Quantitative analysis of capsular microvasculature in relation to the thickness of chronic subdural hematoma

Kvantitativna analiza kapsularne mikrovaskularizacije u odnosu na debljinu hroničnog subduralnog hematoma

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Abstract

Background/Aim. Chronic subdural hematoma (CSDH) is an extra-axial, encapsulated, slow-growing hemorrhagic collection of blood, accompanied by local coagulopathy. This contributes to continuous re-bleeding from the newly formed capsule of hematoma, which leads to slow but progressive enlargement of the hematoma, with the potential to develop into a compressive intracranial lesion. The aim of this study was to investigate the relationship between the proliferation of sinusoid blood vessels and the growth and diameter of the CSDH. **Methods.** In this study, 33 cases of CSDH treated operatively were analyzed. A biopsy specimen (average size 3 × 3 mm) was obtained from the parietal capsule of the hematoma. The biopsied tissue samples were fixed in aqueous 4% buffered formaldehyde, routinely processed into paraffin-embedded slides, and immunohistochemically stained for the presence of the CD34 antigen. The profiles of microvascular bed blood vessels marked for CD34 were quantified, and the number of capillaries and sinusoids was expressed *per* one mm². **Results.** The variables age and number of blood vessels showed a statistically significant association with the increase in hematoma volume (β = 0.422, *p* = 0.007; β = 0.486, *p* = 0.022, respectively). Older patients had a higher risk of enlarged hematoma volume, as did patients with a larger number of sinusoidal blood vessels. **Conclusion.** The number of sinusoids in the parietal capsule of CSDH *per* surface unit of 1 mm² positively correlates with hematoma thickness, which emphasizes the importance of vascular theory in the development of a hematoma. Although CSDH is one of the most common neurosurgical diseases, its pathogenesis is still not fully understood. Further research in this field is necessary to develop potential new therapeutic options that would provide more comprehensive treatment modalities.

Keywords:
biopsy; blood vessels; capillaries; hematoma, subdural, chronic; immunohistochemistry.

Apstrakt

Uvod/Cilj. Hronični subduralni hematom (*chronic subdural hematoma* – CSDH) je ekstraaksijalna, inkapsulirana, sporo rastuća kolekcija krvi, praćena lokalnom koagulopatijom. To doprinosi kontinuiranom ponovnom krvarenju iz novoformirane kapsule hematoma, što dovodi do sporog, ali progresivnog uvećanja hematoma sa potencijalom da se razvije u kompresivnu intrakranijalnu leziju. Cilj rada bio je da se ispita odnos između proliferacije sinusoidnih krvnih sudova i rasta i prečnika CSDH. **Metode.** U ovoj studiji, analizirana su 33 slučaja CSDH koja su operativno lečena. Uzet je uzorak biopsije iz parijetalne kapsule hematoma (prosečne veličine 3 × 3 mm). Uzorci tkiva dobijeni biopsijom fiksirani su u 4% vodenom rastvoru formaldehida, rutinski su pripremljeni parafinski preseci na pločicama i obojeni imunohistohemijskim metodama u cilju detekcije prisutva CD34 antigena. Profili krvnih sudova mikrovaskularne mreže koji su ispoljavali CD34 su kvantifikovani, a broj CD34 pozitivnih kapilara i sinusoida izražen je po jednom mm². **Rezultati.** Variable starost i broj krvnih sudova pokazale su statistički značajnu povezanost sa povećanjem zapremine hematoma (β = 0,422; *p* = 0,007; β = 0,486; *p* = 0,022, redom). Stariji bolesnici imali su veći rizik od uvećanja zapremine hematoma, kao i bolesnici sa većim brojem sinusoidnih krvnih sudova. **Zaključak.** Broj sinusoida u parijetalnoj kapsuli CSDH po jedinici površine od 1 mm² pozitivno korelira sa debljinom hematoma, što naglašava značaj vaskularne teorije u razvoju hematoma. Iako je CSDH jedno od najčešćih neurohirurških oboljenja, njegova patogeneza još uvek nije potpuno razjašnjena. Dalja

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istraživanja u ovoj oblasti neophodna su kako bi se razvile potencijalno nove terapijske opcije koje bi pružile sveobuhvatnije modalitete lečenja.

Introduction

Chronic subdural hematoma (CSDH) is defined as a chronically progressive accumulation of blood in the space between the *dura mater* and arachnoid, usually caused by minor, often unnoticed head injury, with the highest incidence in the elderly. The CSDH is accompanied by hypocoagulability, which results in slow but progressive enlargement of the hematoma, with the potential to develop into a compressive intracranial lesion [1–3]. In everyday clinical practice, CSDH is often considered one of the largest "imitators" due to the wide range of non-specific symptoms [3, 4]. Symptoms of CSDH in most cases include the following: a headache, cognitive alterations, dizziness, nausea, vomiting, lethargy, weakness, apathy, as well as epileptic seizures [2–4].

Meningeal (bridging) veins, measuring 1–3 mm in diameter, drain venous blood from the leptomeningeal region, traversing the subdural space in a relative length of 1–2 cm. Their wall thickness varies considerably in the subdural segment (10–600 μm) compared with their subarachnoid portion (50–200 μm). Variable wall thickness, together with a substantial presence of fibrous connective tissue in their walls, makes these veins susceptible to trauma [1, 2, 4].

At the *dura mater*–arachnoid interface (subdural space), there are also other constitutional weak spots potentially targeted by a traumatic event. *Dura mater* is composed of two indistinctly divided layers. The thick outer layer (periosteal) contains venous sinuses of the skull, larger blood and lymphatic vessels, and nerve fibers. The inner (meningeal) layer of the *dura mater* is thinner and composed of dense fibrous connective tissue with microvasculature. Facing the subdural space, the *dura mater* is lined by squamous-shaped fibroblasts-the border cell layer, which lacks the extracellular collagen, thus representing its structural *locus resistentiae minoris*, with potential for regional vulnerability [1–4].

In the course of subdural hematoma chronification, the formation of neomembrane (capsule) around its blood collection is a crucial event [4–8]. The capsule of developing CSDH has an outer (parietal) layer that contains numerous capillaries and sinusoids, with a vascular lumen wider than 40 μm in diameter. On the inner side of the hematoma, the visceral pseudomembrane is formed, which separates the clot from the arachnoid membrane [7, 8]. Based on ultrastructural observations, the visceral membrane is almost avascular, whereas the parietal layer of the capsule exhibits marked and likely more clinically significant pathological vascularization [4–8].

The aim of this study was to investigate the relationship between the proliferation of sinusoid blood vessels (SBV) and the growth and diameter of the CSDH.

Methods

The study included 33 patients surgically treated due to CSDH at the Clinic of Neurosurgery, University Clinical Center Niš, Niš, Serbia. The study was approved by the Ethics Committee of the University Clinical Center Niš (No. 9328, from January 19, 2024).

The examined population comprised 25 (75.8%) men and 8 (24.2%) women, and the results were analyzed in relation to three age groups. The first group included patients under 65 years of age, the second group patients between 65 and 80, and the third group patients over 85 years of age. An analysis of sinusoid vasculature *per* mm^2, hematoma osmolality, cerebrospinal fluid osmolality, and hematoma volume was performed. In terms of the number of SBV (NSBV)/mm^2, all patients were classified into three categories. The first category included patients with fewer than 30 sinusoids/mm^2 the second group comprised those with 30–80 sinusoids/mm^2, and the third group included patients with a vascular density greater than 80 sinusoids/mm^2. The largest number of patients, 20 (61%), had a value of this indicator between 30 and 80 mm^2, 12 (36%) patients had over 80 blood vessels/mm^2, while only one patient had a vascular density below 30/mm^2. Depending on the size of the hematoma, the patients were divided into three groups: the first with a volume of less than 50 mL, the second with a volume of 50 to 70 mL, and the third with a hematoma volume greater than 70 mL. In the majority of patients, 15 (46%), the size of the hematoma was between 50 and 70 mL, in 12 (36%) patients the volume was lower than 50 mL, while in 6 (18%) patients, it was greater than 70 mL.

All patients were operated on under general anesthesia. The decompression procedure consisted of a conventional burr hole craniotomy. One burr hole was placed at the tuber parietale of the parietal bone, after which a cross-shaped opening was made on the *dura mater*. The hematoma was irrigated. Drainage was placed subdurally, and the soft tissues were sewn *en bloc*. From each case of CSDH, a biopsy of the parietal hematoma capsule layer was taken, with average dimensions of 3 × 3 mm. Postoperatively, drainage was active for 1–3 days (typically 2). The biopsied tissue samples of the parietal layer were fixed in aqueous 4% buffered formaldehyde and routinely processed to paraffinized tissue slices, which were stained with hematoxylin and eosin, as well as immunohistochemically marked for the presence of CD34 antigen.

Immunohistochemistry

The adhered tissue sections were exposed to trypsin antigen retrieval for 60 min, and tissue peroxidases were

blocked with 3% hydrogen peroxide solution for 10 min. The monoclonal antibody to CD34 (anti-CD34, Dako, M716501, dilution 1 : 50) was applied to the rehydrated tissue sections overnight, at a temperature of 4 ºC, and then to the secondary antibody conjugated with horseradish peroxidase (EnVision-Flex, Dako). Between the mentioned steps, the preparations were washed with phosphate buffer (pH = 7.2). After exposure to a chromogen (diaminobenzidine), the tissue samples were counterstained with Mayer's hematoxylin, dehydrated, cleared, and mounted using Canada balsam and coverslips.

The microscopic slides were analyzed using a light microscope BX50 (Olympus, Japan), equipped with a digital camera Leica DFC295 (Leica Systems, Germany). Digital images of the whole hematoma capsule samples, immunohistochemically marked for CD34, were captured at ×200 magnification. Morphometric analysis of digital images of the CSDH capsule was performed using ImageJ version 1.53 (Wayne Rasband, National Institutes of Health, USA). The profiles of microvascular bed blood vessels marked on CD34 were quantified, and the number of macro-capillaries and sinusoids was expressed *per* one mm^2. From the standpoint of the $NSBV/mm^2$, all patients were classified into three categories. The first consists of patients whose value is less than 30. The second consists of patients whose value is between 30 and 80. The third consists of patients whose value of this indicator is higher than 80.

Statistical analysis

Data entry and tabulation were performed using Microsoft Excel 2016. The results of the statistical analysis were presented in tables. Statistical calculations were performed using SPSS software v23.0 (IBM Inc, USA). Of the basic descriptive statistical parameters, standard statistical methods were used for qualitative and quantitative assessment of the obtained results: absolute and relative numbers (%). Normality testing was performed using the Kolmogorov-Smirnov test. To test differences between variants that exhibited a normal distribution, the Student's test and analysis of variance were used when analyzing three or more groups. In cases where the distribution was not normal, the Mann-Whitney U test was used, as well as the Kruskal-Wallis test for three or more groups. The χ^2 test was used to test the statistical significance of the differences in absolute frequencies between samples. The interdependence between continuous variations was assessed using the Pearson correlation coefficient, and statistically significant correlations were subsequently presented. In order to determine predictive factors, univariate regression analysis was used, followed by multivariate multiple regression for variables that showed statistical significance. The statistical hypothesis was tested at the significance level for the risk of $\alpha = 0.05$, i.e., the difference between samples was considered significant if $p < 0.05$.

Results

The parietal membrane of the analyzed CSDH capsule consisted of immature dense connective tissue, with numerous fibroblast-like cells, as well as variable presence and density of mononuclear inflammatory cell infiltrates. In capsular connective tissue, structural components of the microvasculature, narrower capillaries and capsule sinusoids, were confirmed by the presence of CD34, immunohistochemically visualized with diaminobenzidine chromogen (Figure 1). The examined population consisted of 33 patients, composed of 25 (75.8%) men and 8 (24.2%) women. The average age was 71.30 ± 11.93 years, and the results were analyzed in relation to three age groups. Statistical analysis revealed no significant differences ($\chi^2 = 2.404$, $p = 0.301$) between men and women. Comparative analysis of the hematoma osmolality, cerebrospinal fluid osmolality, NSBV, and hematoma volume in relation to male and female genders is shown in Table 1. None of the examined parameters showed statistically significant differences based on gender.
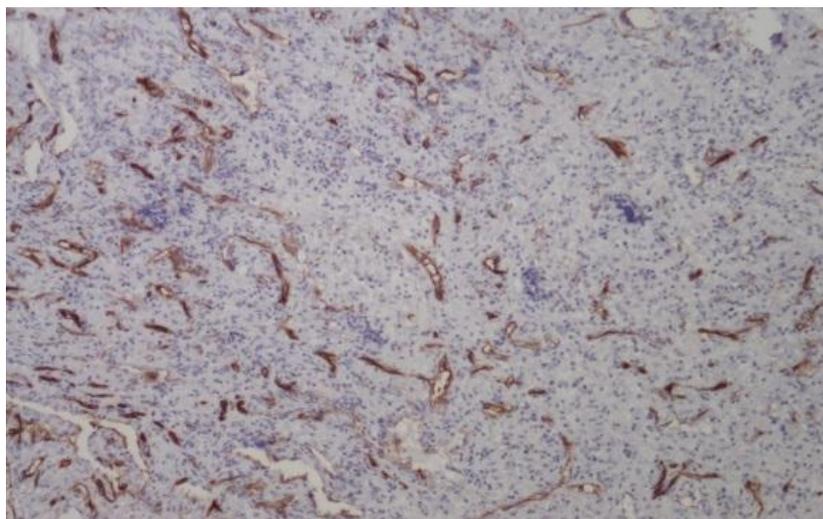

Fig. 1 – Numerous sinusoids in the hematoma capsule.
Immunohistochemical staining for CD34 (×100 magnification).

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Table 1

**Hematoma osmolality, cerebrospinal fluid osmolality,
number of sinusoid blood vessels, and hematoma volume in relation to gender**

Parameters	Gender		χ^2/t^*	p-value
	male	female		
Hematoma osmolality				
< 300 mmoL	16 (64.0)	5 (62.5)		
300–400 mmoL	9 (36.0)	3 (37.5)	0.006	0.939
Cerebrospinal fluid osmolality	280.88 ± 3.03	282.13 ± 1.81	1.094*	0.283
Number of sinusoid blood vessels				
< 30/mm^2	1 (4.0)	0 (0)		
30–80/mm^2	16 (64.0)	4 (50.0)		
> 80/mm^2	8 (32.0)	4 (50.0)	1.056	0.590
Hematoma volume, mL				
< 50	7 (28.0)	5 (62.5)		
50–70	13 (52.0)	2 (25.0)		
≥ 70	5 (20.0)	1 (12.5)	3.143	0.208

All values are given as numbers (percentages) or mean ± standard deviation.
Note: ***Student's *t*-test was used.**

Table 2

**Hematoma osmolality, cerebrospinal fluid osmolality,
number of sinusoid blood vessels, and hematoma volume in relation to patient age**

Parameters	Age, years			χ^2/F	p-value
	< 65	65–80	≥ 85		
Hematoma osmolality					
300–400 mmoL	4 (66.7)	13 (61.9)	4 (66.7)		
> 400 mmoL	2 (33.3)	8 (38.1)	2 (33.3)	0.075	0.963
Cerebrospinal fluid osmolality	283.17 ± 2.86	280.90 ± 2.98	283.17 ± 0.75	2.129	0.137
Number of sinusoid blood vessels					
< 30/mm^2	0 (0)	0 (0)	1 (16.7)		
30–80/mm^2	3 (50.0)	14 (66.7)	3 (50.0)		
> 80/mm^2	3 (50.0)	7 (33.3)	2 (33.3)	5.225	0.265
Hematoma volume, mL					
< 50	4 (66.7)	6 (28.6)	2 (33.3)		
50–70	1 (16.7)	12 (57.1)	2 (33.3)		
≥ 70	1 (16.7)	3 (14.3)	2 (33.3)	4.740	0.315

***F* – Fisher's analysis of variance based on the F test.**

All values are given as numbers (percentages) or mean ± standard deviation.
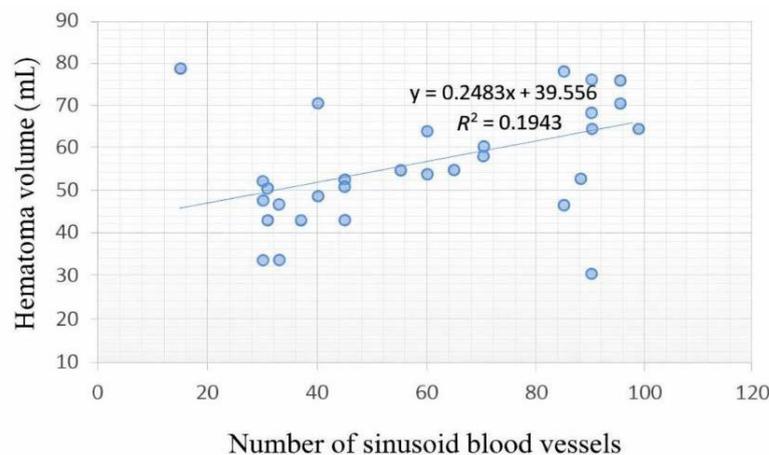

**Fig. 2 – Correlation of the number of
sinusoid blood vessels and hematoma volume.**

Comparative results of hematoma osmolality, cerebrospinal fluid osmolality, NSBV, and hematoma volume according to the age distribution of the subjects, without a statistically significant association, are shown in Table 2.

Furthermore, a statistically significant correlation was proven between the NSBV and the hematoma volume ($r = -0.441$, $p = 0.010$) (Figure 2). As the number of sinusoids increases, so does the volume of the hematoma.

Table 3

Univariate multiple regression analysis of gender, age, biochemical parameters, hematoma osmolality, cerebrospinal fluid osmolality, and number of sinusoid blood vessels in relation to hematoma volume

Parameters	Unstandardized coefficient		Standardized coefficient ß	95% confidence interval bounds for ß		p-value
	B	SE		lower	upper	
Gender	-4.425	5.914	-0.133	-16.487	7.637	0.460
Age	-0.387	0.206	0.319	-0.034	0.807	0.070
Sodium	-0.036	0.512	-0.013	-1.079	1.008	0.945
Potassium	-0.069	0.094	-0.131	-0.260	0.122	0.469
Urea	-0.216	0.141	-0.265	-0.504	0.072	0.136
Glucose	0.200	0.112	0.305	-0.029	0.429	0.084
Hematoma osmolality	0.014	0.085	0.029	-0.159	0.186	0.871
Cerebrospinal fluid osmolality	-1.710	0.871	-0.332	-3.487	0.067	0.059
Number of sinusoid blood vessels	0.248	0.091	0.441	0.063	0.434	0.010*

SE – standard error.
Note: *Indicates statistical significance at $p < 0.05$.

Table 4

Multivariate multiple regression analysis of age, glucose, cerebrospinal fluid osmolality, and number of blood vessels in relation to hematoma volume

Parameters	Unstandardized coefficient		Standardized coefficient ß	95% confidence interval bounds for ß		p-value
	B	SE		lower	upper	
Age	0.512	0.177	0.422	0.148	0.875	0.007*
Cerebrospinal fluid osmolality	0.130	0.095	0.198	-0.065	0.324	0.182
Number of sinusoid blood vessels	-1.265	0.753	-0.246	-2.809	0.278	0.104
Glucose	0.274	0.081	0.486	0.108	0.440	0.002*

SE – standard error.
Note: *Indicates statistical significance at $p < 0.05$.

Gender, age, biochemical parameters (sodium, potassium, urea, and glucose), hematoma osmolality, cerebrospinal fluid osmolality, and the NSBV were analyzed using univariate multiple regression analysis as independent predictive factors in relation to hematoma volume. The only statistically significant independent factor for hematoma volume was the NSBV (β = 0.441, p = 0.010) (Table 3). Within the multivariate multiple regression model used to predict hematoma volume, NSBV and age were statistically significant as individual independent factors to the criterion of significance for $p < 0.01$ (Table 4). The entire model was statistically significant (F = 6.758, p = 0.001). The model as a whole explains 49.1% of the variance of hematoma volume (corrected r^2 = 0.419). The variables age (β = 0.422, p = 0.007) and NSBV (β = 0.486, p = 0.022) showed a statistically significant contribution to the model. Elderly patients were at greater risk of increased hematoma volume, as were the patients with a greater NSBV.

Discussion

In 1857, Virchow was the first to provide a precise histological description of the pathological entity of CSDH. The term *pachymeningitis hemorrhagica interna*, introduced by Virchow as "hemorrhagic inflammation of *dura mater* producing blood collection on its inner side", remains valid even today, in light of recent research highlighting the role of inflammatory cells in its structure [2]. The key features of

CSDH, such as re-bleeding, progressive increase in size, rich vascularization, and inflammation of the parietal membrane, have been known since Virchow. In 1932, Gardner proposed that the osmotic gradient present between the hematoma and the adjacent capsular vessels may also be a driver of hematoma enlargement [9]. The CSDH growth based on continuous bleeding, caused by local hypocoagulation and hyperfibrinolysis, was previously precisely analyzed [8, 10]. The contents of most CSDHs are liquid. Increased levels of fibrin and fibrinogen degradation products in the hematoma contents, as well as the presence of tissue activator in the outer membrane of the hematoma, have been shown histologically [11]. Ito and others have found high concentrations of tissue plasminogen activator in the vessel walls of the outer membrane (parietal layer), whereas it was significantly lower or absent in the inner membrane (visceral layer). This would account for the increased hypocoagulation and transudation into the hematoma. Soluble tissue plasminogen activator then diffuses into the hematoma, where it converts plasminogen into the active fibrinolytic enzyme plasmin, which further degrades fibrin and fibrinogen. Hyperfibrinolysis caused by increased tissue plasminogen activator may be expected to interfere with the hemostatic mechanism and induce the enlargement of subdural hematoma [12–15].

The NSBV to 1 mm^2 is a determinant statistically significant in positive correlation with hematoma thickness. In this way, the starting assumption that the NSBV to 1 mm^2

has a statistically significant influence on the hematoma thickness is confirmed. This indicates the importance of SBV quantity elevation in the context of hematoma growth. Microscopic findings of fresh erythrocytes marked with chromium-51 were proven in subdural hematoma, and their movement was observed from sinusoids through increased inter-endothelial gaps towards the hematoma [1, 16]. This observation, to some extent, supports the sinusoid-vascular theory of CSDH formation, given that sinusoids are very fragile and porous, due to their atypical morphology. They are so fragile that they are prone to continuous transudation and recurrent bleeding as a result of constant pulsations of the brain parenchyma [17, 18]. The correlation diagram, which shows the relationship between NSBV and CSDH volume, indicates a coefficient of determination (R-squared) of 0.1943, which can be considered statistically and clinically relevant. Bearing in mind that the analysis is based on 33 processed cases, and based on clinical experience and insight into epidemiological patterns, it can be assumed that the value of this coefficient would increase if a larger number of respondents were included.

Weigel et al. [10] tested the hypothesis that the CSDH may be considered a member of the angiogenic disease family and that enhanced expression of growth factors may also be involved in the higher vascularization of the parietal membrane and the maintenance of CSDH. They have found 41 times higher concentrations of vascular endothelial growth factor in the hematoma fluid than in the serum levels. Comparably high concentrations have been described by Suzuki et al. [19]. However, Weigel et al. [10] did not find a significant correlation between growth factor concentrations and patient age or computed tomography, which indicated hematoma thickness.

Moskala et al. [20] reported dynamic changes in the cellular and vascular organization of traumatic CSDH capsules that parallel hematoma duration and are expressed in gradual morphological changes in the developing hematoma capsule. This process initially includes angiogenic and aseptic inflammatory reactions, followed by progressive proliferation of fibroblasts and collagen fibril production. As a result of neo-angiogenesis, numerous capillaries are observed mainly in young hematomas, removed between 15 and 21 days after trauma. More numerous capillaries and thin-walled, larger-diameter blood vessels-sinusoids were evidenced in the "older" hematomas (about 40 days after trauma). In the "oldest" hematoma capsules (60 or more days after trauma), they reported that blood vessels were frequently occluded by clots. In our study, univariate multiple regression analysis included gender, age, hematoma osmolality, and hematoma volume in relation to the number of sinusoids. According to the results, hematoma volume was the only statistically significant independent predictor of NSBV. This finding suggests that even a moderate increase in hematoma volume may contribute to continuous sinusoidal damage and perfusion, with consequent release of inflammatory compounds and mediators that initiate and maintain a nonspecific inflammatory response, which further promotes angiogenesis.

As previously pointed out, the increased fragility of these vascular structures reflects their morphological peculiarities. To a significant extent, they resemble sinusoidal-type blood vessels described in brain gliomas, which additionally confirms their tendency to rupture and their role in the pathophysiology of CSDH progression [21, 22].

By analyzing our findings based on the quantification of microvascular structures (sinusoids), we observed that repeated bleeding from fragile sinusoids represents a key mechanism of the progressive increase in CSDH size. The highest density of sinusoids was recorded in the 65–80-year age group, within the range of 30–80 sinusoids/mm^2. This finding coincides with data showing that the highest percentage of patients with hematoma volumes corresponding to a maximum thickness of 50–70 mm (46%) was observed in this age group.

As previously emphasized, the available literature describes in detail the factors that contribute to the fragility of sinusoids, including their histological characteristics and vasoactive molecules released as a result of vascular damage, which indirectly stimulate angiogenesis [1, 10, 21]. According to recent research, angiogenesis in the capsule of CSDH involves multiple complex, interconnected mechanisms. Kim et al. [23] showed that pathological, sinusoidal, and extremely fragile capillaries were formed in the outer membrane of the CSDH, the formation of which is closely related to the branching and terminal branches of the *arteria meningea media* (middle meningeal artery – MMA). Histological analysis of these newly formed vessels indicates that the MMA is the primary source of blood to the neovascularized membrane and that continuous blood flow and recurrent microbleeding occur through this arterial system. This is in accordance with the modern understanding that recurrence of CSDH is often based on a pathological vascular pattern whose primary hemodynamic "trigger" is MMA, which also provides a clear physiological basis for the increasingly widespread use of MMA embolization in the treatment of recurrent hematomas. Given the previously mentioned characteristics of CSDH, as well as the fact that existing surgical treatments are not always effective, leading to recurrences in up to 20% of cases, MMA embolization has emerged as a promising treatment modality with excellent results, although some recommend its use within a research context [6, 7].

Osuka et al. [21] additionally demonstrated that the N-terminal fragment of osteopontin is found in the hematoma fluid, which *via* integrins α9 and β1 activates signaling pathways related to focal adhesion kinase phosphorylation, cytoskeleton reorganization, and proliferation of endothelial cells in the outer membrane. These processes lead to the progressive development of immature, structurally unstable blood vessels, which contribute to further neovascularization and potential re-bleeding. Watanabe et al. [24] documented intense microvascular proliferation within clots in acute subdural hematomas, which provides insight into the early phase of acute to chronic hematoma transformation, a process that involves the formation of new, underdifferentiated vessels with a very similar phenotype to

those in the CSDH outer membrane. Together, these findings clearly demonstrate that CSDH progression represents an active, dynamic biological response based on inflammation, stimulated angiogenesis, and the hemodynamic effects of MMA, with fragile and immature blood vessels playing a key role in recurrent bleeding and further hematoma enlargement.

To the best of our knowledge, there are no such studies in the available literature that have systematically assessed the density of sinusoids *per* mm² in relation to the volume of CSDH. Therefore, we believe that quantitative monitoring of this parameter is of particular importance for confirming and better understanding the angiogenetic mechanisms in the pathophysiology of CSDH. The low number of patients in our study is related to the strict selection criteria, designed only to obtain valid results by achieving between-group homogeneity. While it does limit the external generalization, this is a trade-off to provide more accurate analysis and more reliable comparisons within our specific cohort. Further research in this field is required so that the potential new therapeutic options targeting the cause of the disease may be developed.

Conclusion

The quantity of capillaries and sinusoids in the parietal capsule of chronic subdural hematoma *per* surface unit is a determinant in positive correlation with hematoma thickness, which emphasizes the importance of vascular theory in the development of a hematoma. Even though chronic subdural hematoma is one of the most common neurosurgical diseases, its pathogenesis is still not fully understood. Further research in this field is required so that the potential new therapeutic options targeting the cause of the disease may be developed.

Conflict of interest

The authors declare no conflict of interest.

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