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Traumatic axonal injury, a clinical-pathological correlation

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ABSTRACT

Traumatic axonal injury (TAI) is a distinct clinicopathological entity that can cause serious impairment of the brain function and can sometimes be found as a concrete cause of death. It has been discussed from the perspective of its biomechanical importance, and also from the standpoint of certain criteria for the pathological diagnosis of TAI. However, since the time when DAI (diffuse axonal injury) was initially described, there have been few, if any, discussions about the clinical-pathological correlation in TAI. This paper is an attempt to address this issue.

For the purpose of certain pathological diagnoses of TAI, 63 cases with closed head injuries have been subjected to the complete forensic-neuropathological examination, involving immunohistochemistry with antibody against β-APP. In the diagnosis of TAI strict criteria have been followed. Then, retrograde analysis of the clinical parameters has been performed in order to determine some clinical-pathological correlation. The following two most reliable parameters of the impairment of the brain function have been analyzed: the impairment of the consciousness and the time of survival. Comparing the two groups, the one with TAI and the other without TAI, and using appropriate statistical evaluation, our results show that TAI is not a significant contributing factor to the lethal outcome in the early post injury period (24 h), but it is undoubtedly a contributing factor for the severe impairment of the brain function indicated through the status of the consciousness.

1. Introduction

Diffuse axonal injury (DAI), as classically named, is a distinct clinicopathological entity that is found in closed head injuries can cause 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.

In the initial and very profound descriptions of Adams, DAI has been understood as a clinicopathological entity of traumatic origin, clinically[1–3] defined with immediate and prolonged unconsciousness leading to death or severe disability, typically in the absence of any mass lesion, and pathologically by the widespread and diffuse damage of the axonal fibers. Later, with the introduction of the immunohistohemistry in the process of diagnosing of DAI, there were found series of other conditions but trauma that can cause axonal damage. Soon thereafter prominent authors reported certain differences in the findings (appearance, pattern and distribution of damaged axons) that are indicative of the origin of the axonal damage, traumatic or ischemic. The term traumatic axonal injury (TAI) was preferred instead of DAI to describe axonal damage of traumatic origin and by analogy, the term ischemic axonal injury was introduced. Certain criteria for the pathological diagnosis of TAI have been specified, paying particular attention to distinguishing traumatic axonal damage from secondarily occurring ischemic axonal damage.[4–10]

The medico-legal importance of TAI lies in the fact that sometimes it is the sole reason for the impairment of the brain function and in a forensic medicine setting it can be found as a concrete cause of death.[6] With the purpose of establishing the diagnosis of TAI, a complete forensic neuropathological examination of the brain must be undertaken,[4–6,11] so it certain criteria have to be met before it is interpreted as a cause of death.[4–6] Another significant

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aspect of TAI in forensic medicine is its biomechanical importance. TAI occurs as a result of acceleration forces of longer duration,[12–15] and is mostly found in road traffic accidents (RTA), but can be found in other events associated with acceleration, such as in cases of falling from a considerable height. DAI is very rare in cases of a simple fall, and in cases of a blow to the head.[10,16,17]

Since the time when Adams made the initial descriptions of DAI,[1,2] there have been few, if any, discussion about its clinico-pathological correlation. Previously, most of the efforts were focused on a certain post-mortem diagnosis of TAI, and nowadays efforts are also being made for its clinical and radiological diagnosis***. In order to identify some clinicopathological correlation of TAI and its diagnosis on a pathological level, a retrograde analysis of the clinical parameters should be performed. This paper is an attempt to address this issue. The impairment of consciousness and the time of survival have been analyzed as the two most reliable indicators of the impairment of the brain function. The hypothesis under consideration is that TAI is constantly accompanied with the state of coma and can be found as a significant contributing factor to death in the first 24 h after the closed head injury.

Two crucial questions to be answered are:

1. Is the impairment of consciousness (state of coma) a constant accompanying element of TAI, as classically defined?
2. Is TAI a significant contributing factor to the fatal outcome in the early post injury period (24 h post injury).

2. Materials and method

A total of 63 cases with fatal closed head injuries have been investigated by performing a forensic-medicine autopsy and a forensic-neuropathological examination (age ranged from 5 to 94 years old, 48 males and 15 females). In all 63 cases, a fatal closed head injury was found to be the cause of death. All open head injury and polytrauma cases have been excluded, to avoid the possibility of any other cause of death. The post-mortal interval had to be up to 24 h and the time of survival between 2 h (long enough to be admitted to hospital and also for pathological evidence of axonal damage) and 1.5 month. The clinical information, as well as the information about the traumatic event, had to be available for all the cases included. Table 1 displays the information about the type of traumatic event where the closed head injury occurred.

The injury mechanism was analyzed, based on the injuries of the scalp, skull, intracranial structures (epidural, subdural and subarachnoidal haemorrhage) and the brain tissue (focal and diffuse brain injuries). Then a complete forensic-neuropathological examination of the fixed brain was performed (fixed in a 10% buffered formalin solution). Macroscopic examination of 1 cm thick coronal sections has been documented in photographs. Samples for microscopic examination were taken from brain areas already known as predilection for the occurrence of TAI: the body and the splenium of corpus callosum including parasagittal white brain matter; posterior limb of the internal capsule; pons and cerebellar peduncles.

Table 1
Cases with diagnosed TAI.

Type of traumatic event	Total	TAI	%	no TAI	AI-ish
Traffic accident	49	26	53	17	6
Pedestrain	26	13	50	12	1
Cyclist	10	3	30	3	4
Motorist	4	3	75	1	0
Driver	5	5	100	0	0
Passenger	2	1	50	0	1
Railroad accident	2	1	50	1	0
Fall	11	4	36	4	3
Simple fall (<2 m)	6	0	0	4	2
Fall of a height (<2 m)	5	4	80	0	1
Blow-assault	3	0	0	2	1
Total	63	30	48	23	10

* TAI – cases diagnosed with diffuse axonal injury; no TAI – cases without diffuse axonal injury; AI ish – axonal injury of ischemic origin.

For the purpose of visualization of damaged axons, additionally to the conventional haematoxylin and eosin staining, immunohistochemical staining was performed with the application of antibodies to β–APP, by the method of Sheriff et al.[18]: antigen retrieval in citrate buffer (pH 5.0), incubation with antibody against β–APP (Mouse anti-Alzheimer precursor protein A4 monoclonal antibody, clone 22 C 11, diluted 1:200, Chemicon International, Temecula, CA) overnight at 4C. The enzyme complex used was ABC (Universal VECTASTAIN ABC-Peroxidase kit, Vector Labs, Burlingame, CA) with a secondary antibody - biotinylated anti-mouse IgG (Biotinylated Anti-mouse IgG, produced in horse, Vector Labs). Diaminobenzidine (Peroxidase Substrate Kit (DAB) Vector Labs) was used for visualization.

In the process of TAI diagnosing, the pathological criterion was based on the grading system of Adams et al.[19] according to which the presence of a focal lesion in the corpus callosum was regarded as DAI 2, while a focal lesion in the rostral brainstem was regarded as DAI 3. The diagnosis of DAI 1 had to be established by a microscopic finding of widespread axonal damage with traumatic pattern in the absence of any macroscopic feature.[20]

In the histological determination of TAI, damaged axons with a typical traumatic appearance and distribution had to be seen in at least three different brain regions, of which at least one located above and one below the tentorium.[4,5] We regarded the “typical traumatic appearance and distribution of damaged axons” as the occurrence of single or small groups of swollen “varicosity”-like β-APP-positive axons or torn axons seen as “retraction balls” diffusely distributed throughout the white matter and particularly present in the white matter bundles[4–10](Fig. 1).

The feature of circumscribed foci or a linear pattern of β-APP positive axons, frequently described as a “zig-zag” or “Z-shaped” pattern, which are densely distributed in one or two brain regions (most often in the pons) was considered a predominantly hypoxic-ischemic finding and was not taken into consideration in the diagnosing of TAI[4–10] (Fig. 2).

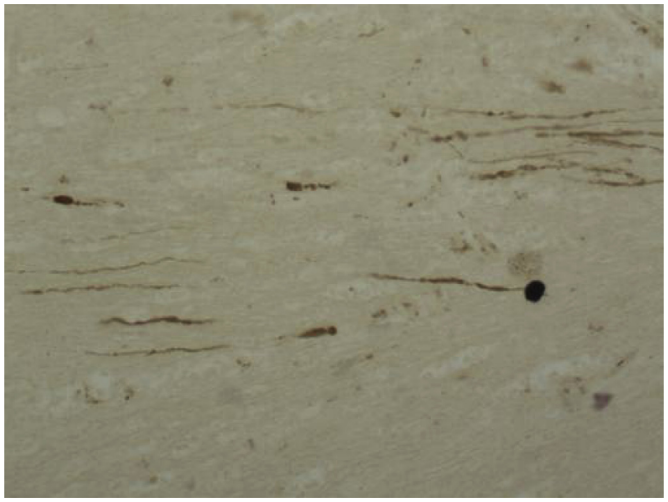

Fig. 1. Typically traumatic pattern and distribution of β-APP-positive axons are seen in Corpus calosum, in a case with a time of survival of 8 days. Single or small groups of swollen “varicosity”-like or torn axons seen as “retraction balls” are diffusely distributed throughout the white matter and particularly present in the white matter bundles.