folia medica

Folia Medica 63(2):163-70
DOI: 10.3897/folmed.63.e53709

Review

# Contemporary Insight into Diffuse Axonal Injury

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**Received:** 27 Apr 2020 ♦ **Accepted:** 12 May 2020 ♦ **Published:** 30 Apr 2021

**Citation:** Angelova P, Kehayov I, Davarski A, Kitov B. Contemporary insight into diffuse axonal injury. Folia Med (Plovdiv) 2021;63(2):163-70. doi: 10.3897/folmed.63.e53709.

## Abstract

Diffuse axonal injury (DAI) is present in approximately 50% of the cases with severe traumatic brain injury. It is one of the leading causes of morbidity and mortality among children and young individuals worldwide. Generally, DAI occurs as a result of high-velocity accidents. Typically, it presents with loss of consciousness for at least 6 hours and neurological deficit dependent on the brain area that is affected by the injury. The final diagnosis is confirmed by neuroimaging studies such as computed tomography and magnetic resonance imaging. According to the injured brain site, DAI is classified into three grades: Grade I–DAI with axonal lesions in the cerebral hemispheres; Grade II–DAI with focal axonal lesions in the corpus callosum; Grade III–DAI with focal or multiple axonal lesions in the brainstem. Each of the three grades is associated with different outcome. Due to the high disability and mortality rate, DAI represents an important medical, personal and social problem. The aim of the current review is to address the unsolved issues connected with the pathogenesis, diagnostics, treatment and outcome of the diffuse axonal injury.

## Keywords

CT, diffuse axonal injury, MRI, traumatic brain injury, treatment

## INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality among children and young individuals worldwide.[1] It commonly results from high-velocity vehicle accidents, falls, assaults and sport injuries.[2,3] A subtype of TBI is the diffuse axonal injury (DAI), which represents axonal damage that occurs at the transition between the gray and white brain matter due to a sudden acceleration-deceleration or rotation of the head and brain. These mechanisms cause stretching, torsion and multiple ruptures of the axons that trigger a series of biochemical events leading to disruption of neural connections in the brainstem, corpus callosum, the parasagittal white brain matter and the cerebellum.[4-7] The diagnosis of DAI should be supported by the data obtained from the patient's clinical status immediately after the trauma and the neuroimaging studies.[8]

The aim of the current paper is to provide contemporary analysis of the different clinical characteristics, the diagnostic and treatment methods as well as the outcome of DAI, based on profound literature review.

## EVOLUTION OF THE DAI CONCEPT

Historically, the knowledge about DAI as a separate nosology evolves through several periods. The first period began in 1956, when Strich studied autopsies from 5 patients with severe closed brain trauma and connects the degene-

ration of the diffuse white matter with a physical damage to nerve fibers.[9] The second period began in 1961, when Strich again found that the same shearing forces of the rotational acceleration of head that lead to TBI, also caused avulsion of nerve fibers and evoked diffuse degeneration of the affected cerebral hemisphere and the brainstem.[10] The third period began in the 1980s, when Adams and Gennerelli thoroughly studied the mechanisms of occurrence of DAI and made prominent achievements, which provided an opportunity for an accurate definition and classification of this type of traumatic brain injury.[11]

## EPIDEMIOLOGY

The incidence of DAI cannot be accurately calculated due to its frequent combination with other traumatic intracranial pathologies.[12] DAI is diagnosed in about 40-50% of the cases with severe TBI and lead to fatal outcome in about one-third of them.[5,13] Thus, DAI becomes the third leading cause of disability and mortality worldwide.[1] Some authors consider that this subtype of brain damage affects the majority of traumatic patients who suffer loss of consciousness after vehicle accidents, i.e. in moderate and severe TBI.[14-16] DAI is more common in men, as the male-to-female ratio reaches 80%:20%.[13] Most of the patients fall into class II and class III of the histopathological classification of DAI, corresponding to poor outcome.[1,17]

## ETIOLOGY

In approximately 50% of the cases, DAI occurs as a result of high-velocity vehicle accidents, falls and assaults.[5,14,15] According to Moe et al., the same mechanisms of damage are observed in low-velocity traumatic accidents like sport injuries, falls from stairs or standing height, i.e. can also lead to DAI.[19]

## PATHOGENESIS

DAI is commonly associated with a sudden mechanism of acceleration-deceleration and/or rotation of the head and brain.[8,20] Generally, the damage of the shearing forces caused by the rotational mechanism occur along the axis of the rostral part of the brainstem and the transitional zones between the gray and white brain matter which have different density. DAI affects typical brain areas such as the frontal and temporal lobes, corpus callosum, cerebellum and the brainstem.[1,8] Similar forces that cause DAI can also disrupt superficial brain vessels which results in traumatic subarachnoid or intraventricular hemorrhage. This process is indicative of severe mechanism of damage of the traumatic agent. The presence of blood in the ventricles is associated with DAI located in corpus callosum or the brainstem and is clinically associated with poor outcome.[21]

## PATHOPHYSIOLOGY

The term DAI is a misnomer as it is not a diffuse injury to the whole brain, rather it is mostly in discrete areas of the brain.[5] The profound understanding of the complex pathophysiological and biochemical processes that accompany DAI is of great importance for its diagnosis, proper management and outcome. The mechanism of injury leads to primary and secondary axonal damage.[7] The primary axonal damage is related to the direct impact of the shearing forces that cause disruption, retraction, edema of the axons, finally resulting in the formation of the so-called "retraction bulbs". These cellular alterations impede the normal transport of proteins and electrolytes through the membrane of the neuron body resulting in secondary axonal damage. Subsequently, the axonal membrane permeability is compromised and the intra-axonal calcium concentration is increased. Thus, it triggers calpain-mediated necrosis and caspase-mediated apoptosis which disrupt the axonal cytoskeleton.[22] Secondary axonal injury causes mostly mitochondrial damage, including swelling and breakage of the mitochondrial crest and membrane. This leads to calcium influx and changes in the permeability of the mitochondrial membrane.[23] The created imbalance of the transport function of the mitochondrial membrane disrupts the cell metabolism. The combination of these events that finally lead to cellular death is associated with high mortality poor outcome of DAI.[10,16] Apart from the axonal damage, DAI is accompanied by glial reaction that also plays important role in the progression and prognosis of the disease.[5] It is caused by the processing of damaged brain tissue at the site of injury which forms multiple glial scars which, in turn, leads to the secretion of wide range of growth factors as an attempt to limit neuronal death. However, glial cells become activated further, to the point of over-reactivation and continuously release inflammatory factors, such as TNF$\alpha$. High concentrations of TNF$\alpha$ impair the ability of microglia to eliminate glutamate, and this causes excitatory toxicity and injures neurons. Over-reactivation of glial cells releases proinflammatory substances which elicit inflammatory responses, cause oxidative stress in the brain tissue, and directly or indirectly induce neuronal death. It remains unclear if the activation of glial cells promotes injury or repair.[10,16] Severe primary brain damage following TBI is often lethal, and long-term survivors usually experience severe debilitating neurological deficit. Some studies suggest that increased microglial activity may be present not only during the acute phase of the trauma, but persist long after discharge. Positron-emission tomography (PET) imaging demonstrated increased metabolic brain tissue changes in survivors up to 17 years post-TBI, suggesting persistent microglial activation.[24] On the other hand, hypothalamic-pituitary-adrenal axis dysfunction accompanies 50% of the cases after severe traumatic brain injury, including DAI.[25] Patients with critical DAI-related corticosteroid insufficiency are prone to poor outcome.[25,26]

Intraventricular hemorrhage (IVH) on initial scanning is associated with axonal lesions in the corpus callosum (CC). CC connects the left and right cerebral hemispheres and represents the largest brain commissure maintaining cognitive function, working memory, bimanual coordination and motor function. It is one of the most vulnerable neural structures in the brain susceptible to injury and elevated intracranial pressure (ICP) due to its midline location **(Fig. 1)**.[27,28]

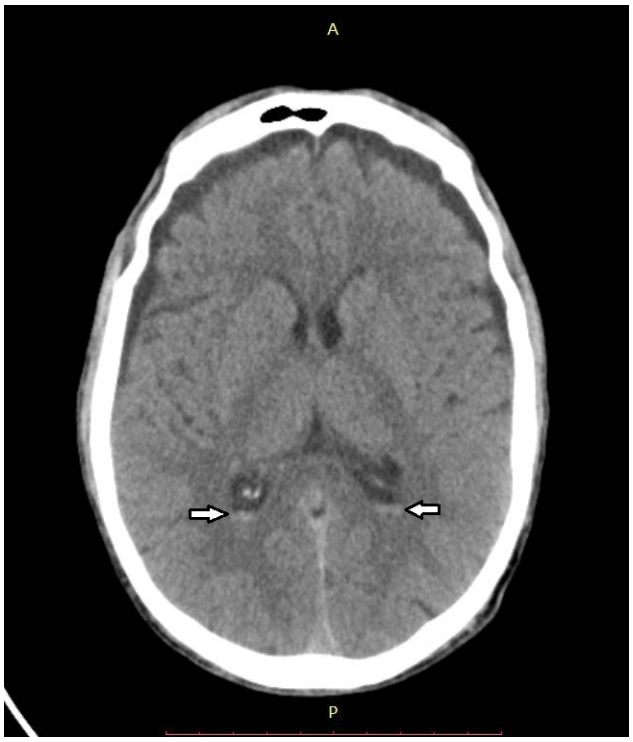


**Figure 1.** CT of a 47-year-old patient with severe TBI with intraventricular hemorrhage (white arrows) after a fall from height.

Hamdeh et al. suggest that increased ICP occurs in approximately one-third of patients with severe TBI accompanied by DAI.[29] It is also often associated with interhemispheric or perimesencephalic traumatic subarachnoid hemorrhage due to rupture of brain vessels following the same shearing mechanism that underlies severe diffuse axonal injury **(Fig. 2)**.[21]

## CLINICAL PRESENTATION

DAI presents with a wide range of consciousness disorders, varying from full alertness to deep coma. Most of the patients with DAI fall into the group of severe TBI that are scored less than 8 points on Glasgow Coma Scale (GCS), provided that the comatose condition should last for at least 6 hours after trauma.[12] This clinical manifestation is not an absolute diagnostic criterion for DAI. There is little evidence supporting the efficacy of the 6-hour loss-of-consciousness criterion to distinguish between concussion and DAI, considering that axonal lesions have also been detected in concussion patients with loss of consciousness less than 6 hours.[8] Following mild TBI with diffuse axonal lesions, autonomic nervous system dysfunction is often evident and accounts for many of the symptoms commonly seen in concussed patients such as dizziness, headache, vomiting, palpitations, blood pressure variations, sweating and other vegetative symptoms.[30] Hypothalamic-pituitary-adrenal axis dysfunction with corticosteroid deficiency is observed in 52.2% of the patients with severe TBI and 22.5% of the patients with moderate TBI accompanied by DAI.[25] Corticosteroid deficiency is related to an increased risk of gastrointestinal bleeding, hospital-related pneumonias and increased mortality within 28 days from the onset of the trauma.[25] DAI may lead to permanent debilitating behavioral changes and cognitive impairments.[31]

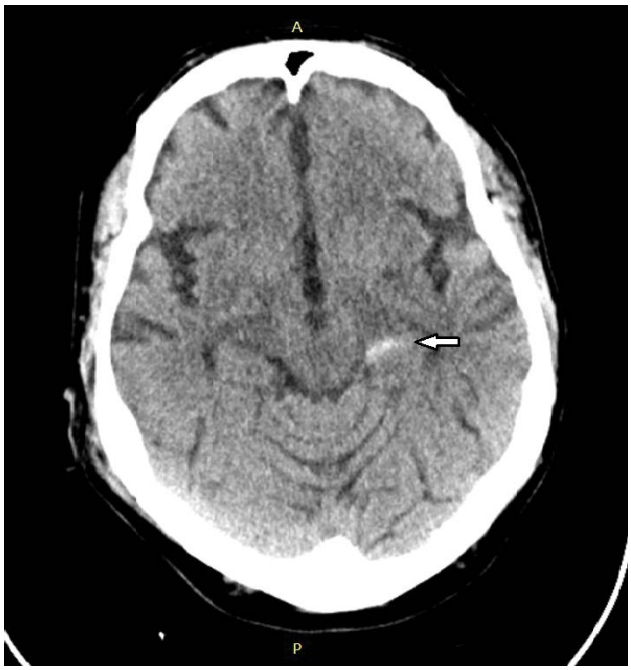


**Figure 2.** CT of a 30- year-old patient with severe TBI with traumatic perimesencephalic subarachnoid hemorrhage in cisterna ambiens (white arrow) after a road traffic accident.

## CLASSIFICATION

As a part of TBI, DAI is divided into mild, moderate and severe, depending on the score on the GCS. Score between 13 and 15 points indicates mild injury; 9 and 12 points – moderate injury; less than 8 points – severe injury.[14] The definitive diagnosis is established postmortem based on the results from the brain autopsy. According to the histopathological findings, Adams et al. classified DAI into three grades: Grade I – DAI with axonal lesions in the cerebral hemispheres; Grade II – DAI with focal axonal lesions in the corpus callosum; Grade III – DAI with focal or multiple

axonal lesions in the brainstem. Each of the three grades is associated with different outcome.[32] Abu Hamdeh et al. suggested extended classification system with additional Grade IV – substantia nigra or tegmentum of the midbrain lesions.[33] Another classification of DAI is based on the MRI findings: Grade I – lesions in the hemispheric and/or cerebellar white matter; Grade II – lesions in the corpus callosum; and Grade III – lesions in the brainstem in areas typical for DAI.[19,34]

## DIAGNOSTICS

The diagnosis of DAI is based on the data from the clinical examination and contemporary neuroimaging studies obtained immediately after the traumatic event. DAI is a clinical diagnosis that should be suspected in patients who have suffered from sudden acceleration-deceleration or rotational TBI. The clinical symptoms may vary from mild to severe neurological deficit but, usually, these are patients with severe TBI with a score of less than 8 points on the GCS with duration of at least 6 hours.[12] Furthermore, the diagnosis is confirmed by means of neuroimaging in order to exclude concomitant traumatic intracranial injuries. The presence of DAI is an important prognostic factor that influences recovery which necessitates early and accurate diagnosis.[35] The CT examination is still the gold standard for imaging of DAI in terms of emergency. The CT scan may be negative or it can demonstrate the typical findings of DAI that include multiple hemorrhagic lesions located at the gray-white matter interface with diameter of 5 to 15 mm **(Figs 3, 4)**.[20]

The major disadvantage of the CT is its limited sensitivity to detect non-hemorrhagic lesions or microscopic "needle-like" hemorrhages. The typical DAI lesions, such as those in the corpus callosum, can often be omitted on regular CT scanning. Therefore, the final diagnosis in these cases is supported by other modern neuroimaging methods such as MRI, DTI-MRI, MRI spectroscopy, PET and single-photon emission computed tomography (SPECT).[10,16,20] MRI is the recommended tool for imaging of DAI but its availability is limited compared to the CT, especially in the emergency setting. According to Gentry et al., MRI can demonstrate diffuse, small, focal abnormalities limited to white-matter tracts. When present they tend to be multiple and non-hemorrhagic. Hemorrhage within diffuse axonal lesions occurs more often in those portions of the white matter with the greatest vascularity such as internal capsule and lobar white matter. Peripheral lesions tended to be smaller than central ones. DAI lesions are typically found near the corticomedullary interface of the lobar white matter or in the large white-matter fiber bundles (corona radiata, corpus callosum, internal capsule).[34] Therefore, it may be difficult to identify DAI using only imaging diagnostic methods in the acute stage of TBI. There are tests for detecting serum biomarkers, spe-

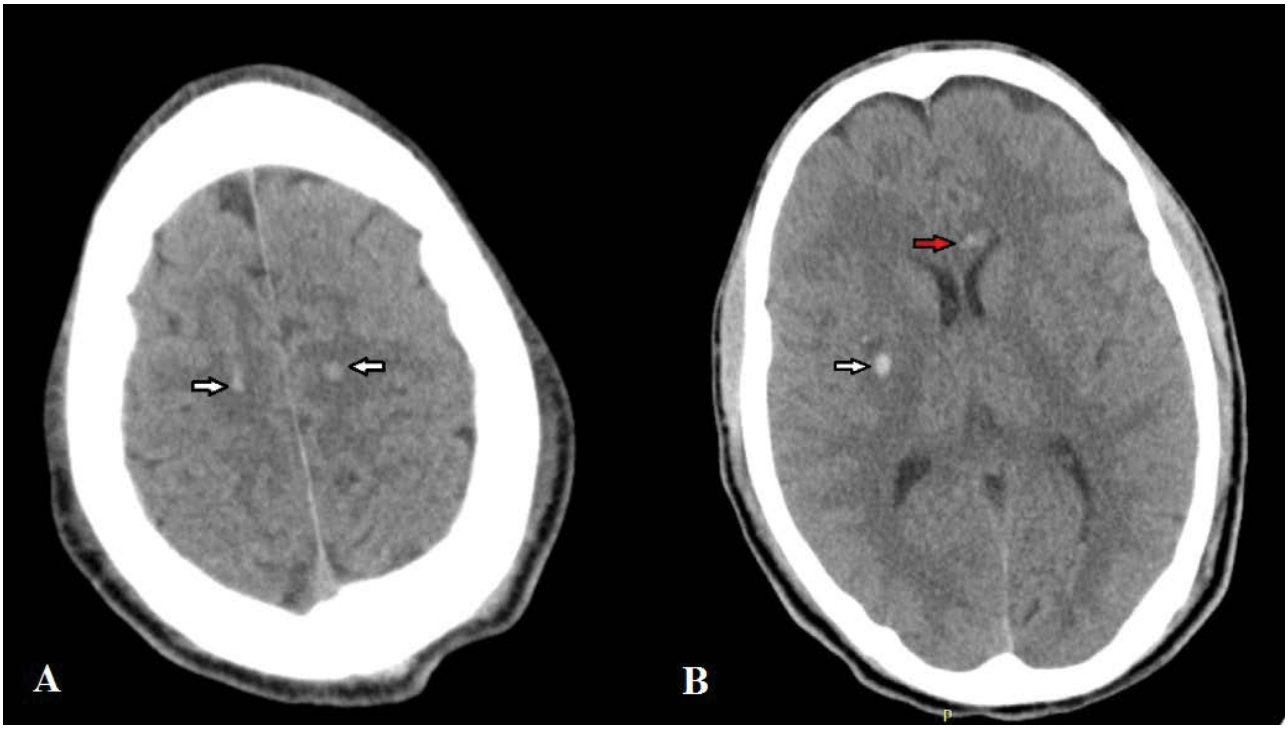


**Figure 3.** CT of a 22-year-old patient with severe TBI and clinical manifestation of DAI after a road traffic accident: **A):** DAI Grade I with bilateral hemispheric hemorrhagic lesions (white arrows); **B)**: DAI Grade II with basal ganglia (white arrow) and corpus callosum hemorrhagic lesions (red arrow).

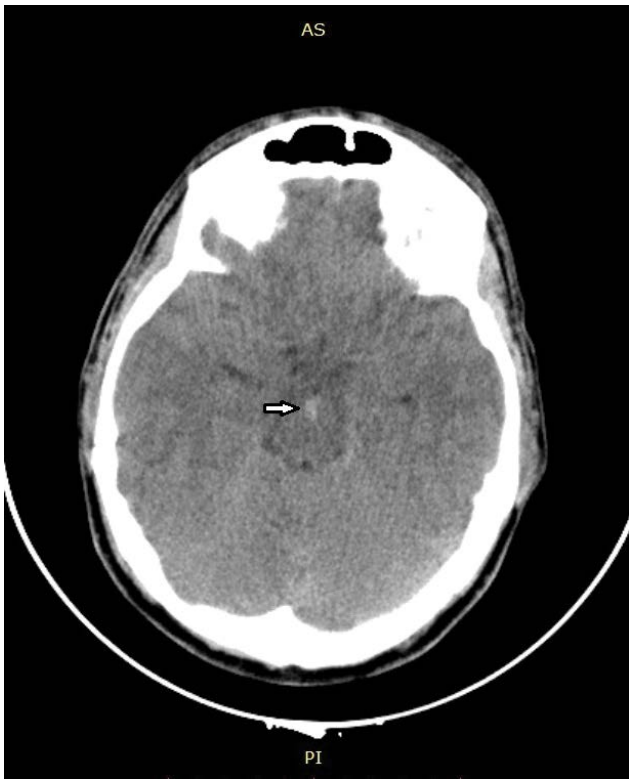


**Figure 4.** CT of a 17-year-old patient with severe TBI and clinical manifestation of DAI – Grade III with hemorrhagic lesions in the brainstem (white arrow) after an assault.

cific for the early phase of DAI. They are normally found in the axons and are released in increased concentration in the serum as a result of axonal damage. Some of these biomarkers are structural proteins like fibrin breakdown products, neurofilaments, tau protein, and amyloid protein. The fact that these biomarkers are accepted to arise directly from axons suggests that their elevation in TBI is likely to be a reflection of the axonal component of TBI pathology and thus a reference to DAI. When searching for DAI serum biomarkers, there is an advantage of combining several different biomarkers to optimize prediction models rather than relying on a single biomarker.[22,36]

## MANAGEMENT AND REHABILITATION

The main contributing factor to secondary injury is the neuro-inflammatory process caused by the damaged axons and glial cells that leads to pro-inflammatory cytokine release and oxidative stress. It is fundamental to initiate treatment with anti-inflammatory and neuroprotective drugs immediately after TBI, if possible within 4 hours post-injury, to achieve optimal outcome. These drugs inhibit the inflammation, necrosis and neuronal apoptosis.[37] Another factor that worsens the neurological status and outcome is the elevated intracranial pressure (ICP) due to posttraumatic brain edema. This requires the use of hyperosmolar agents (mannitol, hypertonic sodium solution) and steroids. There are also selected non-pharmacological therapies to reduce ICP that are employed in the acute trauma phase such as elevating the head in bed to 30 degrees, brief episodes of hyperventilation to maintain $pCO_2$ within 28-33 mm Hg aiming vasoconstriction and reduction of cerebral edema, as well as surgical CSF diversion.[38] Decompressive craniectomy may also be considered for severe cases with extreme elevation of ICP, precipitating imminent death.[39] Primary and secondary injury after TBI leads to both local and systemic reactions. The disease makes patients susceptible to acute catabolic state associated with extreme weight loss, negative nitrogen balance, dysglycemia, and cerebral metabolic dysfunction. This is why adequate and balanced nutrition therapy is a cornerstone in the management of patients suffering from severe TBI.[40] In the long term, along with pharmacological and non-pharmacological management of TBI, effective, individually targeted, continuous rehabilitation programs should also be employed. This therapy aims to recover impaired cognitive functions and to restore the ability for independent life.[41] This necessitates the use of established protocols for individual cognitive, behavioral, emotional and social rehabilitation.[41,42]

## PROGNOSIS AND OUTCOME

Diffuse axonal injuries cause severe physical, cognitive and behavioral changes, leading to reduced quality of life of patients and their relatives. These changes can persist long after the acute phase of the TBI and represent enormous medical, personal and social burden.[12] The presence of DAI in patients with TBI worsens the disease outcome.[43] The latter can be assessed by the widely used Extended Glasgow Outcome Scale (GOS-E). This scale has eight categories and allows adequate long-term follow-up of traumatic patients. Vieira et al. reported that 30% of the patients had died as a consequence of the trauma or its complications at six months following DAI. Among patients who survived, almost 90% achieved favourable outcome with independent life assessed by the GOS-E, whereas 10% were dependent and required assistance.[12] According to the DAI classification of Adams et al., the outcome was better in patients in Grade I and Grade II compared to patients in Grade III.[44] Apart from the localization of axonal injuries, the presence of hemorrhagic areas, visible on CT is also evaluated. The presence of hemorrhagic DAI on CT was not associated with worse short-term and long-term outcome compared to non-hemorrhagic DAI on CT. Paradoxically, hemorrhagic DAI was independently associated with increased survival and improved 1-year outcomes, despite high injury severity and prolonged intensive care unit stay.[45] Other factors linked to poorer outcome were low GCS score immediately after the traumatic

accident, six or more hemorrhagic axonal lesions visible on CT, concurrent intracranial traumatic injuries, hyperglycemia and symptoms of dysautonomia.[46] TBI can trigger progressive neurodegeneration and dementia. The incidence of post-traumatic dementia is observed in 5% of the cases. The risk for dementia in mild TBI is low but it substantially increases in moderate and severe TBI cases with negative impact on quality of life.[47]

## CONCLUSIONS

DAI commonly leads to permanent debilitating neurological and somatic deficit, even death. Therefore, it represents a therapeutic challenge to neurotraumatology and intensive care. It is accompanied by substantial social and economic impact on patients, their families and communities. The limited availability of some expensive and complex neuroimaging modalities in the emergency setting turns DAI into a diagnostic challenge as well. The CT remains the most available and widely used study for immediate imaging diagnostics. Its major disadvantage is the low sensitivity to detect some typical morphological changes in the brain and commonly relies on indirect criteria. Currently, there is no unified and widely accepted protocol for the correct diagnosis and management of DAI

DAI is frequently associated with extensive damage to other organs and systems in the body. The presence of polytrauma prolongs hospital stay and substantially increases the risk for complications which worsens disease outcome and prognosis. Generally, DAI requires multidisciplinary approach to provide adequate conservative, intensive, surgical and rehabilitation therapeutic support depending on the stage of the disease. The selection of appropriate treatment and rehabilitation care increases the percentage of survivors who cope with the disease burden and manage to return to normal functioning and life.

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# Современное понимание диффузного аксонального повреждения

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**Дата получения:** 27 апреля 2020 ♦ **Дата приемки:** 12 мая 2020 ♦ **Дата публикации:** 30 апреля 2021

**Образец цитирования:** Angelova P, Kehayov I, Davarski A, Kitov B. Contemporary insight into diffuse axonal injury. Folia Med (Plovdiv) 2021;63(2):163-70. doi: 10.3897/folmed.63.e53709.

## Резюме

Диффузное аксональное повреждение (ДАП) присутствует примерно в 50% случаев тяжёлой черепно-мозговой травмы. Это одна из основных причин заболеваемости и смертности среди детей и подростков во всём мире. Как правило, ДАП возникает в результате дорожно-транспортных происшествий на большой скорости. Обычно оно проявляется потерей сознания на срок не менее 6 часов и неврологическим дефицитом в зависимости от области мозга, пострадавшей в результате происшествия. Окончательный диагноз подтверждается методами нейровизуализации, такими как компьютерная томография и магнитно-резонансная томография. По месту повреждения ДАП подразделяется на три степени: 1 степень – ДАП с поражением аксонов полушарий головного мозга; 2 степень – ДАП с очаговым поражением аксонов мозолистого тела; 3 степень – ДАП с очаговыми или множественными поражениями аксонов в стволе головного мозга. Каждая из этих степеней ассоциируется с разным исходом.

Из-за высокой частоты травм и смертей ДАП представляет собой важную медицинскую, личную и социальную проблему. Целью этого обзора является рассмотрение нерешённых вопросов, связанных с патогенезом, диагностикой, лечением и исходом диффузного аксонального повреждения.

## Ключевые слова

КТ, диффузное аксональное повреждение, МРТ, черепно-мозговая травма, лечение