Psychiatr. Pol. 2021; 55(1): 171–180
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/112404

Diffuse axonal injury – an interdisciplinary problem. Current knowledge and two case reports

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Summary

Diffuse axonal injury (DAI) is a microscopic damage of axons in the brain. Its occurrence results from head trauma with acceleration or deceleration. This article presents current knowledge about DAI and two cases of patients who experienced DAI as a consequence of a traffic accident. A 26 years old man was brought to hospital after traffic accident during which his vehicle had overturned. Computed tomography (CT) showed features of brain edema and disseminated small petechiae. Psychiatric consultation on ninth day of hospitalization showed memory deficits presenting as retrograde and anterograde amnesia, attention deficits and lack of criticism in regard to his condition. A 38 years old woman who was hit by a car while cycling was admitted to hospital. CT scan showed features of brain edema, subarachnoid hemorrhage and multiple fractures. On the tenth day of hospitalization the patient was confused, did not remember new information, her psychomotor drive was increased and she presented lack of criticism in regard to her condition. While suspecting DAI we should be vigilant, particularly in cases of patients hospitalized due to traffic accidents with behavioral problems, features of amnestic syndrome and without significant focal neurological symptoms.

Key words: diffuse axonal injury, memory disorders, craniocerebral trauma

Introduction

Each day in Poland there is almost ninety traffic accidents and only in 2017 they resulted in injuries of 32,760 people [1]. Communication events often lead to head trauma and they are the second cause of traumatic brain injury (TBI) following falls

The publication was prepared under the project financed from the funds granted by the Ministry of Science and Higher Education in the "Regional Initiative of Excellence" program for the years 2019–2022, project number 016/RID/2018/19, the amount of funding 11,998, 121.30 PLN

[2]. Patients may present small head injuries, but such trauma often leads to nervous tissue damage, which is a strong negative prognostic factor for survival and long-term patient functioning. Among head injuries related to brain, the first place is occupied by diffuse axonal injury (DAI), which, according to some authors, develops in each case of head trauma related to acceleration or deceleration with loss of consciousness [3, 4]. Due to low sensitivity of CT in its detection, DAI often remains unrecognized. This is particularly important due to its mortality which is estimated to stand at nearly 62% [3]. Diagnostic difficulties, lack of effective therapeutic methods, co-occurrence of other trauma and lack of awareness among medical staff account for negative prognosis [5].

DAI and its mechanism

DAI is defined as microscopic lesions of axons of the brain pathways, corpus callosum and brainstem. Clinically it is diagnosed in cases of comma lasting over 6 hours as a result of head trauma after ruling out causes such as cerebral edema or stroke. Its occurrence poses the most important prognostic factor for mortality, disability or persistent vegetative state following head trauma. Due to the mechanism of the injury, which allows for development of pathologic lesions in various locations, DAI can have heterogeneous clinical presentation. It may lead to development of physical, cognitive or personality changes influencing future social functioning, productivity and quality of life of patients [6].

The mechanism of DAI is related to sudden change of acceleration during which inertia forces are developed between the tissues of various density, such as grey and white matter. As a consequence, the surfaces located at the borders of these substances and small blood vessels are most likely to be injured. The lesions of white matter axons result in dysfunction of axonal transport, swelling of nerve fibers and in cases of axotomy – sudden degeneration of the distal part of severed axon resulting from activation of specific cell death pathway, called Wallerian degeneration [7–9].

Sudden extension of an axon may lead to a complete disruption of axon continuity (axotomy) or a partial injury resulting from significant tearing and extending forces. As a consequence, pathological lesions resulting from DAI can be divided into primary and secondary ones. The primary lesions are characterized with disconnection and change of shape of severed nerve fibers. Microscopic swellings of the distal part of axons are called axon retraction balls or retraction bulbs and may result from abnormal axonal transport and deposition of amyloid precursor protein (APP). The secondary lesions derive from many interrelated pathologies associated with axon dysfunction and regenerative attempts. Changes to the axolemma permeability with a progres-

sive influx of calcium ions and change of axonal transport direction to retrograde are considered one of them [3, 8].

Diagnostics

Computed tomography (CT) remains the first choice imaging test for head injuries. Various sources estimate its sensitivity in DAI detection for merely 20–50%. Among patients with mild head injuries whose CT was negative, up to 30% test positive in Magnetic Resonance Imaging (MRI). Although MRI remains less available and is not routinely performed, sensitivity of its distinct sequences in DAI detection reaches nearly 97% [4]. Its use is particularly indicated when normal CT result does not correlate with patient's state. It is recommended to perform T2-weighted imaging 3–7 days after the trauma, when characteristic multifocal lesions in the corpus callosum can be observed [10]. Among MRI sequences, the highest sensitivity have FLAIR (Fluid Attenuation Inversion Recovery), DWI (Diffusion-weighted Imaging), SWI (Susceptibility-weighted Imaging), and especially GRE (Gradient-recalled Echo), which detects presence of hemosiderin – hemoglobin metabolite, in the lesion location [3, 11, 12]. SPECT (Single-photon Emission Computed Tomography) and PET (Positron Emission Tomography) can also be used for DAI [13].

The search for effective DAI diagnostics is also conducted on the blood tests level. Ljungqvist et al. [14] reported that neurofilament light chain blood concentrations increase up to 30-fold as a result of brain trauma. Low awareness and availability of such tests in diagnostic laboratories remain an obstacle in taking advantage of this marker. Other markers evaluated in relation to their usefulness in head trauma diagnostics are: alfa-II-spectrin, GFAP, tau protein, amyloid-β, S100-β, and NSE [3, 7].

The psychiatric examination and neuropsychological evaluation prove to be effective diagnostic tools. Detecting cognitive impairment with HRB (Halstead-Reitan Neuropsychological Battery), LNNP (Luria-Nebraska Neuropsychological Battery) or GOAT (Galvestone Orientation and Amnesia Test) protocols may hint accurate diagnosis even before ordering imaging test. The repetitive neuropsychological evaluation bears significance in relation to prognosis, despite not being sufficient for final diagnosis of DAI [3, 15].

Clinical presentation and prognosis

DAI can have very heterogeneous clinical presentation due to various possible locations of lesions. It is necessary to differentiate DAI with fat embolism especially in presence of multiple trauma and bone fractions. Loss of consciousness may

sometimes be significantly delayed, which is associated with secondary pathology, e.g., glutaminergic toxicity or cysteine proteases activation followed by axonal swelling [10].

From the psychiatrists point of view head trauma is mainly associated with memory deficits. Post-traumatic anterograde amnesia may last from few minutes up to a couple of months and usually involves circumstances of the accident. Head trauma may also cause long-lasting memory impairment, which is especially noticeable in short-term and prospective memory. This is associated with dysfunctions in memorizing and storing information [16, 17].

The duration of anterograde amnesia directly correlates with duration of post-traumatic comma and poses the most important risk factor for further intellectual, cognitive or executive functions of patients [15]. Importantly, memory deficits may be the first indication of DAI regardless of the Glasgow Coma Scale (GCS) score, which can remain normal. Hence, the early implementation of neuropsychological evaluation may significantly influence the therapeutic process in head trauma patients [3, 18]. Post-traumatic amnesia following head trauma often remains undetected in the ERs, especially when the GCS score is high. However, with time the occurrence of amnesia becomes the most important factor influencing distant treatment results [19]. Sole amnestic disorder in the course of head trauma bears dual importance for further development of psychiatric disorders in patients. On the one hand its occurrence favors further cognitive impairment and secondarily – changes in patient's personality [20]. On the other hand its short duration (under 1 hour) is related to increased risk of developing PTSD (Post-traumatic stress disorder) [21].

Treatment

There are no standards of treatment specific for DAI so far. The attempts of implementing psychostimulants (amantadine, metylphenidate or modafinil) did not influence duration of amnestic disorders or patients' prognosis [15]. Studies on animals reported neuroprotective effect of combining tacrolimus with therapeutic hypothermia. There are also some case reports on the use of substances which decrease permeability of cellular membranes and on the use of deep brain stimulation (DBS) [17, 22, 23].

Case 1

A 26 years old male was brought to the hospital after a traffic accident during which the vehicle had overturned. The initial physical examination revealed superficial abrasions on his face and a blunt injury of the left parietal region. Blood tests detected ethanol (1.84 per mil) and ecstasy (MDMA), other biochemical results were normal. No organ injuries were detected with polytrauma CT protocol.

Head CT without contrast revealed overall brain edema and minor blotches in the left frontal and temporal regions indicating DAI. The ventricular system was visible, without any dilations or compressions. There were no fractures of facial skeleton or neurocranium. Intracranial fluid spaces and encephalon were normal.

During the ER stay the patient remained without logical contact. Due to anxiety and agitation he was sedated with midazolam. The patient scored 9 in GCS: he opened his eyes in response to pain (E2), he performed purposeful movements towards the painful location (M5), but his speech consisted only of groans (V2).

Control head CT performed without contrast after 6 hours presented image as above, diffuse, minor hyperdense effusions in the subcortical and cortical regions and single minor hemorrhagic foci in the left frontal and temporal regions were still visible, with the addition of a subcutaneous hematoma of 8 mm width in the left parietal region.

The patient was transferred to the neurosurgical ward. Due to the patient's behavior described as "wandering around the ward, disorientation, not remembering provided information, speaking 'odd content' and illogical contact", the psychiatric examination was conducted on 9th day of hospital stay. Such clinical presentation suggested initial psychotic disorders. During the consultation patient was co-operative, with his speech intelligible but poor in content. Retrograde and anterograde amnesia were reported. The patient remembered his personal information. He was susceptible to distractions and his attention was impaired. He was unaware of his surroundings, time and location. Despite preserved immediate repetition of current information, he made mistakes and confabulated at a recall. He made mistakes while counting in the range of 100 and 10. His affect was anxious and intentional activity impairment was observed. He showed lack of criticism in regard to own physical and mental state.

Post-traumatic amnestic disorder resulting from diffuse axonal injury was diagnosed. The use of 1–2 mg haloperidol before sleep, sodium valproate 300–0–500 mg and cognitive rehabilitation were recommended. The patient was released home where he was cared for by his family.

Case 2

A 38 years old woman with a university degree, married, with two children and professionally active. She was hit by a car while cycling at the crossroads. During the accident she was wearing a helmet. She probably hit the ground with her chin.

During the ER stay she was conscious, with efficient respiration and circulation. Physical examination showed droopy left eyelid, left ear canal bleeding and an upper lip laceration.

Laboratory tests did not detect any psychoactive substances or other findings. Polytrauma CT protocol showed no organ injuries within torso and limbs.

CT scan of neurocranium and facial skeleton showed a small cerebral hemorrhage in the left frontal region of 2 mm width, features of small subarachnoid hemorrhage in the fronto-temporal location and cerebral edema. Middle structures were not dislocated. Numerous skull fractures were revealed: bilateral, multi-segmental fracture of the occipital bone base (including a margin of the foramen magnum and posterior part of both occipital condyles), a fracture of the left lateral wall of sphenoid sinus and occipital scale including both occipital condyles, transverse fracture of the left temporal bone pyramid with a fissure passing through artery channel and the internal jugular vein foramen on the left side. The presence of blood in tympanic and mastoid cavity and in the mastoid cells on the left side was observed. The fractures of facial skeleton included: a fracture with dislocation of left condylar process and mental part of the mandible on the left side without significant dislocation, comminuted fracture of anterior part of the mandibular body on the right side with dislocation. Air bubbles were revealed in suboccipital tissues and submandibular tissues on both sides.

Follow-up examinations performed after 6 hours still presented hemorrhagic lesions in both temporal regions with majority on the right side and smaller size at the base of both frontal lobes. In the ER, the patient was lying, sleepy, with efficient respiration and circulation. An examination revealed wide and unreactive left pupil, immobile eyeball and droopy left eyelid. Additionally, a blood leak from the left ear canal was described. The patient scored GCS 10: she opened her eyes on command (E3), she did not make verbal contact (V1), she followed simple commands – clenched her fists and moved her lower limbs – without any significant features of limb paresis (M6).

No need for surgical intervention was found during neurosurgical consultation. The patient was transferred for observation in the intensive care unit and next to the maxillofacial surgery unit. Control MRI (7 days after the injury) revealed small hematomas in evolution phase in both fronto-temporal regions of the width up to 5mm on the right side and 2mm on the left side. There was also discreet cerebellar hematoma on the left side and numerous hemorrhagic contusion foci visible in the middle part and predominantly at the base of both temporal and frontal lobes. Similar lesions, but in lower number, were observed in both occipital lobes and a single one in the left external capsule. Another small contusion area was located in the left hemisphere of the cerebellum and in the region of soft suboccipital tissue. In the left mastoid process and sphenoidal sinus blood was present.

Psychiatric consultation took place on the 10th day of hospitalization due to behavioral problems such as wandering around the ward, confusion, inability to collect

anamnesis, and doubts about the patient's informed consent for surgery needed to treat fractures of the mandible. In addition, she did not remember any information given to her. The patient repeatedly spoke "odd content" and repeated herself.

During the psychiatric consultation, the patient was co-operative, her speech was easily distracted. Paraphases, perseverations and memory gaps filled with confabulations were present. Although the patient gave correct personal data, her allopsychic orientation was incorrect and variable. Direct repetition of information was preserved, but there were errors at recall. The affect was merry with clear features of disinhibition. Increased drive, disorganization of intentional activity, disturbed rhythm of sleep and wakefulness as well as lack of criticism of her own mental and somatic state were observed.

Post-traumatic amnestic disorder resulting from diffuse axonal injury was diagnosed. The use of an antipsychotic drug (haloperidol 0.5–0–2 mg per night) and rehabilitation of cognitive functions were recommended. It was stated that due to deficits of cognitive functions, the patient is unable to give informed consent to the proposed treatments and medical procedures.

Discussion

Traffic accidents are associated with various physical injuries. Both psychogenic (such as PTSD) and biological (such as intracranial trauma) consequences may affect the psychological state. Diagnosis of brain trauma presenting as DAI in traffic accidents victims with hardly any physical consequences seems to be a new issue. Such injury is revealed progressively with behavioral problems directly following the accident and severe memory impairment later on.

The above-described cases illustrate a situation in which the main consequence of traffic accidents, both car and bicycle one (with all the protection and safety elements), are mental repercussions, such as amnestic syndrome resulting from DAI. As mentioned in the introductory part, the intracranial imaging may not always allow to unambiguously diagnose DAI. Memory deficits with potential behavioral problems indicate necessity to repeat imaging tests. Behavioral problems and memory deficits resulting from DAI may have heterogeneous presentations. Confabulation and attention deficits significantly impact logical contact with a patient and may mislead physicians, which can lead the diagnostic process in the direction of psychotic disorders with delusions and lack of concentration. Neuropsychological evaluation can be unavailable in the conditions of common wards or it is only conducted with the use of the Mini Mental State Examination or Clock Drawing Test, which are insufficiently sensitive. Psychiatric consultation and thorough psychiatric examination remain the basic diagnostic tool.

A necessity of planned surgical treatment of non-life-threatening injuries may be impeded in common practice by patient's inability to give informed consent due to memory deficits, lack of abstract thinking and reasoning.

Conclusions

1. Diffuse axonal injury may be the sole or main consequence of a traffic accident.
2. DAI should be considered when memory deficits and behavioral problems with features of disinhibition and disorganization are present without significant focal symptoms.
3. Diffuse axonal injury results in psychopathological image of amnestic syndrome with less or more vivid confabulations and behavioral problems, which can lead to inaccurate diagnosis of first-time psychotic disorders due to illogical contact and behavioral problems derived from memory deficits.
4. It is recommended to perform T2-weighted MRI after 3–7 days from injury, which often reveals multifocal lesions in the corpus callosum region. Sensitivity of CT is insufficient, especially in the early post-traumatic period.
5. Due to its high prognostic value, it is recommended to perform neuropsychological evaluation repeatedly.
6. DAI treatment focuses on correcting behavioral disorders, but there are no standards for cognitive functions rehabilitation among these patients.

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