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The importance of the secondary brain injuries in the daily forensic medicine practice

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Abstract

With the introduction of the concept of primary and secondary brain injuries, it became clear that primary brain injury is not decisive for the outcome of one particular cranial-cerebral injury, but it greatly depends on the secondarily initiated mechanisms. The latter are actually responsible for the occurrence of secondary brain injuries, mainly as a result of raised intracranial pressure (ICP).
The ICP is a clinical parameter which can be measured only ante mortem. During the post mortem examination, what we can conclude about the increased ICP is only by its effects on the brain tissue and the occurrence of secondary brain injuries: signs of internal herniation as sequelae of increased intracranial pressure and a hypoxic-ischemic brain injury as a result of decreased cerebral perfusion pressure (CPP).
This paper discusses our findings on the sequelae of increased intracranial pressure (signs of internal herniation) and diffuse hypoxic-ischemic brain injury based on neuropathological examination (macroscopic and microscopic examination, involving immunohistochemistry) of 80 forensic cases of closed head injury with a survival until 1,5 months. Our findings indicate that ischemic lesions can be found by macroscopic examination at 6 – 7 hours post injury and by histopathological examination that may be perceived even three hours after the injury. The most convenient method for detection of early ischemia (3 hours post injury) is ß-APP immunohistochemistry.

Key words: ischemia, herniation, secondary brain injuries, β-amyloid precursor protein

Abstrakt

Zavedením konceptu primárneho a sekundárneho poranenia mozgu sa ukázalo, že primárne poranenie mozgu nie je rozhodujúce pre výsledok jedného konkrétneho kraniálno-cerebrálneho poranenia, ale veľmi závisí od sekundárne iniciovaných mechanizmov. Tie sú v skutočnosti zodpovedné za výskyt sekundárnych poranení mozgu, najmä v dôsledku zvýšeného intrakraniálneho tlaku (ICP).
ICP je klinický parameter, ktorý je možné merať iba *ante mortem*. Pri pitve môžeme zistiť len účinky zvýšeného ICP na mozgové tkanivo a výskyt sekundárnych poranení mozgu: príznaky vnútornej herniácie ako následky zvýšeného intrakraniálneho tlaku a hypoxicko-ischemické poškodenie mozgu ako výsledok zníženého cerebrálneho perfúzneho tlaku (CPP).
Práca diskutuje zistenia následkov zvýšeného intrakraniálneho tlaku (príznaky internej herniácie) a difúzneho hypoxicko-ischemického poškodenia mozgu na základe neuropatologického vyšetrenia (makroskopické a mikroskopické vyšetrenie vrátane imunohistochemického) 80 forenzných prípadov uzavretého poranenia hlavy s prežitím do 1,5 mesiaca. Naše zistenia ukazujú, že ischemické lézie možno identifikovať makroskopickým vyšetrením 6 – 7 hodín po úraze a histopatologickým vyšetrením už tri hodiny po úraze. Najvhodnejšou metódou na detekciu včasnej ischémie (3 hodiny po poranení) je imunohistochemické vyšetrenie na *ß-amyloid precursor protein*.

Kľúčové slová: ischémia, herniácia, sekundárne poškodenie mozgu, *β-amyloid precursor protein*

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Introduction

With the introduction of the concept of primary and secondary brain injuries, it became clear that primary brain injuries (focal and diffuse brain injuries inflicted directly by forces of impact) are not decisive for the outcome of one particular cranial-cerebral injury, but greatly depend on the secondarily initiated mechanisms. The latter are actually responsible for the occurrence of secondary brain injuries: signs of internal herniation and hypoxic-ischemic brain injury which develop as a result of raised intracranial pressure (ICP) (1-5) and decreased cerebral perfusion pressure (CPP). The forensic relevance of the secondary brain damage results from the pointing to the survival time.

The intracranial cavity is a space of limited volume, where three main contents are present: the brain 80%; the blood 2 – 11%; and the cerebrospinal liquor 10%. When the equilibrium of these contents is impaired, an increase in ICP occurs. The ICP is a clinical parameter which can be measured only ante mortem. Normal values are below 2 kPa (1 kPa = 7,5 mm Hg), elevation to 3 kPa is considered mild, to 4 kPa moderate, and values exceeding 5 kPa are considered as severe intracranial hypertension (6). The lethal upper limit of ICP is of 8 – 10 kPa.

During the post-mortem examination, what we can conclude about the increased ICP is only by its effects on the brain tissue and the occurrence of secondary brain damage: signs of internal herniation (3, 4, 6) and diffuse hypoxic-ischemic brain injury.

The herniation of the brain represents the movements of particular parts of the brain, from one compartment to another. The increased pressure in the supratentorial region leads to herniation against the edge of the *tentorium cerebelli* i.e. transtentorial herniation where the most exposed part is the temporal lobe uncus, including the *hippocampus* and the parahippocampal region. The increased pressure in the infratentorial compartment leads to herniation through the *foramen magnum* i.e. infratentorial herniation. This is associated with brainstem compression and death. The midline shifts of the medial parts of the brain hemispheres (*gyrus cinguli*) to the left or right under the *falx cerebri* is known as subfalcine herniation (5,6).

In addition to herniation, increased ICP results in decreased cerebral perfusion pressure (CPP is the difference between the middle arterial blood pressure and the intracranial pressure) and consequential occurrence of diffuse hypoxic-ischemic brain injury. Hence, every situation of increased ICP causes a decrease in CPP and subsequent ischemia. It has been shown that immediately after the impact, some increase in the blood flow occurs, but several minutes later the blood flow decreases to the level of one third of the normal, and the normalization process starts 40 minutes after (7). After a certain period of decreased CPP (under the 6 kPa), reperfusion of the brain tissue does not occur leading to hypoxic-ischemic changes of the brain tissue. In case of the most severe, extreme and irreversible form of global hypoxia, with irreversible cessation of the cerebral blood flow, brain death occurs (8).

Brain ischemia is very diverse in its appearance. By pathological examination, it can be seen as global (diffuse) or local; it may be obvious by macroscopic examination or it can be documented only by histopathological examination; it might initially occur in some predilection regions that are particularly vulnerable to hypoxia and ischemia (the cerebral *neocortex*, the *hippocampus*, the basal nuclei and also the Purkinje cells in *cerebellum*). Therefore, in order to properly confirm ischemic lesion, systematic and methodological brain examination approach is required. Here, the employment of complete forensic neuropathological examination is essential (9, 10). Generally, it has been accepted that ischemia is visible by gross examination 12 to 24 hours after cessation of the blood flow (11). The brain that suffered severe ischemic injury may show none or minimal changes, if there is not enough time for the pathological feature to develop (12). Ischemic brain is soft and friable, with discoloration of the grey matter to dusky grey and elements of violet discoloration (8). Sometimes the dusky discoloration is more prominent in the depths of the sulci, particularly seen in the regions which are known as watershed areas of the anterior and middle cerebral arteries (8). Another important finding of ischemia is the cortical laminar necrosis, necrosis and disintegration of the cortical ribbon with a subsequent separation from the underlying white matter.

In fact, ischemia develops much earlier when it can only be diagnosed using proper microscopic examination. The degeneration of the neurons i.e. eosinophil neuronal degeneration begins to be visible at least 6 to 12 hours post injury and the reactive cellular response (hypertrophy and proliferation of microglia and astrocytes) occurs even later (11).

Studies based on the expression of β-APP positivity in the last 30 years have shown that axonal damage (degeneration of the axons) sometimes occurs as a result of ischemia. It has been reported that there is a difference in the histopathological findings indicative of the origin of the axonal damage: traumatic or ischemic (13, 14). Based on those descriptions, the finding of single or small groups of scattered and diffusely arranged β-APP positive axons, seen as "varicosity-like" swollen axons or as "retraction balls", is considered as traumatic aetiology of axonal damage. The finding of circumscribed foci of β-APP accumulation, or linear and geographical patterns, frequently described as a "zig-zag" or "Z-shaped" pattern, is considered as hypoxic-ischemic finding (15). Hence, the β-APP has been found to be another tool for the detection of early ischemia.

In this study, the sequelae of increased intracranial pressure i.e. signs of internal herniation and hypoxic-ischemic brain injury have been analysed from the aspect of time of survival, particularly the following issues: how early after initial injury can ischemia

be visible by macroscopic examination; which histological methods, especially those involving immunohistochemistry are of best relevance for the early detection of ischemic changes; we explored the correlation between herniation and survival time to see when herniation is most probable to occur; and finally, the mutual correlation between hypoxic-ischemic brain damage and the signs of internal herniation. The overall purpose of this study has been to contribute to the neuropathological criteria for determining the secondarily occurred brain changes.

Material and methods

The study included 80 cases with fatal closed head injury (57 males, 23 females, age ranged from 5 to 94 years), already presented in another study (15), have been now analysed for the appearance and distribution of hypoxic-ischemic brain injury and the signs of internal herniation.

The inclusion criteria included post-mortem interval up to 24 h and the availability of data concerning: clear evidence of the type of the traumatic event (15), the known time of survival and full autopsy information. Clinical information was obtained for cases that survived long enough to be clinically investigated.

The survival period ranged from instantaneous death to 1.5 months (12 of the examined cases died quickly after the traumatic event, 25 of them survived 24 hours, 22 cases survived 1 week and the rest 21 cases survived more than 1 week, the longest survived 1,5 month).

All cases have been subjected to a forensic neuropathological examination of fixed brains in 10% buffered formalin (9, 10, 15, 16).

Finding uncal notching or haemorrhages and necroses in the *hippocampus* and the parahippocampal area and infarctions of the inferior surfaces of both occipital lobes resulting from posterior cerebral artery compression have been considered to be a sign of transtentorial herniation. The characteristic finding of the cerebellar tonsillar notching and the secondary brainstem haemorrhages which typically occur in the midline of the midbrain and pons (the so called Duret haemorrhages) have been considered to be a sign of infratentorial herniation (8).

Finding of a soft and friable brain tissue, with discoloration of the grey matter and areas with cortical laminar necrosis has been regarded as the finding of ischemic lesion (8).

In addition to the conventional haematoxylin–eosin staining, immunohistochemical reaction was performed with the application of the following antibodies: antibody against β–APP (15, 16, 17) for visualization of the axonal damage; antibody against CD-68 for visualization of the microglia reaction (18, 19), and also the method for visualization of the glial reaction using GFAP (glial fibrillary acidic protein) (19, 20). By employing the β-APP immunohistochemistry, only the pattern and the distribution of the β-APP positive axons suggestive for hypoxic-ischemic finding (15, 16, 21-23) has been taken as proof of an existing ischemia.

Statistical evaluation was made using Pearson Chi-Square test of independence and Kaplan-Mayer procedure for the analysis of the survival time.

Results

Using the criteria given above, signs of the internal herniation have been perceived in 46 (57,5%) of the cases (Tab. 1).

Type of internal herniation	No. of cases	%
	46	57.5
Transtentorial herniation	16	20
Infratentorial herniation	9	11.25
Subfalcine herniation	1	1.25
Transtentorial and infratentorial herniation	12	15
Transtentorial and subfalcine herniation	2	2.5
Infratentorial and subfalcine herniation	3	3.75
Transtentorial, infratentorial and subfalcine herniation	3	3.75

Tab. 1 Finding signs of herniation in the examined cases

Table 2 presents the time of survival for all cases diagnosed with internal herniation.

Case	Type of the herniation	Time of survival
1	Transtentorial herniation	9 days
2	Infratentorial herniation	10 days
3	Subfalcine and transtentorial herniation	2 days
4	Infratentorial herniation	2 – 4 hours
5	Infratentorial herniation	6 days
6	Transtentorial herniation	until 1 hour
7	Subfalcine and infratentorial herniation	2 days
8	Infratentorial herniation	until 1 hour
9	Transtentorial and infratentorial herniation	3 days
10	Transtentorial and infratentorial herniation	12 days
11	Transtentorial and infratentorial herniation	10 days
12	Transtentorial and infratentorial herniation	10 days
13	Transtentorial herniation	immediately
14	Transtentorial and infratentorial herniation	2 days
15	Transtentorial and infratentorial herniation	1,5 month
16	Subfalcine herniation	3 weeks
17	Subfalcine and infratentorial herniation	3 days
18	Subfalcine herniation, transtentorial and infratentorial herniation	8 days
19	Transtentorial herniation	until 1 hour
20	Transtentorial herniation	immediately
21	Transtentorial herniation	immediately
22	Transtentorial herniation	15 days
23	Subfalcine herniation, transtentorial and infratentorial herniation	4 days
24	Transtentorial and infratentorial herniation	5 days
25	Subfalcine and infratentorial herniation	7 days
26	Transtentorial herniation	4 hours
27	Subfalcine herniation, transtentorial and infratentorial herniation	6 hours
28	Transtentorial herniation	immediately
29	Transtentorial herniation	6 hours
30	Transtentorial herniation	immediately
31	Transtentorial herniation	until 1 hour
32	Infratentorial herniation	10 days
33	Transtentorial and infratentorial herniation	2 – 4 hours
34	Infratentorial herniation	4 days
35	Transtentorial and infratentorial herniation	7 hours
36	Infratentorial herniation	10 days
37	Infratentorial herniation	2 days
38	Transtentorial herniation	6 days
39	Transtentorial herniation	6 days
40	Transtentorial and infratentorial herniation	24 hours
41	Subfalcine and transtentorial herniation	7 days
42	Transtentorial herniation	2 days
43	Infratentorial herniation	3 days
44	Transtentorial and infratentorial herniation	minutes
45	Transtentorial and infratentorial herniation	8 days
46	Transtentorial herniation	2 days

Tab. 2 Time of survival for all cases diagnosed with internal herniation

Upon the data from the Table 2, it has been explored the interdependence between the occurrence of any type of herniation in the 46 of the examined cases and the survival time, presented on Table 3.

No. of cases in total	Cases with herniation	Percentage
Until 10,5 days	42	91 %
Until 2 days and 6 hours	23	50 %
Until 24 hours	14	30 %

Tab. 3 The interdependence of survival time with the occurrence of the herniation in 46 of the examined cases.

The results shown on Table 3 demonstrate that:
- in 91% of the cases with herniation, the herniation occurred within the first 10,5 days after the injury;
- in 50% of them, the herniation occurred in less than two days and 6 hours;
- in 30% of the cases, the herniation occurred within in the first 24 hours.

Regarding the hypoxic-ischemic lesion, from a total of 80 examined cases it was diagnosed in 42 (52,5%) of the cases. All cases with diagnosed ischemic lesion commonly had oedema of the brain and in all but one case some type of intracranial haemorrhage was present. Hence, all of those cases had raised ICP while alive. In order to objectively demonstrate the correlation between the occurrence of the hypoxic-ischemic lesion and the raised ICP expressed by signs of herniation, a statistical analysis was undertaken showing a strong association between the hypoxic-ischemic lesion and the herniation (Chi square = 11,10; ss = 1; p = 0,0009<0,01) (Tab. 4).

Hypoxic-ischemic lesion*Herniation correlation	Herniation	Non herniation	Total
Ischemia	31	11	42
Non ischemia	15	23	38
Total	46	34	80

Tab. 4 Correlation between hypoxic-ischemic lesion and herniation

Discussion

Object of this study was analysis of 80 cases of fatal closed head injury for the occurrence of secondary brain changes resulting from the increased ICP.

Signs of internal herniation as the sequelae of the raised ICP were present in 57,5% of the examined cases, which is in accordance with other studies: 56% by Adams et al. (24) and 55% of 85 examined cases by Adams et al. (25).

Signs of transtentorial herniation have been found in 33 (41,25%) of the cases (Fig. 1). Signs of infratentorial herniation have been found in 27 (33,75%) of the cases (Fig. 2), whereas signs of subfalcine herniation have been found in 9 (11,25%) of the examined cases. In a study with 434 analyzed cases, signs of transtentorial herniation have been found in two thirds of the cases, and signs of infratentorial herniation in 68% of cases (4).

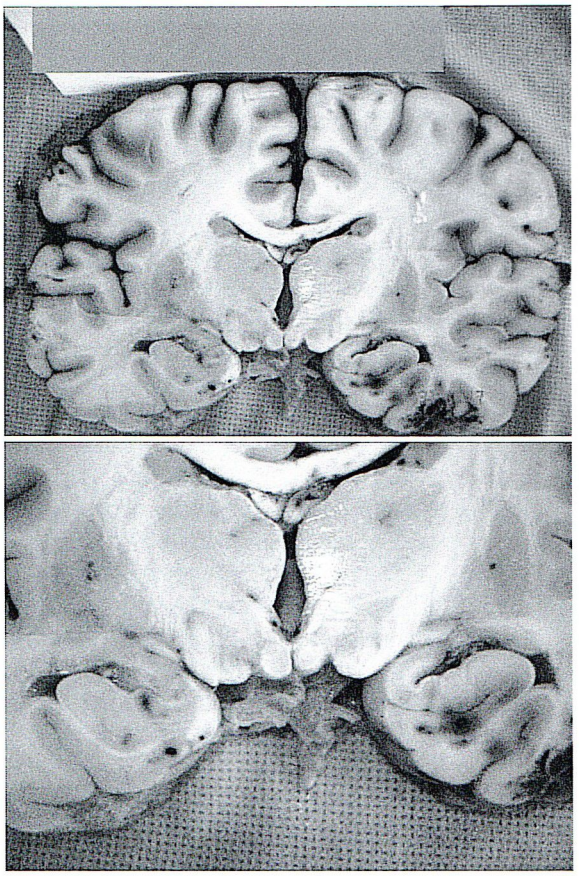

Fig. 1 Transtentorial herniation. Case with survival time of 3 – 4 hours and the brain weight of 1.503 grams. On the section of the level of mammilary bodies have been seen haemorrhages in the hippocampus and the parahippocampal region on both sides.

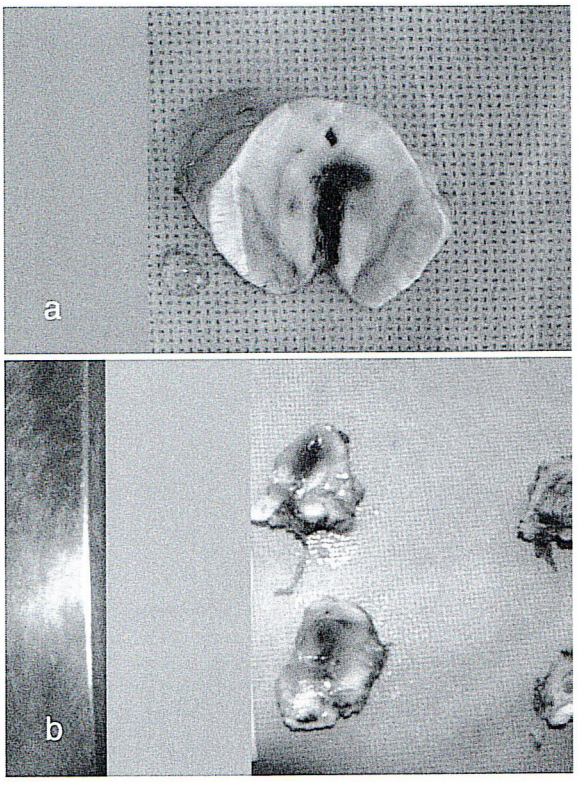

Fig. 2 Infratentorial herniation. The secondary Duret haemorrhages which are typically midline

located in the midbrain and pons can be seen.
a. Case with a survival of 7 hours and the weight of the brain of 1.487 grams;
b. Case with a survival of 8 days and the brain weight of 1.512 grams.

In 91% of the cases with internal herniation, as shown by the results in this study, herniation occurred within the time frame of 10.5 days post injury, implying that the threat of internal herniation is highest in the first 10 days after injury. Accordingly, in 50% of the cases, the herniation occurred in less than 2 days and 6 hours and in 31% of the cases it occurred in the first 24 hours. This analysis is mostly of clinical importance, obtaining information about the occurrence threat of internal herniation in cases with closed head injuries and possible time window for therapeutic intervention. From a forensic neuropathological point of view, besides the correlation with the survival time and proof for the existence of raised ICP ante mortem, this study emphasizes the morphological feature of herniation as it has been classically outlined.

Regarding the diffuse hypoxic-ischemic lesion, in our case material the most frequent macroscopic finding was found to be the "dusky" discoloration of the grey brain matter (Fig. 3 a). It was present on the brain surface, especially in the transition zones between the anterior and middle cerebral arteries, and also in the subcortical grey matter: basal nuclei, especially the *putamen* and the *hippocampus* (Fig. 3 b). Finding of cortical laminar necrosis was another sign of a prolonged ischemia (Fig. 4).

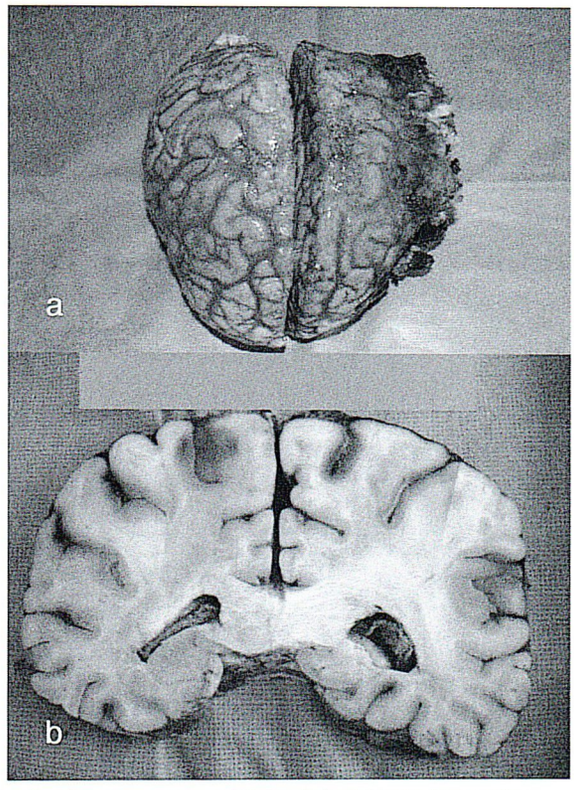

Fig. 3 Appearance of the global brain hypoxia
a. Case of a 20 years old female, injured as a pedestrian and with a survival time of 7 days: global and severe hypoxic-ischemic lesion with the typical „dusky" discoloration of the grey matter can be seen and the expansion of the left hemisphere;
b. Case with a survival of 7 hours, the case with the shortest survival time where ischemia could be seen by macroscopic examination. „Dusky" discoloration of the grey brain matter in the transition zones between the anterior and middle cerebral arteries can be perceived

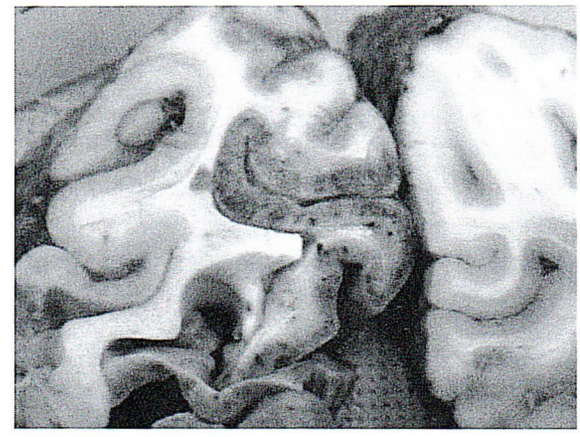

Fig. 4 The cortical laminar *necrosis* as a finding in brain ischemia. A case with a survival time of 10 days

According to the aforementioned criteria, the diffuse hypoxic-ischemic lesion was found in 42 (52,5%) of all cases and in 85% of the cases that survived more than three hours in our case material. In a study with cases of closed head injury that survived more than a month, diffuse ischemic lesion cases were found in 67% of the cases (25). The frequency of 91% has been published in another similar study, which greatly depends on the survival time of the included cases (3).

It is generally accepted that the ischemic lesion becomes visible 12 to 24 hours following the injury event. That was the reason why we paid particular attention to the correlation between the ischemic lesion and the survival time. As demonstrated on Figure 3 b, a clear macroscopic finding of ischemia was perceived 7 hours post injury in our case material. Earlier, it could be confirmed only by microscopic examination. When employing the classical H&E staining, the ischemic area showed pallor and eosinofile (acidophilic) neuronal degeneration, but it isn't likely to occur until 6 – 7 hours post injury (26). The neurons started to shrink after the first 24 – 36 hours and after 36 to 48 hours the neurons began to disappear except for the parts of the incrustrated nuclei.

The cellular reaction occurred even later. At least 1 – 2 hours after the *necrosis* some emigration of the neutrophils can be perceived. The activation of the first microglia (CD 68 immunoreactive) is starting at least 24 hours post injury (27) and a typical for microglia stellate grupations could be detected

around the focuses of damage approximately on 10th – 11th day post injury (18). Seemingly, the presence of the first reactive astrocytes could be seen at the edge of the necrotic focus after 4 – 6 days (7, 28) and astroglial reactivity is visible even several months following injury.

Hence, the visualization of the ischemic axonal damage in the first 6 hours after the injury is possible only by using the ß-APP immunohistochemistry (15, 16, 21-23). In our examined material the most-early ß-APP immunoreactivity with the typical ischemic pattern and distribution has been evidenced in two cases, the one with 3-hours survival and the other with 4-hours survival (Fig. 5). This makes the ß-APP immunohistochemical method a powerful tool for the evidencing ischemic changes in the early hours after injury (29). The most sensitive region where the axonal damage of ischemic origin can be manifested most-early was found to be the pons (16).

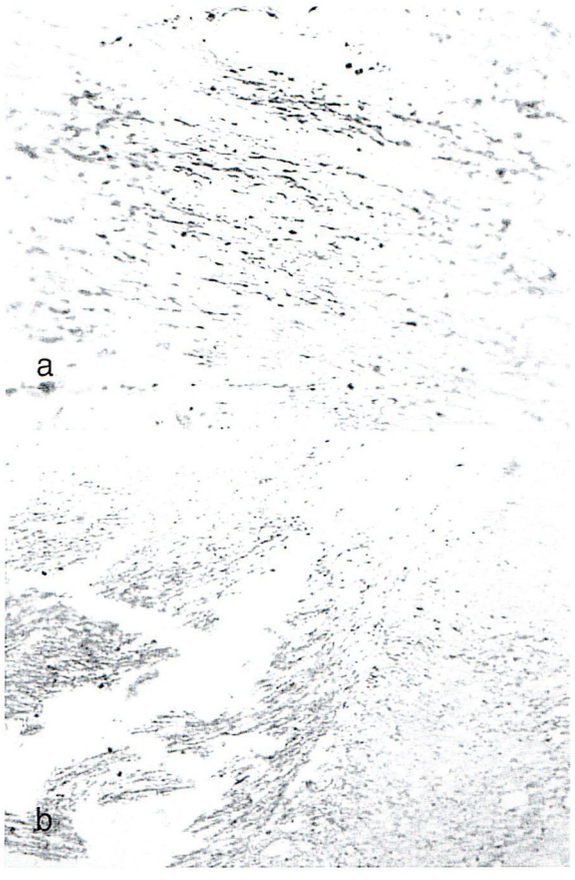

Fig. 5 Ischemic axonal injury expressed by β-APP immunoreactivity
a. Case with 3 hours of survival;
b. Case with 4 hours of survival

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.

As a conclusion, the results of the present study indicate that ischemic lesions can be found by macroscopic examination up to 6 – 7 hours post injury and by histological examination they may be perceived even three hours after the injury. The most convenient method for detection of early ischemia (3 hours post injury) is ß-APP immunohistochemistry.

Finally, the diffuse brain hypoxia and the internal herniation are associated processes, both of them occurring as a result of the raised ICP.

References

1. Adams H, Mitchell DE, Graham DI et al. Diffuse brain damage of immediate impact type. Its relationship to "primary brain stem damage" in head injury. Brain 1977; 100 (3): 489-502.
2. Adams HJ, Corsellis JAN, Duchen LW (Eds). Greenfield's neuropathology. 4th edition. New York; John Wiley & Sons, 1984.
3. Graham DI, Adams JH, Doyle D. Ischemic brain damage in fatal non-missile head injuries. J Neurol Sci 1978; 39: 213-234.
4. Graham DI, Lawrence AE, Adams JH et al. Brain damage in non-missile head injury secondary to high intracranial pressure. Neuropathol Appl Neurobiol 1987; 13: 209-217.
5. Graham DI, Gennarelli TA, McIntosh TK. Diffuse (multifocal) brain damage. In: Graham DI, Lantos PL (Eds) Greenfield's neuropathology 7th edn, vol. 1. London; Arnold, 2002: 854-875.
6. Miller JD, Ironside JW. Raised intracranial pressure, oedema and hydrocephalus, 1997. In: Graham DI, Lantos PL (Eds) Greenfield neuropathology, 6th edn. London; Arnold, 2002: 157-195.
7. Oehmichen M, Auer RN, Konig HG (Eds) Forensic neuropathology and associated neurology. Berlin Heidelberg; Springer-Verlag, 2006: 660 p.
8. Dolinak D, Matshes E (Eds) Medicolegal neuropathology. New York; CRC Press, 2002: 280 p.
9. Kalimo H, Saukko P, Graham D. Neuropathological examination in forensic context. Forensic Sci Int 2004; 146: 73-81.
10. Davceva N, Janevska V, Ilievski B et al. The importance of the detail forensic-neuropathological examination in the determination of the diffuse brain injuries. Soud Lek 2012; 57 (1): 2-6.
11. Itabashi HH, Andrews JM, Tomiyasu U et al. (Eds) Forensic neuropathology. A practical review of the fundamentals. London; Elsevier, 2007: 481 p.
12. Shcrum MJ, Ramsay DA. Forensic pathology of trauma, common problems for the pathologist. Totowa New Jersey; Humana Press, 2007: 646 p.
13. Graham DI, Smith C, Reichard R et al. Trials and tribulations of using β-amyloid precursor protein immunohistochemistry to evaluate traumatic brain injury in adults. Forensic Sci Int 2004; 146: 89-96.
14. Reichard RR, Smith C, Graham DI. The significance of β-APP immunoreactivity in forensic practice. Neuropathol Appl Neurobiol 2005; 31: 304-313.
15. Davceva N, Janevska V, Ilievski B et al. The occurrence of acute subdural haematoma and diffuse

axonal injury as two typical acceleration injuries. J Forensic Leg Med 2012; 19: 480-484.
16. Davceva N, Janevska V, Ilievski B et al. Dilemmas concerning the diffuse axonal injury as a clinico-pathological entity in forensic medical practice. J Forensic Leg Med 2012; 19: 413-418.
17. Sheriff FE, Bridges LR, Sivaloganatham S. Early detection of axonal injury after human head trauma using immunocytochemistry for beta-amyloid precursor protein. Acta Neuropathol 1994; 87: 55-62.
18. Geddes JF, Whitwell HL, Graham DI. Traumatic axonal injury: practical issues for diagnosis in medico legal cases. Neuropathol Appl Neurobiol 2000; 26: 105-116.
19. Oehmichen M, Walter T, Meissner C et al. Time course of cortical haemorrhages after Closed Traumatic Brain injury: Statistical Analysis of Posttraumatic histomorphological alterations. Journal of Neurotrauma 2003; 20: 87-103.
20. Hausmann R, Riess R, Fieguth A et al. Immunohistochemical investigations on the course of astroglial GFAP expression following human brain injury. Int J Leg Med 2000; 113: 70-75.
21. Graham DI, Smith C, Reichard R et al. Trials and tribulations of using β-amyloid precursor protein immunohistochemistry to evaluate traumatic brain injury in adults. Forensic Sci Int 2004; 146: 89-96.
22. Reichard RR, Smith C, Graham DI. The significance of beta-APP immunoreactivity in forensic practice. Neuropathol Appl Neurobiol 2005; 31: 304-313.
23. Smith C, Graham DI, Geddes JF et al. The interpretation of β-APP immunoreactivity: a response to C. Neiss et al. Acta Neuropathol 2002; 104: 79. Acta Neuropathol 2003; 106: 97-98.
24. Adams JH, Graham DI, Muray LS et al. Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases. Ann Neurol 1982; 12: 557-563.
25. Adams JH, Jannet B, Murray LS et al. Neuropathological findings in disabled survivors of a head injury. J Neurotrauma 2011; 28: 701-709.
26. Finnie JW. Forensic pathology of traumatic brain injury – Review. Veterinary Pathology 2016; 53 (5): 962-978.
27. Geddes JF, Vowles GH, Beer TW et al. The diagnosis of diffuse axonal injury: implications for forensic practice. Neuropath Appl Neurobiol 1997; 23: 339-347.
28. Ekmark-Lewen S, Lewen A, Israelsson C et al. Vimentin and GFAP responses in astrocytes after contusion trauma to the murine brain. Restor Neurol Neurosci 2010; 28 (3): 311-321.
29. Kubo S, Kitamura O, Orihara Y et al. Immunohistochemical diagnosis and significance of forensic neuropathological changes. J Med Invest 1998; 44 (3-4): 109-119.