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## Possible Coexistence of Traumatic Cerebral Microbleeds and Axonal Injury? Postmortem Immunohistochemical Analysis

هل من المكن وجود نزيف دماغي دقيق الناتج عن رضة وتضرر في الألياف العصبية معًا؟ تحليل ما

بعد الوفاة باستخدام الأجسام المضادة

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#### المستخلص

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# type of ains a suggest إصابات الدماغ الرضية، ولا يزال اكتشافه يشكل تحديًّا سريريًّا كبيرًا. تشير وي الألياف العصبية بالدماغ (DAI) نوعًا شائعًا من suggest إصابات الدماغ الرضية، ولا يزال اكتشافه يشكل تحديًّا سريريًّا كبيرًا. تشير y serve similar تكون مؤشرات غير مباشرة لتلف المحاور العصبية (العصبونات). نظرًا للآليات المتشابهة الكامنة وراء تكوين تلف المحاور العصبية وحالات النزيف الدقيقة الدماغية، فإن الهدف من هذه الدراسة هو التحقيق في العلاقة المحتملة بين eserve المتشابهة الكامنة وراء تكوين تلف المحاور العصبية وحالات النزيف الدقيقة ولا يمن المتشابهة من هذه الدراسة هو التحقيق في العلاقة المحتملة بين ولا تحمي من الصدمات الدماغية.

في العينة الكلية الكونة من 36 دماغًا، تم الكشف عن تلف الحاور العصبية في 32 حالة (88.9%)، وهو ما يطابق تمامًا نسبة حدوث حالات النزيف الدقيقة الدماغية الرضية. كان التفاعل المناعي لبروتين (βAPP) موزعًا بشكل متساو نسبيًا عبر مناطق الدماغ التي تم فحصها، مع تعبير أقوى قليلاً في مناطق الدماغ الخلفية وكان أعلى معدل لظهور قوي للمواد المناعية موجودًا في منطقة يشير اختبار مربع كاي (2%)، جنبًا إلى جنب مع اختبار ارتباط سبيرمان، إلى يشير اختبار مربع كاي (2%)، جنبًا إلى جنب مع اختبار ارتباط سبيرمان، إلى وجود ارتباط بين حالات النزيف الدقيقة الرضية في الجزء الأمامي من الجسم الثفني والتفاعل المناعي لبروتين (βAPP) في جميع مناطق الدماغ الأربعة التي لوحظت، مع أقوى ارتباط لوحظ في الجزء الأمامي من الجسم الثفني (p=0.01).

**الكلمات المُتاحية:** علوم الأدلة الجنائية، إصابة الدماغ الرضية، تلف المحاور العصبية المنتشر، النزيف الدماغي الرضي الدقيق، ببتيدات بيتا الأميلودية.

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### Abstract

Diffuse axonal injury (DAI) is a common type of traumatic brain injury, whose detection remains a significant clinical challenge. Recent studies suggest that traumatic cerebral microbleeds (TCMs) may serve as indirect indicators of axonal injury. Given the similar mechanisms underlying the formation of axonal injury and cerebral microbleeds, the aim of this study is to investigate the potential association between these two types of cerebral trauma.

In the total sample of 36 brains, axonal injury was detected in 32 cases (88.9%), identical to the incidence of traumatic cerebral microbleeds.  $\beta$ APP immunopositivity was relatively evenly distributed across the examined brain regions, with slightly stronger expression in the posterior brain regions and the highest frequency of intense immunopositivity in the pons, albeit without statistical significance. The  $\chi$ 2 test, along with the Spearman correlation test, indicates an association between traumatic microbleeds in the genu of the corpus callosum and  $\beta$ APP immunopositivity in all four observed brain regions, with the strongest correlation observed in the genu of the corpus callosum (p=0.011).

**Keywords:** Forensic sciences, Craniocerebral trauma, Diffuse axonal injury, Traumatic cerebral microbleeds, Amyloid beta-peptides.



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 $\beta$ APP immunohistochemical staining revealed a relatively uniform distribution of axonal injury and microhemorrhages throughout the examined mid-sagittal brain structures. A slightly stronger  $\beta$ APP expression was detected in the pons, though without statistical significance. The observed positive correlation between traumatic cerebral microbleeds and axonal injury in the anterior aspects of the corpus callosum aligns with current assumptions that the mid-sagittal brain regions are critical for the relationship between these two types of cerebral lesions.

#### 1. Introduction

Craniocerebral injuries are among the leading causes of disability and mortality worldwide, posing a significant challenge and burden to the healthcare sector of any society. Their incidence varies from country to country depending on data collection methodologies, but relevant studies report approximately 70 million craniocerebral injuries annually or a global incidence of 939 cases per 100,000 people per year [1, 2].

A particular issue in craniocerebral traumatology is diffuse axonal injury (DAI), which is considered to be present in the majority of severe head trauma cases, particularly those resulting from traffic accidents involving loss of consciousness. DAI is diagnosed in 40-50% of severe craniocerebral injuries, with one-third of cases proving fatal [3, 4]. Unfortunately, the exact incidence of DAI is not well known due to diagnostic challenges and frequent overlap with other types of cerebral lesions. Axonal injury occurs due to acceleration-deceleration mechanisms. usually accompanied by head rotation, which causes shearing and stretching of specific layers of brain tissue. Rotational and lateral head movements lead to more intense shearing of tissue layers and more severe axonal injury compared to sagittal head movements. The most vulnerable structures are the central brain regions, including the corpus callosum and the upper brainstem [5, 6]. Detecting axonal injury remains a major clinical challenge

كشف التلوين المناعي الهيستولوجي لبروتين (βAPP) عن توزيع موحد نسبيًا لتلف الحاور العصبية وحالات النزيف الدقيقة في جميع البنى الدماغية الواقعة في الخط الناصف التي تم فحصها. تم الكشف عن تعبير أقوى قليلاً لبروتين (βAPP) في الجسر، على الرغم من عدم وجود دلالة إحصائية. يتوافق الارتباط الإيجابي الملحوظ بين حالات النزيف الدقيقة الدماغية الرضية وتلف الحاور العصبية في الجوانب الأمامية من الجسم الثفني مع الافتراضات الحالية بأن مناطق الدماغ الواقعة في الخط الناصف ضرورية للعلاقة بين هذين النوعين من الإصابات الدماغية.

despite significant technological advancements in radiological diagnostics. Recent studies cautiously suggest that traumatic cerebral microbleeds (TCMs) may serve as indirect indicators (radiological markers) with prognostic significance in verifying axonal injury. Additional difficulties in radiological research of TCMs arise from the phenomenon that these lesions may "appear and disappear" on MRI scans during the acute post-traumatic phase. Consequently, the optimal timing for radiological assessment of the presence, number, and size of these cerebral microbleeds as potential prognostic factors remains an open question requiring further research [7, 8]. TCMs result from the rupture of the smallest blood vessels in brain tissue, typically occurring at the gray-white matter interface and in the corpus callosum, forming perivascular spaces in a more radial and/or linear pattern, in contrast to predominantly round hemorrhagic foci observed in pathological cerebral microvasculature changes.[9] TCMs are commonly defined as round hemorrhagic foci with a diameter of less than 5 mm[10] or as oval hemorrhagic foci measuring 2-10 mm in diameter [11].

Given the similar mechanisms underlying axonal injury and cerebral microbleeds (stretching and shearing of brain tissue layers), this study aims to investigate the potential association between the occurrence of these two types of cerebral trauma.

#### 2. Methods

For this study, approval was obtained from the Ethics Committee of the University Clinical Center of the Republic of Srpska in Banja Luka (Nr. 01-9-443.2/15, date 11/2/2015) and the Ethics Committee of the Faculty of Medicine at the University of Novi Sad (Nr. 00-82/21, date 04/23/2021).

The material for this study comprised brain tissue from individuals who suffered fatal accelerationdeceleration injuries, autopsied at the Institute of Forensic Medicine of the Republic of Srpska in Banja Luka. The research sample consisted of brain tissue sections from 36 deceased adults, involved in acceleration-deceleration mechanisms including traffic accidents (drivers and passengers in motor vehicles, pedestrians, cyclists, motorcyclists), falls from height, and head impacts. The examined brain regions were selected as predilection sites for axonal injury, including the parasagittal white matter of the frontal lobe, genu of the corpus callosum (CCG), splenium of the corpus callosum (CCS), and the rostral pons. Data on the exact time and cause of injury, as well as time of death, were obtained from police reports and medical documentation. After death, the bodies were kept in the mortuary refrigerator, and autopsies were performed within the next 24 to 36 hours postmortem. The control group consisted of brain tissue from 10 deceased adults without verified craniocerebral injuries, epilepsy, neurodegenerative, diffuse ischemichypoxic, hypoglycemic, or inflammatory changes in brain. Cases were excluded from the study if the manner or time of injury was unknown, if there was brain destruction, if the individuals were younger than 16 years, or if they exhibited global ischemichypoxic brain changes, confirmed hypoglycemia, neurodegenerative or inflammatory brain changes, epilepsy, or a known history of craniocerebral trauma.

In addition to axonal injury, the analysis included gender and age of the deceased, type of trauma, and presence of microscopically verified perivascular erythrocyte extravasations massive gu to macroscopic hemorrhages measuring up to 10 mm in diameter. Macroscopic examination of the brain was conducted using cross-sections approximately 1 cm thick, with horizontal sections of the brainstem and cerebellum about 0.5 cm thick. Tissue blocks were collected from the parasagittal white matter of the frontal lobe, genu and splenium of the corpus callosum, and the rostral pons. After fixation in buffered 10% formalin, standard tissue processing and histological slide preparation were performed. Hematoxylin-eosin staining was used to identify the presence of microbleeds, manifested as abundant extravasation of fresh and/or lysed erythrocytes with a hemosiderin component and localized macrophage reaction. For immunohistochemical analysis, monoclonal antibodies for β-amyloid precursor protein (BAPP - Monoclonal Mouse Anti-Human β-Amyloid, Dakocytomation, Cat. No. M 0872) were used, along with antigen-antibody complex labeling via the streptavidin-biotin link (LSAB, Dakocytomation, Cat. No. K 0690) and visualization of sections using diaminobenzidine (DAB, Dakocytomation, Cat. No. K 3466). The presence of **BAPP** positivity in the analyzed samples was identified by the presence of axonal spheroids and/or varicosities and was semi-quantitatively assessed according to the Gentleman scale [12]: "0" – no positivity

 "+" – weak positivity (isolated, sporadically scattered axonal varicosities)

• "++" - typical positivity (individual or grouped axonal spheroids and varicosities)

• "+++" – very pronounced positivity (diffuse staining throughout the white matter, covering a large portion of the visual field).

Statistical analysis was performed using the SPSS 16.0 software. Gender and age distribution, as well as the mode of injury, were presented numerically and as percentages, using mean values and medians. Categorical variables were compared and their interrelation was examined using the non-parametric  $\chi^2$  test and Fisher's exact test. The correlation between two ordinally scaled variables was analyzed using Spearman's rank correlation coefficient. The threshold for statistical significance was set at p < 0.05.

#### 3. Results

Table 1 presents the basic demographic characteristics and the mechanism of injury.

In the total sample of 36 brains, the presence of axonal lesions was confirmed in 32 cases (88.9%). Axonal injuries were identified11 in the parasagittal white matter in 75% of cases, in the CCG in 72.2%, in the CCS and pons in 77.8% of cases each.  $\beta$ APP immunostaining showed a relatively uniform distribution of axonal lesions across the observed brain tissue regions, with slightly stronger immunopositivity in the posterior brain structures and the highest frequency of strong immunopositivity in the pons, Table 2, and Figure 1.

TCMs observed as macroscopic hemorrhages up to 10 mm in diameter and microscopically verified hemorrhages in the examined brain regions, were found in 88.9% of cases Figure 2, and Figure 3.

The presence of TCMs in the observed brain regions was slightly more frequent in the posterior compared to the anterior brain regions, similar to the distribution of axonal lesions, Fig. 4.

Figure 4 shows Frequency of axonal lesions and TCM in the observed brain regions.

The  $\chi^2$  test indicates a correlation between traumatic microbleeds in the CCG and  $\beta$ APP immunopositivity in all four observed brain regions,

**Table 1-** Demographic characteristics and mechanism of injury

Variable	N (%)
Sample: total (m/f)	36- 30m/6f (83.3/16.7)
Age: range mean median	18 – 81 y. 48 year (SE 3.253) 51 year (SD 19.518)
Injury mechanism: driver/passenger in the vehicle pedestrian cyclists/motorcyclists fall from height blow to the head	12 (33.3) 10 (27.8) 8 (22.2) 4 (11.1) 2 (5.6)

**Table 2-** Distribution of  $\beta$  APP immunoexpression in observed brain regions

Imunopositivity	*Front. (N)	CCG (N)	CCS (N)	Pons (N)
+	15	8	8	7
++	10	16	17	9
+++	2	2	3	12
0	9	10	8	8



**Figure 1-** shows βAPP immunopositivity in the pons after 50 hours of survival following trauma (54 years old cyclist Legend: Numerous varicose axonal thickenings. Woman, 54 years old, cyclist. βAPP immunostaining, 40x magnification

with the strongest association between these two variables found in the CCG (p = 0.011).



Figure 2- TCM in the parasagittal white matter of the frontal lobe

Legend: TCM at the border of white / gray matter of the frontal lobe.



**Figure 3-** TCM in the parasagital white matter of the frontal lobe. Legend: Numerous perivascular massive extravasations of erythrocytes (microhaemorrhages). H&E staining, 10x

Table 3- Possible correlation of βAPP immunopositivity	(according to	Gentleman's scale)	) and traumatic micr	obleeds in the
observed brain regions.				

	TCM Front.	TCM CCG	TCM CCS	TCM Pons
βAPP Front.	0,138 (0,297*)	0,024 (0,417*)	0,613 (0,060*)	0,815 (0,031*)
βAPP CCG	0,544 (0,101*)	0,011 (0,312*)	0,695 (0,144*)	0,376 (-0,217*)
βΑΡΡ CCS	0,498 (-0,109*)	0,023 (0,130*)	0,723 (0,058*)	0,638 (-0,062*)
βAPP Pons	0,385 (-0,033*)	0,047 (0,176*)	0,944 (0,062*)	0,160 (0,010*)

Table 4- Relationship between axonal injury (grouped data) and traumatic microbleeds in observed brain regions.

	TCM Front	TCM CCG	TCM CCS	TCM Pons
βAPP Front.	0,028	0,030	0,574	0,486
βAPP CCG	0,282	0,004	0,321	0,518
βAPP CCS	0,926	0,030	0,653	0,842
βAPP Pons	0,354	0,030	0,653	0,112

Table 3 presents possible correlation between  $\beta$ APP immunopositivity (according to Gentleman's grading) and traumatic microbleeds in the observed brain regions.

When grouping the data into the presence/ absence of axonal lesions, the  $\chi^2$  test confirmed a statistically significant correlation between the presence of axonal lesions and microbleeds in the white matter of the frontal lobes (p = 0.028, Fisher's exact test 0.046), as well as in the CCG (p = 0.004, Fisher's exact test 0.007), but no significant correlation was found in the CCS and pons, Table 4.

#### 4. Discussion

Craniocerebral injuries are the leading global cause of mortality and disability in young adults (up to 45 years of age), with traffic accidents and falls being the most common causes of head trauma [13, 14]. The results of this study confirm these trends regarding the most frequent mechanisms of





craniocerebral injury, with traffic accidents being the predominant cause (>80%). A significantly higher prevalence of male victims was observed (male-tofemale ratio of 5:1). This pronounced disproportion deviates from recent reports suggesting that men are 1.5 to 3 times more likely to sustain craniocerebral injuries[15, 16] but is similar to findings in some other studies [4, 17,18, 19]. Notably, all female victims in this study sustained injuries in traffic accidents, which may indicate traffic as a potential risk factor for adult women in our region.

DAI represents axonal damage that is diffusely distributed throughout the white matter of the brain, predominantly affecting the corpus callosum, brainstem, and parasagittal white matter of the cerebrum and cerebellum. In this study DAI was confirmed in 88.9% of cases, which aligns with the established understanding that axonal lesions are almost invariably present in severe accelerationdeceleration head injuries [12, 20, 21]. The high success rate of confirming axonal lesions is likely due to postmortem examination of carefully selected cases and the application of an optimal immunohistochemical diagnostic method, which is challenging to achieve in clinical studies. The

overwhelming presence of traffic-related trauma in cases of axonal injury in this study supports current opinions that traffic accidents are among the most common acceleration-deceleration mechanisms of head trauma and can be considered a risk factor for axonal injury in modern life.[22] The four brain regions analyzed in this study, known to be predilection sites for axonal lesions, exhibited a relatively even distribution of axonal injury, ranging from 72.2% to 77.8%. A slightly higher frequency and stronger immunoexpression were observed in the posterior brain regions (CCS and pons), although the differences were not statistically significant. This distribution is understandable, considering that the study sample consisted of the most severe, fatal cases of head trauma. Clinical radiological studies indicate that the localization and number of axonal lesions influence the final outcome of head trauma, although this depends on the research methodology and the applied MRI techniques (advanced MRI technologies are more effective in detecting the smallest foci of microbleeding [23, 24]. Compared to clinical radiological studies, postmortem neuropathological examinations of appropriate cadavers remain superior in detecting direct or indirect (e.g., inflammatory) cellular damage.[25] This study examined the simultaneous distribution of axonal lesions and cerebral microhemorrhages in the observed brain regions to determine whether the same or similar traumatic shear and stretching mechanisms affecting different brain tissue layers simultaneously cause axonal and vascular injury. Numerous studies suggest that trauma-induced microbleeds in the white matter may serve as an indirect marker of axonal lesions, but clear and reliable evidence of this correlation remains lacking [8, 26, 27, 28]. In the 1980s, Adams observed that microhemorrhages and axonal lesions frequently co-occur in the corpus callosum.[29] Similar findings were reported in a recent clinical study by Andreasen et al., conducted using advanced MRI techniques (SWI and DTI), which attempt to explain this by the uniform alignment of numerous axons in the corpus callosum, facilitating the detection of their damage [8]. Other studies suggest that acceleration-deceleration forces acting on the head cause shearing of brain tissue layers, leading to concurrent injury of small blood vessels and axons in the same regions [30, 31, 32]. Griffin et al. did not confirm a definite link between these two types of diffuse brain injury but did not rule out the possibility that traumatic microbleeds in the white matter may coexist in patients with DAI [33].

In this study, TCM were confirmed in 32 out of 36 cases (88.9%). A comparison of the presence of microhemorrhages and  $\beta$ APP immunopositivity in the same observed brain regions revealed a correlation between these two types of lesions in the CCG, confirmed by the  $\chi^2$  test (p = 0.011). When axonal lesion data were grouped (present/ absent), this correlation was found not only in the CCG (p = 0.004) but also in the parasagittal white matter of the frontal lobes (p = 0.028). Additionally, a similar association was observed between the

presence of microhemorrhages in the CCG and axonal lesions in the other three examined brain regions. These results suggest a likely positive correlation between traumatic microbleeds and axonal lesions in central brain structures. Ubukata et al. found a link between axonal lesion-induced chronic cognitive deficits and volumetric and microstructural changes in the corpus callosum, emphasizing that this applies to chronic changes, whereas acute neurological sequelae and injury severity markers may be located in other regions, such as the brainstem [34]. Rutgers et al. found that in mild craniocerebral injuries, corpus callosum lesions are typically localized in the anterior portion and are reversible within three months. In severe head trauma, all regions of the corpus callosum are affected, and the lesions are chronic [35]. The findings of these studies largely correspond with our study results, indicating that in fatal craniocerebral injuries, both anterior and posterior regions of the corpus callosum are affected by axonal lesions, regardless of the somewhat different anatomical characteristics (diameter, myelination status, density) of axonal fibers in various callosal regions. Considering all the above, the observed association between microbleeds in the anterior corpus callosum and axonal lesions in topographically adjacent brain regions is not surprising. Apart from this questionable link between axonal and vascular lesions, some studies suggest that TCMs also have independent clinical significance as a predictor of poor outcomes in craniocerebral trauma[36], although more recent research challenges this notion [37] .

Axonal lesions and TCMs, in addition to their undeniable clinical significance, also have great forensic importance. First and foremost, it is essential to determine their origin - whether traumatic or nontraumatic. Both types of lesions represent vital reactions, confirming their antemortem occurrence. Furthermore, the presence of axonal lesions also indicates that death did not occur immediately after the head injury.

Strengths and limitations of study: Compared to various clinical, primarily radiological studies, a postmortem examination of brain tissue provides more precise and reliable information about the observed axonal and vascular lesion. However, the total sample size, as well as the limited number of analyzed brain tissue locations (only four), restricts the possibilities for statistical analysis and the relevance of the obtained data. Further research on this topic is necessary, involving larger samples, a greater number of analyzed brain tissue locations, and more strictly controlled accelerationdeceleration mechanisms of craniocerebral injury.

#### 5. Conclusions

This study identified a positive correlation between the presence of microhemorrhages and  $\beta$ APP immunopositivity in the anterior aspects of the corpus callosum, supporting current perspectives that there is likely a connection between traumatic cerebral microbleeds (TCM) and axonal lesions in mid-sagittal brain regions.

#### **Conflict of interest**

The authors declare no conflicts of interest.

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