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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).

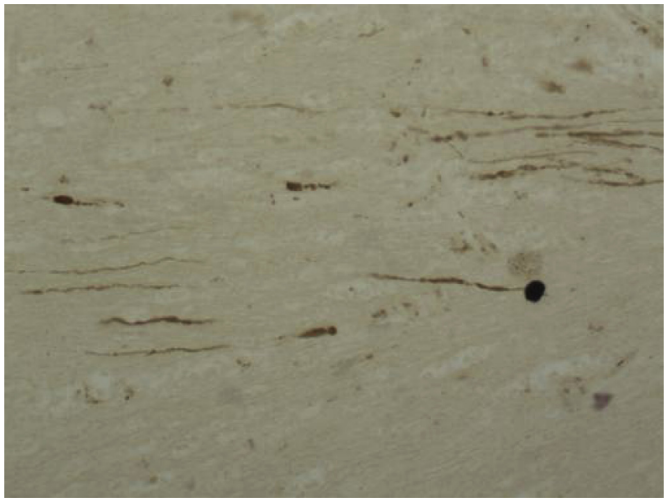

Fig. 1. Typically traumatic pattern and distribution of β-APP-positive axons are seen in Corpus calosum, in a case with a time of survival of 8 days. Single or small groups of swollen “varicosity”-like or torn axons seen as “retraction balls” are diffusely distributed throughout the white matter and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

The degrees of the Glasgow Coma Scale (GCS, 3–15) have been taken as the indicator of the impairment of consciousness. In accordance with this scale, the head injury has been classified as severe with GCS ≤8 manifested clinically with coma or stupor; moderate with GCS = 9–12, manifested as somnolence; and minor GCS ≥ 13.[21]

In order to analyze the clinical-pathological correlation of TAI, comparative statistics has been performed between these three groups:

1. Cases with diagnosed TAI – TAI cases;
2. Cases without TAI – no TAI cases;
3. Cases with Axonal Injury (AI), where the appearance, pattern and distribution of the β-APP immunoreactivity suggested its ischemic origin.

Statistical evaluation was performed using the Pearson Chi-Square test of independence with the significance level used is $\alpha = 0.05$.

3. Results

TAI has been diagnosed in 47,6% of the examined cases as shown in Table 1.[16] (published in: N.Davceva et al./Journal of Forensic and Legal Medicine 19 (2012) 480–484). Table 1 also shows the correlation between the occurrence of TAI and the type of the traumatic event that caused the head trauma.

The frequencies of the major autopsy findings, such as skull fractures, intracranial hemorrhages, contusions and the frequency of TAI are presented in Table 2.

Table 3 presents the pathological findings of 30 cases with diagnosed TAI, along with the clinical information about their state of consciousness and the time of survival. Results show that 80% of them have been in primary coma, and in the rest of the cases, 6 of them, moderate disturbances of consciousness have been observed.

Analyzing the group of cases without TAI, shown in Table 4, a primary coma was present in 7 cases (30% of the total of 23 cases). In the rest of the cases, moderate or mild disturbances of consciousness occurred.

Table 5 presents cases diagnosed with ischemic axonal injury.

Fig. 2. Axonal injury of hypoxic-ischemic origin, in a case who survived 3 days after injury. There is a feature of linear and geographical pattern of β-APP positive axons, which are densely distributed on wide planes. The positive axons are rather with a granular appearance than neatly shaped axons which can be seen in traumatically damaged tissue.

Table 2
Frequencies of the major autopsy findings.

Fractures	37	59%
ICH, SDH, EDH, SAH	46	73%
FBI-contusions	23	36,50%
TAI	30	47,60%

*Fractures - fractures of the skull; ICH - intracranial haemorrhage (SAH - subarachnoidal haemorrhage, EDH - epidural haematoma, SDH - subdural haematoma); FBI - focal brain injury –contusion; TAI - diffuse axonal injury.

All these cases died in a state of coma.

Statistical evaluation explored the interdependence between the occurrence of TAI and the state of consciousness. Three groups of cases have been investigated comparatively, Table 6. Statistically, a significant interdependence was shown between the occurrence of TAI and the occurrence of primary coma (Chi square = 29, 99; df = 2, p < 0, 00001). Also, as perceived before, the analysis shows the presence of coma in all AI cases.

As a next step, an additional investigation was conducted into the correlation between the state of coma and the post-mortem β-APP positive immunoreactivity found on pathological substrate, as a specific and direct indicator of the damage of the axonal fibers, Table 7. Statistically significant association has been shown (Chi - square = 29, 83; df = 2, p < 0, 00001).

As another indicator of the severe impairment of brain function, the two groups of cases, the one with diagnosed TAI and the other without TAI, have been analyzed comparatively in terms of the time of survival. The time of survival ranged: until 24 h, until 1 week, and until 1.5 months, as shown on Table 8. The statistical evaluation did not show any significant association between the occurrence of TAI and the time of survival (Chi square = 4, 75; df = 2; p = 0, 0929 > 0.01).

4. Discussion

The results of the present study demonstrate that the impairment of consciousness (state of coma) is a constant accompanying element of TAI, as classically defined.[1,2,12,13] 80% of the cases with TAI were in primary coma, and the remainder showed a moderate disturbance of consciousness. In comparison, primary or immediate coma was observed in 30% of the cases that did not show TAI in the neuropathological examination.

The results in the third group of cases diagnosed with axonal injury of ischemic origin were particularly revealing, as all of them were in coma. Since the differences in the appearance, pattern and distribution of the damaged axons have been widely discussed before,[4–10] it should be pointed out that the occurrence of β-APP immunoreactivity to one or two samples, of which at least one is from a brain stem and with a predominantly granular deposition on wide “geographic” planes, is a characteristic ischemic feature. If the ischemic feature is found next to a traumatic axonal damage, then it can be interpreted as a case of TAI with secondarily occurring ischemia.

Hence, the analysis indicated significant statistical interdependence between the axonal damage (regardless of whether they showed a traumatic pattern, as in the TAI cases, or an ischemic feature as in AI cases) and the occurrence of primary coma. This association triggered another statistical evaluation which revealed the strong interdependence between β-APP immunoreactivity found on a pathological substrate and the state of coma. One of the advantages of this study is that, all cases in coma demonstrated clear β-APP immunoreactivity on a pathological substrate, implying that axonal damage indicated by β-APP disposition, from traumatic or ischemic origin, is in clear correlation with the state of coma. This

Table 3
Presentation of the cases diagnosed with TAI.

	No	A-G	Trauma	TS	Consiousness	Fr and ICH
12800/165-04	1	F 13	TA -ped	9 d	Coma, GCS = 7	Fr,EDH, SDH
12887/252-04	6	M 17	TA -motor	3 w	Coma, GCS = 6	SDH, SAH
12891/256-04	0	M 33	TA -driver	3 d	Coma	Fr, EDH, SAH
12893/258-04	7	F 73	TA -ped	24 h	Coma, GCS = 3	SDH, SAH
12905/270-04	10	M 39	TA -driver	4-5 h	Coma	
12907/272-04	0	M 75	TA -ped	5 d	Stupor, Coma	
12916/281-04	11	M 89	TA -ped	3 h	Coma	
12917/282-04	12	M 23	TA -driver	2 d	Coma, GCS = 3	
12979/62-05	16	M 40	TA -ped	11 d	Coma	
13010/93-05	17	M 33	TA -driver	3 d	Coma, GCS = 3	
13018/101-05	18	M 26	F -hight	12 d	Coma, GCS = 3	
13135/217-05	22	M 30	TA -motor	10 d	Coma, GCS = 5	Fr, SAH, SDH
13163/245-05	25	M 55	F -hight	1, 5 m	Coma, GCS = 3	EDH, SAH
13186/268-05	27	F~ 70	TA -ped	3 d	Stupor	Fr, SDH, SAH, IVH
13191/273-05	29	M 10	TA -ped	8 d	Coma, GCS = 4	
13210/292-05	33	M 81	TA -cyc	15 d	Coma	Fr, SDH, SAH
13211/293-05	34	F 64	TA -ped	4 d	Coma, GCS = 3	Fr, SDH, SAH
13221/303-05	35	M 61	TA -cyc	5 d	Coma	Fr, SAH, IVH
13227/309-05	37	M~30	TA -pass	4 h	Coma	
13255/24-06	39	M 60	TA -ped	1 m	Coma, GCS = 8	SDH, SAH, IVH
13280/149-06	43	M 30	TA -driver	2-3 h	Coma	Fr, SAH
13342/111-06	49	F 46	TA -ped	24 h	Coma	SAH
13380/149-06	50	M 25	TA -motor	4 d	Stupor	
13465/234-06	54	M 67	TA -ped	2, 5 d	Stupor	Fr, SDH, SAH
13469/238-06	55	F 72	TA -ped	6 d	Coma, GCS = 6	Fr, SDH, SAH
13481/250-06	57	M 58	F -hight	6 d	Coma	Fr, SDH, SAH
13541/11-07	59	F 20	TA -ped	7 d	Coma	Fr, EDH, SDH, SAH
13550-20-07	60	M 50	RA	2 d	Stupor	Fr, SAH
13578/48-07		F 24	F -hight	3 d	Stupor	SAH
13616-86-07		M 78	TA -cyc	8 d	Coma, GCS = 3	Fr, EDH, SDH, SAH

* A-G - age and gender; Trauma - type of traumatic event where closed head injury occurred: TA - traffic accident (ped - pedestrian, cyc - cyclist, mcyc - motorcyclist; pass - passenger; RA - railway accident), F - fall (F-simple - fall from one's own height, F-height - fall from a height of more than 2 m), B-F - blow and fall; TS - time of survival (imm - immediate death; h -hour; d -day, w -week, m - month); Consciousness - state of consciousness immediately after the impact (GCS - Glasgow Coma Score); Fr - fractures of the skull, ICH - intracranial haemorrhage (SAH - subarachnoidal haemorrhage, EDH - epidural haematoma, SDH - subdural haematoma, IVH - intraventricular haemorrhage); FBI - focal brain injury (cont - contusion, cont c-c - contusion coup-contra-coup, ICH - intracerebral haemorrhage); DBI - diffuse brain injury (TAI 1, 2, 3 - diffuse axonal injury - Adams grading system (Adams 1989); DVI - diffuse vascular injury; ISH - ischemia; Swell - brain swelling.

Table 4
Cases without TAI.

A-G	Trauma	TS	Consiousness	Fr and ICH	FBI	DBI
M 48	TA-ped	3-4 h	Concussion	SAH		Swell
F 23	TA-cyc	10 d	GCS = 8	SDH	Cont	Swell, ISH
M 61	TA-cyc	14 d	Concussion	Fr, SDH, SAH	Cont	Swell
M 70	TA-ped	1 d	Concussion	Fr, SAH		Swell
M 52	TA-ped	2-4 h	Concussion			Swell
M 41	TA-ped	6 h	Coma, GCS = 3	Fr, SAH		Swell, ISH
M 60	TA-motor	5 d	Somnolency	SDH, SAH	Cont	Swell
M~60	F-hight	3,5 w	Stupor	Fr, SDH, SAH	Cont	Swell
M 15	TA-ped	10 d	Somnolency GCS = 14	Fr, EDH	Cont c-c	Swell, ISH
M~50	RA	10 d	Coma	Fr		Swell
F 80	TA-ped	8 d	Consciousness			Swell, ISH
M 57	TA-ped	2 d	Consciousness			Swell
F 40-50	TA-ped	1,5 m	Concussion			Swell
M 37	F-simple	5 d	Stupor		Cont	Swell
F 74	TA-ped	3-4 h	Stupor	SAH		Swell, ISH
M 70	TA-ped	4 h	Coma	Fr, SAH		Swell, ISH
M 33	TA-cyc	2-4 h	Coma	Fr, SDH, SAH	Cont	Swell, ISH
M 88	TA-ped	8 h	Concussion			Swell, ISH
M 74	TA-ped		2 h	Stupor		Swell
F 94	Blow	1-2 h	Stupor	Fr, SAH, IVH		
M 55	B-F	5 d	Coma	Fr, SDH, SAH	Cont	Swell
F 66	F-simple	3-5 h	Stupor	SAH		
M 59	F-hight	24 h	Coma, GCS = 4	Fr, SDH, SAH	Cont c-c	Swell, ISH

*A-G - age and gender; Trauma - type of traumatic event where closed head injury occurred: TA - traffic accident (ped - pedestrian, cyc - cyclist, mcyc - motorcyclist; pass - passenger; RA - railway accident), F - fall (F-simple - fall from one's own height, F-height - fall from a height of more than 2 m), B-F - blow and fall; TS - time of survival (imm - immediate death; h -hour; d -day, w -week, m - month); Consciousness - state of consciousness immediately after the impact (GCS - Glasgow Coma Score); Fr - fractures of the skull, ICH - intracranial haemorrhage (SAH - subarachnoidal haemorrhage, EDH - epidural haematoma, SDH - subdural haematoma, IVH - intraventricular haemorrhage); FBI - focal brain injury (cont - contusion); DBI - diffuse brain injury; ISH - ischemia; Swell - brain swelling.

Table 5
Group of cases diagnosed with ischemic axonal injury.

A-G	Trauma	TS	Consiousness	Fr and ICH	FBI	DBI
M 59	TA-cyc	2 d	Coma	Fr, EDH, SDH, SAH,	Cont c-c	AI-ish, Swell, ISH
M 5	TA-ped	15 d	Coma, GCS = 3	Fr		AI-ish, Swell, ISH
M~35	F-hight	2 d	Coma, GCS = 4	Fr, EDH, SDH, SAH	Cont c-c	AI-ish, Swell, ISH
M 69	TA-cyc	3 w	Coma	Fr, SDH, SAH	Cont c-c	AI-ish, Swell, ISH
M 60	F-simple	7 d	Coma	SDH, SAH	Cont c-c	AI-ish, Swell, ISH
M~50	Blow	3-5 h	Coma, GCS = 3	Fr, SDH, SAH, IVH	Cont	AI-ish, Swell, ISH
F 20	TA-pass	10 d	Coma	Fr, SAH	Cont	AI-ish, Swell, ISH
M~50	TA-cyc	7 h	Coma, GCS = 4	Fr, SAH	Cont c-c	AI-ish, Swell, ISH
M 63	F-simple	10 d	Coma, GCS = 7	Fr, EDH, SAH	Cont c-c	AI-ish, Swell, ISH
M 43	TA-cyc	2 d	Coma, GCS = 3	Fr, EDH, SDH, SAH, IVH		AI-ish, Swell, ISH

* A-G - age and gender; Trauma - type of traumatic event where closed head injury occurred: TA - traffic accident (ped - pedestrian, cyc - cyclist, mcyc - motorcyclist; pass - passenger; RA - railway accident), F - fall (F-simple - fall from one's own height, F-height - fall from a height of more than 2 m), B-F - blow and fall; TS - time of survival (imm - immediate death; h -hour; d -day, w -week, m - month); Consciousness - state of consciousness immediately after the impact (GCS - Glasgow Coma Score); Fr - fractures of the skull, ICH - intracranial haemorrhage (SAH - subarachnoidal haemorrhage, EDH - epidural haematoma, SDH - subdural haematoma, IVH - intraventricular haemorrhage); FBI - focal brain injury (cont - contusion, cont c-c - contusion coup-contra-coup); DBI - diffuse brain injury; Ai-ish – axonal injury of ischemic origin; ISH - ischemia; Swell - brain swelling.

Table 6
Association between the occurrence of TAI and the occurrence of the primary coma.

	Coma, Stupor	Concussson, Somnolency	Total
TAI cases	28 (44,43%)	2 (3,17%)	30 (47,61%)
No TAI cases	7 (11,10%)	16 (25,39%)	23 (36,50%)
AI cases	10 (15,87%)	0	10 (15,87%)
Total	45 (71,42%)	18 (28,57%)	63 (100%)

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

Table 7
Association between the state of the coma and the post-mortem. β-APP positive immunoreactivity.

	Coma, Stupor	Concuss, Somnolency	Total
β -APP +	38 (60,31%)	2 (3,17%)	40 (63,49%)
β -APP -	7 (11,10%)	16 (25,39%)	23 (36,50%)
Total	45 (71,42%)	18 (28,57%)	63 (100%)

* ß -APP + – cases who show ß -APP positivity on pathological substrate; ß -APP - – cases who don't show ß -APP positivity on pathological substrate.

Table 8
Association between occurrence of the TAI and time of survival.

TAI*Time of survival	24 h	1 week	1,5 months	Total
TAI cases	6	14	10	30
No TAI cases	14	8	11	33
Total	20	22	21	63

*TAI – cases diagnosed with diffuse axonal injury; no TAI – cases without diffuse axonal injury.

correlation has been noted by other authors as well[22,23] but more profound studies are needed in order to establish more definite observations that can shed a new light to the neurophysiology of coma. In a previous study[10] we investigated the correlation between different pathological grades of TAI and the depth of the coma. The majority of the cases in deep coma (GCS = 3–5), demonstrated pathological grade 3 of TAI, and two cases that clinically showed somnolence (GCS 11–14) had grade 1 of TAI. Also, in other study has been shown that the prognosis worsens in direct relationship to the extent of injury, especially to the injury of the brainstem.[24]

The time of survival has been analyzed here as another indicator of the severity of the brain impairment as a result of the head injury. It has been shown that only 6 subjects (20% of all the cases with diagnosed TAI) died within the first 24 h, in comparison with 14 subjects (42% of the cases where TAI was not diagnosed) who died in the first 24 h. Furthermore, from the total of 20 cases that died in the first 24 h, only 6 (30% of them) were diagnosed with TAI. Comparatively, in the group of cases that had survived for one week, there were 14 (64% of 22) with a TAI diagnosis. These considerations demonstrate that the presence of TAI is not the factor which contributes to the fatal outcome in the first 24 h. Finally, this correlation of TAI with the time of survival has been explored statistically and no significant association has been found. In one of the aforementioned studies[10] the survival time in a correlation with the grade of TAI has also been explored and no significance has been found, but it has been observed that the lower survival time values are more typical of cases with grade 3 of TAI.

5. Conclusion

In this study TAI has not been found to be a significant contributing factor to the lethal outcome from closed head injuries in the early post injury period (24 h), but undoubtedly is a contributing factor for the severe impairment of the brain function indicated through the status of the consciousness.

Presumably, the most contributing factors for lethal outcome in the early post injury period in closed head injuries should be found among the sequels of the raised intracranial pressure which develops as a result of the edema or intracranial haemorrhage.

Conflict of interest

We declare that there isn't any conflict of interests in this paper. All analyses have been done inside the Faculty of medicine of Skopje and this research hasn't been supported by another organization.

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