

# Brief Literature Review on the Mechanisms Involved in Producing Axial Difussion Injury

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## Abstract

Current work reviews the concept, pathological mechanism and the process of diagnosing diffuse axonal lesions (DAI). The pathological mechanism underlying DAI is complicated, including axotomy with the appearance of retraction bulbs, interrupted protein transport along axonal neurofilaments, massive influx of calcium ions and calpain-mediated hydrolysis, axonal cytoskeletal cell degradation, beta-amyloid precursor protein accumulation and changes in glial cells. The transition from primary axotomy to secondary axotomy causes a very complex, calcium-dependent biochemical cascade.

**Keywords:** brain injuries, diffuse axonal injury, axotomy, beta-amyloid;

## 1. Introduction

With an incidence of 235-556 / 100,000 inhabitants, the craniocerebral trauma, whether closed or open, is the most studied area within the forensic expertise. In the case of trauma with exitus, craniocerebral trauma is the first cause of violent death in its various forms, possibly accompanied by legal implications. Craniocerebral trauma is a pathological condition that is caused by the action of forces of a mechanical nature on the cephalic extremity and which, through static

and / or dynamic-acceleration-deceleration mechanisms, result in at least one of the following: change of consciousness, anterograde or retrograde amnesia related to the moment of trauma, hemorrhage fractures, pathological changes such as disorientation, agitation, confusion, cognitive or behavioral disorders, intracranial lesions, neurological disorders such as changes in motor, sensitive or reflex functions, speech disorders or epileptic seizures. For this reason, the diagnosis of severity of the trauma is retrospective, which is established only at the moment of discharge, which is useful in the forensic practice. Brain lesions have two forensic classifications: focal and diffuse. Focal lesions are the result of collision forces acting on the skull, resulting in compression of the cerebral tissue under the impact site (shock) and the opposite side of the impact (reaction). Focal lesions are extradural and subdural hematomas (produced by shock or reaction), intraparenchymatous hematomas, contusion, subarachnoid hemorrhage, the latter being also an entity of cerebral diffuse lesions - vascular diffuse lesions, along with hypoxic-ischemic lesions, edema cerebral and diffuse axonal lesions.

Pathology of diffuse axonal lesions (DAI) was described in 1956 by specialist neurologist Sabina Strich of Oxford University as a clinical syndrome associated with extensive anatomopathological lesions in cerebral white matter (Strich, 1956). The term itself was introduced by Hume Adams et al., defining cases of coma of traumatic etiology greater than 6 hours associated with diffuse and extensive lesions in the white matter, which he classified according to severity in three degrees based on the depth of localization, as follows: Grade 1 - at the interface between the cerebral cortex, the cerebral core and the oval core, Grade 2 - in the calcite, Grade 3 - in the dorsolateral quadrant of the cerebral trunk (Geddes et al., 2000; Meythaler et al. 2001). It has now been established that the diffuse axonal lesion terminology is to be used for human lesions and the traumatic axonal lesion to define both human lesions and those produced on the biobase (Johnson et al., 2013).

## **2. Alternative definitions of DAI**

Scientific literature, also, mentioned others definitions of DAI, such as:

i) a form of brain injury generated by shearing forces that occur between different parts of the brain as a result of rotational acceleration (David, 2011); ii) post-traumatic brain injury which occurs over a broad swath of myelinated tracts of the CNS, resulting in significant neurologic effects, ranging from loss of consciousness to persistent vegetative state (Segen, 2012); iii) a brain injury in which damage in the form of extensive lesions in white matter tracts occurs over a widespread area (Iwata, 2004).

DAI most commonly occurs in motor vehicle crashes when the vehicle suddenly stops, and the corpus callosum together with the brainstem are often affected. Being a major cause of unconsciousness and persistent vegetative state after severe head trauma, DAI is one of the most common and devastating types of traumatic brain injury (Gong et al., 2007).

## **3. Biomechanics of DAI**

Diffuse axonal injury, as the result of traumatic shearing forces which occur when the head is rapidly accelerated or decelerated, as may happen in car accidents, falls, and assaults. The most frequent cause of DAI are vehicle accidents, but it can also occur as the result of child abuse (such as shaken baby syndrome).

Immediate disconnection of axons could be observed in severe brain injury, but the major damage of DAI is delayed secondary axon disconnections slowly developed over an extended time course. Tracts of axons, which appear white due to myelination, are referred to as white matter. Lesions in both grey and white matters are found in postmortem brains in CT and MRI exams.

Besides mechanical breaking of the axonal cytoskeleton, DAI pathology also includes secondary physiological changes such as interrupted axonal transport, progressive swellings and degeneration. Recent studies have linked these changes to twisting and misalignment of broken axon microtubules, as well as tau and APP deposition.

The biomechanics of craniocerebral traumas leading to DAI are explained by sudden changes in brain position leading to diffuse intraparenchymatous forces with neural functional impairment, so-called primary axotomy, followed by a morphological substrate - secondary axotomy; initially the tendon appeared tensioned and subsequently edematiate (swelling axonal) with the occurrence of DAI-specific axonal retraction bulbs-microscopic lesions (Smith, 2003). The retraction bulbs are visible after at least 4-12 hours from craniocerebral trauma, in arginine impregnation and after one hour by immuno-histochemistry techniques that highlight the presence of the beta-amyloid precursor protein at the level of the affected axons, this becoming the main goal of DAI diagnosis. Antibodies that identify the amino-terminal domain of this protein are administered.

During normal head movement, tension in axons is not deleterious, in vitro studies showing that the axon has the ability to stretch up to 100% of its length due to viscoelasticity without causing intra-axonal lesions. Axonal lesion is dependent on magnitude and duration of force. The physical properties of the brain such as its mass and shape are essential (Adams et al., 1982). Density differences between gray and white matter explain why DAIs form at the limit between them by shear, tension and compression forces (Povlishock, 1992). The presence of the falx cerebri can be a barrier, of which the brain hits, especially in lateral movements, which is why these movements are considered more likely to produce DAIs than the antero-posterior ones. Also, in rotational motion, the cerebral hemispheres move away from one another, thus explaining lesions in the calf body. The forces acting on the skull are not fully understood, but are common in both road accidents and precipitations, through acceleration-deceleration mechanisms, and also in the so-called "baby shaken syndrome". The contact forces intervene when the head is blocked or hit directly, producing in most cases only focal lesions. In some cases, however, it has been shown that contact forces also induce rapid acceleration and deceleration, imparting inertial forces to the brain (Adams et al., 1982). In connection with the last pathological entity listed above, Joseph Shapiro has launched a new hypothesis regarding tanatogenesis, claiming that death does not occur as a result of DAI production, but as a result of nerve damage that intimates the diaphragm at the time of movement flexion extension of the neck. Death is caused by respiratory failure, given that at this age, breathing is of the abdominal type, supported by diaphragmatic movements.

### **3.1. *Physio pathological mechanism***

Two pathological forms of injured axons appear after traumatic brain injury. Initially called retraction bulbs, they were identified at the proximal end of the discontinued axon. Later, it was observed that these bulbs are formed by progressive axonal focal dilation, which ultimately leads to secondary axotomy, now denominated as axonal bulbs or reactive axonal swelling. In other axons, these dilations were observed not to evolve, taking the name of axonal varicosities. In humans, this swelling is visible from the first hour after the trauma, appearing as dilations of 10-20  $\mu\text{m}$ , which increase in size, reaching 24-48 hours at 50 $\mu\text{m}$  (Maxwell, 1996; Chamoun et al. 2010; Farkas, 2007, Singh et al., 2006).

#### **3.1.1. *Povlishock's theory***

It has been proposed by Povlishock and others that trauma induces compaction of NFs due to proteolysis of the sidearms resulting in impaired transport with subsequent swelling. Povlishock et al. initially claimed that the mechanical forces act directly on the cytoskeleton and neurofilaments, subsequent disturbance of axonal transport. It has been found that the most affected axons are disturbed by sodium homeostasis and intracellular calcium, elevating its levels which cause progressive focal dissolution in the subaxolemic alpha2-spectrin and subacute ankirin system and the passive accumulation of water contributing to the progression of swelling. Meanwhile swelling can coexist with retraction bulbs and progressive swelling. These include mitochondrial damage with cytoskeletal alteration and axonal transport, resulting in cell debris accumulated in the swelling. This process leads to secondary or delayed axotomy, which disconnects the two axonal

ends, forming the characteristic image of DAI, such as the retraction bulbs, largely characterized by Povlishock et al.

### *3.1.2. Adams's theory*

During this time, Adams et al., along with Bullock et al., were those who argued that secondary axotomy is the result of focal alterations of the permeability of the axolem, with the massive increase in the influx of Ca (Adams, 1982). Interestingly, however, dynamic stretch of axons in vitro did not induce axolemma impermeability to small proteins unless primary axotomy had occurred. In addition, with ion channel blockade, calcium did not freely diffuse into these axons, until primary axotomy occurred with a greater than 75% increase in length (Wolf, 1999). Taken together, these data suggest that changes in axolemmal permeability reflect the most extreme circumstance of traumatic axonal trauma that only occur in severe injury. These circumstances may include immediate disconnection of axons due to tissue tears or a physical wrenching of the tissue across obstructions such as the tentorium and foramen magnum (Genneralli, 1989).

### *3.1.3. Maxwell's theory*

Maxwell et al. revealed a correlation between the two quoted theories, showing that in the end the massive influx of Ca leads to the lysis of the cytoskeleton, especially at the level of myelinated axons. They started from the analysis of Ranvier nodes and paranodal regions rich in channels of Na, Ca channels, Na / Ca exchangers, Ca-ATP dependent pumps, the presence of mitochondria, microtubules and neurofilaments, and cytoskeleton rich in ankrines 3 and alpha 2-spectrin, susceptible to dependent calpain-Ca injury. Moderate to severe injuries operate at the level of Na channels voltage and mechanical dependencies, which have the ability to transform the mechanical stimulus into electrical stimulation through the phenomenon of mechanotransduction. This massive activation of the Na channels will lead to a massive flow of Ca via Ca / Na exchanger and the activation of the L and N voltage-dependent calcium channels along with depolarization, which should normally maintain longer potential of action at the axonal level. Calcium will activate numerous proteolytic enzymes, including dependent calpain-Ca, which will lead to the proteolysis of the H-port inactivation of the dependent Na-voltage channels. Thus, a vicious circle closes, with an influx of Na, which will increase the intracellular Ca influx (Zhang et al., 2009). These phenomena of alteration of axonal ion homeostasis represent the so-called primary axotomy throughout this period (up to one hour), with no morphological changes being visualized.

### *3.1.4. Other theories*

Another mechanism is also the Ca influx via mecano-dependent ISA calcium channels. The traumatic force transferred to the brain tissue will lead to the uncontrolled release of neurotransmitters from presynaptic vesicles, glutamate increasing about 50 times, leading to an excessive influx of calcium and sodium into the neurons, and at the level of glial cells by binding to N-methyl-D-aspartate receptors aspartic acid and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in an over-activation of the channels that are responsible with Na and Ca influx (Gong et al., 2007). Experimental studies have shown that blocking the physopathological chain at this level by administering Nimodipine would lead to a significant limitation of diffuse axonal lesions.

With the progression of the pathophysiology chain take place the axonal dilations with accumulation of mitochondria, neurofilaments and microtubes, with the secondary collapse of the axoloma and the myelin sheath, result lobed and disconnected axonal segments, visible in about 2 hours from the time of trauma. The proximal axonal segment continues to expand by accumulation of intracellular debris via anterograde axonal transport, and the distal one suffers Walerian degeneration. In the case of very severe injuries, the Ca-dependent destructive cascade is accelerated by the micropores formed in the axolem, initially at the Ranvier nodules. The consequences are the same as those mentioned above, with the transformation of anterograde

transport into retrograde and the accumulation of the beta-amyloid precursor protein with proximal axonal swelling, while the distal end fragments and suffers Wallerian degeneration (Michikawa et al., 2000; Hirsch-Reinshagen et al., 2005). It seems that in some axons, apoptosis occurs, in others necrosis. Pathophysiological pathways leading to necrosis are: 1) Enzyme activation CA dependednt eNOS and nNOS, producing nitric oxide and cell lysis, cell death and necrosis; 2) activation of Ca-dependent calpain, lysosomal lysis, cathepsin release, generalized proteolysis, cell death and necrosis; 3) reactive oxygen species at the mitochondrial level, membrane micropores, with increasing Ca influx, cell death, necrosis. Apoptosis is the consequence of the release of cytochrome C at the mitochondrial level, which activates the 1-apaf1 protein, which in turn activates caspase 9, acting on caspase 3, inducing apoptosis (Michikawa et al., 2000). Necrosis occurs in the absence of energy, whereas apoptosis is dependent on the presence of ATP, so functional mitochondria. In neuronal tissue with excessive mitochondrial destruction, cellular necrosis will occur. In programmed cell death no breakdown of the axoloma and inflammatory response was observed. It is suggested that apoptosis or necrosis is dictated by intracellular calcium levels; in neurons with relatively low calcium concentration occurs apoptosis, and vice versa leading to necrosis (Hirsch-Reinshagen, 2005).

#### **4. The diagnosis of DAI**

##### **4.1. Clinical diagnosis**

The clinical diagnosis of DAI is used to describe posttraumatic nosological scenery characterized by the presence of a prolonged coma condition immediately installed post-traumatically in the absence of space replacement processes or ischemic lesions. Depending on the duration of combative state Generalli and col. classified as minor, moderate and major DAIs, as follows: Minor DAI - Glasgow Scale Coma (GSC)  $\leq 8$ , for 6-24 hours with disappearance in case of presence of cerebral trauma within a few hours, moderate DAI: GSC  $\leq 8$ , with duration of days or weeks, with constant signs of cerebral cortex, disappearing after 24 hours, major DAI GSC  $\leq 8$ , lasting weeks to months, with accentuated sympathetic tone (HTA, generalized hyperstimulation, hyperthermia).

##### **4.2. Biochemical diagnosis**

Two biomarkers have been identified that detect the necrosis / apoptosis ratio. These are SBDP150 and 145, resulting from calpain segregation, which are the subjects of necrosis and SBDP120, produced by segregation of caspase 3, correlated with programmed cell death (Wahrle et al., 2004). Taking into account the pathophysiological mechanisms presented up to this point, the therapeutic targets are directed towards the restoration of ionic homeostasis, mitochondrial protection, proteolysis inhibition and cytoskeletal stabilization.

Tau protein is an intracellular microtubule-associated protein highly enriched in axons which levels are connected with related to axonal disruption.

Selectins seems to have a very high predictive value in coma then neurofilaments, presenting more coherent predictive patterns (Vaagenes, 1994).

##### **4.3. Histological diagnosis**

DAI in humans is characterized histologically by widespread damage to the axons of the brainstem, parasagittal white matter of the cerebral cortex, corpus callosum, and the gray-white matter junctions of the cerebral cortex. The deformation of the brain due to plastic flow of the neural structures associated with DAI explains the micropathological findings. Photomicrographs captured two major forms of traumatic axonal pathology revealed by immunoreactivity of accumulating neurofilament protein: first ones are elongated varicose swellings of damaged axons with swollen regions encompassing several hundred micrometers, but no clearly identifiable region of disconnection; second ones are axonal bulbs that demonstrate the characteristic discrete region of

swelling at the terminal stump of disconnected axons. Remarkably, these axonal bulbs are preceded by axonal shafts of relatively normal diameters (bar = 50 $\mu$ m) (Smith, 2003).

The microscopic lesions are highlighted by axonal retraction bulbs. The retraction bulbs are visible at least 4-12 hours after craniocerebral trauma, in arginine impregnation and after one hour by immuno-histochemistry techniques that highlight the presence of the beta-amyloid precursor protein at the level of the affected axons, this becoming the main goal of DAI diagnosis. Antibodies that identify the amino-terminal domain of this protein are administered. Experimental studies revealed on sham animal's different axonal profiles as granular or more elongated, fusiform swellings at both animals with a singular TBI and animals with repetitive TBI, also. APP immunoreactive neurons are only present in the repetitive TBI group, and occasionally observed in the cortex underneath the impact site.

Usual and special staining, as hematoxylin eosin and Luxol fast blue/cresyl violet not always reveal evidence of focal structural pathology of DAI. (Mouzon et al., 2012).

### **5. Genetic predispositions**

Recent studies highlight an inter-human variability of DAI tolerance, experimentally finding a correlation between ApoE epsilon4 allele and notable severity of DAI. In the nervous system, ApoE plays no role in cholesterol homeostasis, but also in synaptogenesis, neuronal plasticity, and glial cell growth. ApoE is produced in the liver, but has been shown not to have the same origin as in cerebrospinal fluid, and it cannot cross the blood-brain barrier. The latter occurs at astrocytic, microglial and neuronal level. Under normal circumstances, astrocyte produces twice the amount of cholesterol than the neuron, so it will exhibit higher levels of ApoE. The transport of ApoE cholesterol involves interaction with the ATP Binding Cassette Transporter A1 (ABCA1), which initiates the intracellular cholesterol efflux to the apoE acceptor protein (Wahrle et al., 2004; Weers et al., 2003). In ABCA1 murine models, apoE expression decreased by 70-80% and was associated with decreased cholesterol efflux and increased amyloid level (Morrow et al., 2000).

The N-terminal end of apoE4 showed a significant decrease in resistance to chemical and caloric denaturation, while ApoE2 was more resistant to pH acid. Proteolysis of apoE, with the accumulation of cytosol-derived fragments, alters the cytoskeleton and disturbs the mitochondrial energy balance (Thomas et al., 2003). Studies published in 2014 by Narayan Yoganandan in which positive and negative ApoE4 murine models were subjected to the same angular acceleration resulted in the production of axonal lesions gr1 at an acceleration of 1200 rad / sec<sup>2</sup> for ApoE4 negative and 900 rad / sec<sup>2</sup> for the ApoE4 positive, axonal lesions gr2 at 1500 rad / sec<sup>2</sup> for the first category, respectively 1100 rad / sec<sup>2</sup> for the second and axonal lesions gr 3 at a angular acceleration of 1700 rad / sec<sup>2</sup> for negative ApoE4 and 1300 rad / sec<sup>2</sup> for ApoE4 positive (Weers et al., 2003).

Smith et al. describe postmortem findings on a series of 239 cases of violent death through craniocerebral trauma. They found a relationship between the ApoE -  $\epsilon$ 4 allele and the severity of ischemic brain contusions and lesions, but not between its presence and other pathological changes after TBI, such as the extension of diffuse axonal lesions.

The mechanisms involved in increasing susceptibility to the severity of contusions in the apoE4 positive population are multiple, proposing the following hypotheses: ApoE4 acts by increasing neuronal sensitivity to the consequences of neurotoxic agents such as amyloid  $\beta$ , traumatic lesions, oxidative stress, ischemia and inflammation, or by the effects prior to the TBI, on vascular wall pathology such as atherosclerosis, amyloid angiopathy or blood clotting mechanisms. (Thomas et al., 2003).

### **6. Conclusions**

The pathological mechanism underlying DAI involves specific biochemical pathways and locations of injury may, in part, explain the severity of prognostic.

Diffuse axonal injury represents a new challenge for medical staff, still being an unknown entity, which causes a serious impairment of the brain function. Much of the attention so far has been paid to the definition of DAI and the criteria for its pathological diagnosis. It has been discussed from the perspective of biochemical importance and also the standpoint of certain criteria for the pathological diagnosis of DAI. However, since the time when DAI was initially described, there have been few discussions about the physiopathological mechanism. This paper is an attempt to address this issue.

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