to bridge the gap between static pathological snapshots and dynamic clinical monitoring [31].

Conclusion

In conclusion, the pathological anatomy of Diffuse Axonal Injury is a distinct and devastating entity defined by the widespread, multifocal disruption of white matter tracts resulting from inertial forces. It is characterized by a progression from biomechanical shear to cytoskeletal collapse, transport failure, and eventual disconnection, rather than immediate tearing. From the gross hemorrhagic markers in the corpus callosum and brainstem to the microscopic beading of APP-positive axons and the molecular ravages of calpain activation, DAI represents a profound systemic failure of the brain's connective infrastructure. As neuroimaging techniques like DTI continue to improve in resolution, they increasingly allow us to visualize the "pathological anatomy" in the living patient, closing the loop between the century-old observations of neuropathologists and modern clinical neurology. The challenge remains to translate this granular understanding of axonal death into therapies that can arrest the cascade, preserve the connectome, and restore function to the injured brain.

References

1. Strich, S. J. (1961). Shearing of nerve fibres as a cause of brain damage due to head injury. The Lancet, 278(7200), 443-448.
2. Meythaler, J. M., Peduzzi, J. D., Eleftheriou, E., & Novack, T. A. (2001). Current concepts: diffuse axonal injury-associated traumatic brain injury. Archives of Physical Medicine and Rehabilitation, 82(10), 1461-1471.

3. Gennarelli, T. A., & Graham, D. I. (2005). Neuropathology of the Head Injuries. Seminars in Clinical Neuropsychiatry, 3(3), 160-175.

4. Gennarelli, T. A., Thibault, L. E., Adams, J. H., Graham, D. I., Thompson, C. J., & Marcincin, R. P. (1982). Diffuse axonal injury and traumatic coma in the primate. Annals of Neurology, 12(6), 564-574.

5. Margulies, S. S., & Thibault, L. E. (1992). A proposed tolerance criterion for diffuse axonal injury in man. Journal of Biomechanics, 25(8), 917-923.

6. Holbourn, A. H. S. (1943). Mechanics of head injuries. The Lancet, 242(6267), 438-441.

7. Adams, J. H., Doyle, D., Ford, I., Gennarelli, T. A., Graham, D. I., & McLellan, D. R. (1989). Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology, 15(1), 49-59.

8. Adams, J. H., Graham, D. I., Murray, L. S., & Scott, G. (1982). Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. Annals of Neurology, 12(6), 557-563.

9. Gentry, L. R., Godersky, J. C., & Thompson, B. (1988). MR imaging of head trauma: review of the distribution and radiopathologic features of traumatic lesions. American Journal of Roentgenology, 150(3), 663-672.

10. Maxwell, W. L., Povlishock, J. T., & Graham, D. L. (1997). A mechanistic analysis of nondisruptive axonal injury: a review. Journal of Neurotrauma, 14(7), 419-440.

11. Povlishock, J. T. (1992). Traumatically induced axonal injury: pathogenesis and pathobiological implications. Brain Pathology, 2(1), 1-12.

12. Povlishock, J. T., & Christman, C. W. (1995). The pathobiology of traumatically induced axonal injury in animals and humans: a review of current thoughts. Journal of Neurotrauma, 12(4), 555-564.

13. Grady, M. S., McLaughlin, M. R., Christman, C. W., Valadka, A. B., Fligner, C. L., & Povlishock, J. T. (1993). The use of antibodies against neurofilament subunits for the detection of diffuse axonal injury in humans. Journal of Neuropathology & Experimental Neurology, 52(2), 143-152.

14. Wolf, J. A., Stys, P. K., Lusardi, T., Meaney, D., & Smith, D. H. (2001). Traumatic axonal injury induces calcium influx modulated by tetrodotoxin-sensitive sodium channels. Journal of Neuroscience, 21(6), 1923-1930.
15. Saatman, K. E., Creed, J., & Raghupathi, R. (2010). Calpain as a therapeutic target in traumatic brain injury. Neurotherapeutics, 7(1), 31-42.
16. Büki, A., Koizumi, H., & Povlishock, J. T. (1999). Moderate injury induces axolemmal permeability dysfunction in focally injured axons within the traumatic penumbra. Journal of Neurotrauma, 16(8), 633-643.
17. Medana, I. M., & Esiri, M. M. (2003). Axonal damage: a key predictor of outcome in human CNS diseases. Brain, 126(3), 515-530.
18. Blumbergs, P. C., Scott, G., Manavis, J., Wainwright, H., Simpson, D. A., & McLean, A. J. (1994). Staining of amyloid precursor protein to detect axonal injury in head injury. The Lancet, 344(8929), 1055-1056.
19. Sherriff, F. E., Bridges, L. R., & Sivaloganathan, S. (1994). Early detection of axonal injury after human head trauma using immunocytochemistry for beta-amyloid precursor protein. Acta Neuropathologica, 87(1), 55-62.
20. Johnson, V. E., Stewart, W., & Smith, D. H. (2013). Axonal pathology in traumatic brain injury. Experimental Neurology, 246, 35-43.
21. Oehmichen, M., Meissner, C., & Reiter, A. (1999). Axonal injury—time of occurrence and reaction of microglia. Forensic Science International, 103, S133-S136.
22. Flygt, J., Djupsjö, A., Linderholm, B., & Marklund, N. (2013). Myelin loss and oligodendrocyte pathology in white matter tracts following traumatic brain injury in the rat. European Journal of Neuroscience, 38(1), 2153-2165.
23. Skandsen, T., Kvistad, K. A., Solheim, O., Strand, I., Folvik, M., & Vik, A. (2010). Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. Journal of Neurosurgery, 113(3), 556-563.
24. Tong, K. A., Ashwal, S., Holshouser, B. A., Shutter, L. A., Herigault, G., Haacke, E. M., ... & Obenaus, A. (2003). Hemorrhagic shearing lesions in children and adolescents

with posttraumatic diffuse axonal injury: improved detection and initial results. Radiology, 227(2), 332-339.

25. Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. American Journal of Neuroradiology, 23(5), 794-802.

26. Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. Nature Reviews Neurology, 10(3), 156-166.

27. Farkas, O., & Povlishock, J. T. (2007). Cellular and subcellular change evoking targeted neuronal remodeling and/or death following traumatic brain injury. International Review of Neurobiology, 82, 105-140.

28. Browne, K. D., Chen, X. H., Meaney, D. F., & Smith, D. H. (2011). Mild traumatic brain injury and diffuse axonal injury in swine. Journal of Neurotrauma, 28(9), 1747-1755.

29. Bramlett, H. M., & Dietrich, W. D. (2007). Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. Progress in Brain Research, 161, 125-141.

30. Smith, D. H., Johnson, V. E., & Stewart, W. (2013). Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nature Reviews Neurology, 9(4), 211-221.

31. Shahim, P., Tegner, Y., Wilson, D. H., Randall, J., Skillbäck, T., Pazooki, D., ... & Zetterberg, H. (2014). Blood biomarkers for brain injury in concussed professional ice hockey players. JAMA Neurology, 71(6), 684-692.