Diffuse Axonal Injury

Subjects: Medicine, Legal

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Diffuse axonal injuries (DAI) are the result of strong rotational and translational forces on the brain parenchyma, leading to cerebral oedema and neuronal death. DAI is typically characterized by coma without focal lesions at presentation and is defined by localized axonal damage in multiple regions of the brain parenchyma, often causing impairment of cognitive and neuro-vegetative function.

Keywords: diffuse axonal injury ; immunohistochemistry markers

1. Introduction

With an incidence of 235-556/100,000 inhabitants, closed or open traumatic brain injury is the most studied area in forensic medicine. In the case of traumatic brain injury accompanied by exitus, traumatic brain injury is the leading cause of violent death, in its various forms, and may or may not be accompanied by legal implications [1]. Sabina J. Strich first reported DAI in 1956 [2]. In her paper, she presented a series of autopsied cases at an interval of 5–15 months after trauma, highlighting a diffuse degeneration of cerebral white matter, which led to lifelong psycho-behavioral changes associated with neurodegenerative pathologies. Adams et al. further explained the biomechanics of DAI, identifying that angular acceleration together with the acceleration–deceleration mechanism cause true shear forces at the boundary between white matter and gray matter. It was concluded, using primate models, that extensive axonal injury is the primary cause of post-traumatic unconsciousness without focal lesions [2][3]. The most common changes have been shown in the subcortical white matter of the frontal and temporal lobes, the corpus and splenium of the corpus callosum, and in the most severe cases, the rostral superior region of the brainstem [4][5][6]. Today, DAI is considered a common finding in patients suffering from TBI, existing in about half of the cases of closed TBI in combination with focal lesions [1][2][3]. Diffuse axonal lesions in isolation, however, are less common [2]. DAI has a negative impact on vital prognosis and quality of life in case of survival, as they are left with severe motor, cognitive and behavioral impairments. Traumatic brain injury is the most common type of trauma encountered in current forensic practice. Investigations into the mechanisms of injury, the timing of traumatic brain injury, and the causes of death remain topical. Determining the time of trauma involves both distinguishing between antemortem and postmortem injuries and considering the post-traumatic survival interval [3][4][5][6][7]. The elucidation of the time of traumatic brain injury from a forensic point of view has not yet been satisfactorily achieved. Finding objective criteria for assessing the time of trauma is essential. Therefore, researchers aims to investigate immunohistochemically apoptotic brain cellular changes, brain reactive astrocytosis processes and tissue inflammatory reactions in relation to the survival interval [8][9]. The classical hypothesis on the development of traumatic brain injury shows that it is the result of primary traumatic injury, due to cell necrosis combined with the brain inflammatory response leading to secondary brain injury [10]. In recent decades, multiple studies have been conducted on the role of the inflammatory response, in the perpetuation of traumatic brain injury, with the observation that microglial and macrophage cells recruited to the brain exacerbate primary neuronal injury. Much experimental research related to traumatic brain injury has focused on the occurrence and progression of tissue necrotic lesions, largely due to direct post-traumatic mechanical effect at the brain level. A clear disjunction has been made between necrosis and apoptosis. Necrosis is cell death that occurs accidentally due to external factors and is unprogrammed, whereas apoptosis represents programmed and directed cell death, with a role in maintaining tissue homeostasis. These changes also apply to diffuse axonal injury, where the necrosis/apoptosis ratio dictates the subsequent course [11][12]. This ratio is dependent on the cellular influx of calcium ions, which will lead, depending on the intracellular concentration of these ions, to the activation of one or another of the caspase or calpain pathways. Post-traumatic neuronal loss has been described as being strictly due to necrosis, while inflammation and cell apoptosis are physiological processes that have no role in this process [13]. Due to recent experimental data, brain cell apoptosis is being re-evaluated. The pathophysiology of traumatic brain injury is far from being fully understood, and the idea that apoptosis may play an even more important role than initially thought is beginning to emerge. More specifically, injured brain cells release neuromodulatory substances that can lead to late neuronal destruction that occurs long after brain necrotic and inflammatory phenomena have ceased to act. These

neuronal cell injuries are responsible for the development of various neurological deficits and post-traumatic sequelae [5][7][14].

2. Biomechanics and Pathophysiology of Axonal Injury

Under normal conditions, brain tissue is elastic and resilient to mechanical stress stretching, having the ability to double its length, due to a capacity called viscoelasticity. Despite this property, in the case of DAI, the main force applied is rotational acceleration-deceleration, leading to dynamic shear, tensile deformation and compression of the brain tissue, dependent on the magnitude and abruptness of the force acting on the cephalic extremity. The higher these forces, the stiffer and more fragile the brain tissue becomes [2], thus damaging the axons and damaging the axonal cytoskeleton. Moreover, the difference in density between white and gray matter causes mass effects, leading to tension in the interface. Although deformations rarely lead to axonal disconnections on impact, these events trigger secondary axotomy. This is a consequence of axonal membrane permeability, which leads to a marked influx of Ca ions, with injury to the cytoskeleton, a phenomenon that starts at the level of the nodule Ranvier, rich in Na channels, Ca channels, Na/Ca exchangers, ATP-dependent Ca pumps, the presence of mitochondria, microtubules and neurofilaments, and ankyrin-3 and alpha-II spectrin-rich cytoskeleton, susceptible to injury by Ca-dependent calpain. Spectrin alpha chain, non-erythroid 1 (UniProt: Q13813; also known as alpha-II spectrin, fodrin alpha chain, spectrin, non-erythroid alpha subunit) is encoded by the SPTAN1 (also known as NEAS, SPTA2) gene (gene ID: 6709) in humans. Non-erythroid spectrin is essential for maintaining membrane stability and cell shape by connecting the cytoskeleton to plasma membranes or intracellular vesicles. Spectrin II is an abundant structural protein in central nervous system neurons and is cleaved into signature fragments by proteases involved in necrotic and apoptotic cell death. It is one of the primary targets cleaved by activated caspases during apoptosis. Spectrin II is involved in secretion, interacts with calmodulin in a calcium-dependent manner and is thus a candidate for calcium-dependent movement of the cytoskeleton at the membrane. Important forces act mainly at the level of Na-voltage and mechano-dependent channels, which have the ability to transform mechanical stimulus into electrical stimulus, thanks to mechanotransduction. This massive activation of Na channels will lead to a massive influx of Ca via Ca/Na exchanger and activation of voltage-dependent L and N calcium channels with depolarization, which should normally maintain a longer action potential at the axonal level. Calcium will activate numerous proteolytic enzymes, including Ca-dependent calpain, which will lead to proteolysis of the H-gate, inactivating Na-voltage-dependent channels. researchers aimed to identify cases with traumatic brain injury showing diffuse axonal lesions by immunohistochemical study with antibodies to GFAP, β-APP, spectrin II, CD68 and NFL in the analyzed samples. Researchers also wanted to analyze the correlation between these lesions and the degree of survival, as well as their dynamics as a function of survival interval.

References

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