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Inflammatory biomarkers differentiate the stage of maturation in chronic subdural hematomas

Teodor Svedung Wettervik *, Jimmy Sundblom, Elisabeth Ronne-Engström

Department of Medical Sciences, Section of Neurosurgery, Uppsala University, SE-751 85 Uppsala, Sweden

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ABSTRACT

Objective: Inflammation is a major pathophysiological driver of the development of chronic subdural hematomas (CSDH), but there is still limited knowledge on the key molecular processes and corresponding biomarkers involved in this disease. In this study, the aim was to study a subset of inflammatory biomarkers and their relation to the clinical status of the patient and the radiological characteristics of the CSDH.

Methods: In this observational study, 58 patients who were operated on with CSDH evacuation, at the Department of Neurosurgery, Uppsala, Sweden, between 2019 and 2021, were prospectively included. The CSDH fluid was collected peri-operatively and was later analyzed with proximity extension assay (PEA) technique (Olink) for a panel of 92 inflammatory biomarkers. Demographic, neurological (Markwalder), radiological (general (Nakaguchi classification) and focal (septa below the burr holes)), and outcome variables were collected.

Results: In 84 of the 92 inflammatory biomarkers, the concentration was above the detection limit in >50% of the patients. There was a significant difference in GDNF, NT-3, and IL-8 depending on the Nakaguchi class, with higher values in the trabeculated CSDH subtype. In addition, those with septa at the focal area of CSDH collection, had higher levels of GDNF, MCP-3, NT-3, CXCL1, CXCL5, IL8, and OSM. There was no association between Markwalder grade and the inflammatory biomarkers.

Conclusions: Our findings support the presence of local inflammation in the CSDH, a shift in biomarker pattern as the CSDH matures towards the trabeculated state, potentially differences in biomarker patterns within the CSDH depending on the focal environment with presence of septa, and that the brain might develop protective mechanisms (GDNF and NT-3) in case of mature and long-standing CSDHs.

1. Introduction

Chronic subdural hematomas (CSDHs) constitute one of the most common conditions that require neurosurgery (Kudo et al., 1992). The disease mostly affects the elderly and the incidence continues to increase as the general population gets older (Tommiska et al., 2022). CSDHs commonly arise 4–8 weeks following head trauma, including both minor and major trauma mechanisms (Sundblom et al., 2022). It is hypothesized that the traumatic forces lead to a separation of the dural border cell layer and elicit a multitude of pathophysiological processes including inflammation, angiogenesis, and local coagulopathy (Edlmann et al., 2017; Edlmann et al., 2021; Holl et al., 2018). This initiates the formation of a subdural capsule, where particularly the outer membrane attracts inflammatory cells and forms fragile and permeable vessels in a locally coagulopathic environment. The fragile vessels tend to bleed repeatedly into the subdural intermembrane space, which predisposes for a gradual growth in CSDH size (Edlmann et al., 2017; Holl et al., 2018). The CSDH then goes through certain stages of maturation, initially from accumulation of homogeneous fluid/blood collections towards a more fibrotic stage characterized by intermembrane trabeculations (Nakaguchi et al., 2001). The development of the CSDH may be modest, not eliciting any symptoms, and resolve without treatment (Lee, 2004). However, in many cases, the expanding CSDH leads to neurological symptoms due to mechanical distortion (Yokoyama et al., 2008), decreased cerebral blood flow (Ikeda et al., 1990; Inao et al., 2001), and cortical irritation (Huang et al., 2011), which mandate interventions. The mainstay of clinical practice is then surgical evacuation (Bartley et al., 2022; Ducruet et al., 2012) and usually this leads to a fast recovery from the symptoms. However, many of these patients are old and fragile. It has been estimated that 10% suffer from postoperative complications (Bartek Jr. et al., 2017), 10–20% experience a CSDH recurrence (Bartek Jr. et al., 2017), and mortality may reach 30% after 1

* Corresponding author.
E-mail address: teodor.svedung-wettervik@neuro.uu.se (T. Svedung Wettervik).

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year (Miranda et al., 2011). Considering the surgical risks and the recurrence rate, pharmacological alternatives have also been explored to counteract some of the pathophysiological mechanisms in CSDH. Some examples include steroids and/or statins to decrease both inflammation and angiogenesis (Edlmann et al., 2017; Hutchinson et al., 2020), angiotensin converting enzyme inhibitors (ACE-i) to decrease angiogenesis (Holl et al., 2018; Poulsen et al., 2014), and tranexamic acid to improve the coagulopathic state (Kageyama et al., 2013), but, at present, with too limited therapeutic efficacy and/or too severe adverse effects to add any clinical benefit. To be able to develop new and better pharmacological agents, there is a need to better understand the complex, underlying disease mechanisms in CSDHs. Currently, some attempts have been made to analyze the CSDH membranes and specific biomarkers of the CSDH fluid (Edlmann et al., 2017; Frati et al., 2004; Hara et al., 2009; Holl et al., 2018; Hong et al., 2009; Osuka et al., 2014; Pripp and Stanišić, 2014; Stanisic et al., 2012; Suzuki et al., 1998), but these have been limited by small cohort sizes and focused on a small number of biomarkers in each study. Consequently, there is a need for larger studies with a greater plethora of potentially important CSDH biomarkers to better understand the CSDH pathophysiology.

The proximity extension analysis (PEA) technique is a relatively new method to semi-quantitatively analyze a large panel of biomarkers, while only using a small amount of fluid (Assarsson et al., 2014). In order to better understand the pathophysiological pathways in CSDH, we used this technique for a panel of 92 inflammation-related biomarkers (Olink, 2023) to study the CSDH fluid.

The primary aim of this study was to determine the presence and variation of inflammatory biomarkers in the CSDH and secondarily their relation to the clinical and radiological subgroups of CSDHs.

2. Materials and methods

2.1. Patients and study design

This was a prospective observational pilot study on a limited number of adult CSDH patients who were operated on with burr-hole evacuation between 2019 and 2021 for CSDH to the Neurosurgery Department, Uppsala University Hospital, Sweden. We aimed to include approximately 60 patients.

2.2. Clinical variables, radiological classifications, and CSDH management

Patients with a symptomatic CSDH, i.e., paresis, dysphasia, seizures, gait disturbances, and/or headache considered to be caused by the CSDH, or asymptomatic CSDH with severe mass effect were admitted to our department. Demography, co-morbidities according to the Charlson co-morbidity index (Sundararajan et al., 2004), medications due to co-morbid conditions (statins, ACE-i, and steroids), previous ipsilateral CSDH surgery, and neurological status at admission according to the Markwalder classification (from 0 (no symptoms) to 4 (comatose)) were assessed at admission (Markwalder et al., 1981). The Nakaguchi classification (Nakaguchi et al., 2001) was used to determine the CSDH maturation state and included the homogeneous, laminated, separated, and trabeculated subtypes based on the preoperative computed tomography (CT) scan. Surgery was done with burr holes, subdural irrigation, and 24 h of active subgaleal drainage postoperatively (Bartley et al., 2022). The presence of membranous septa immediately below the burr holes was assessed in retrospect based on the location of the burr holes on the postoperative CT scan in relation to the CSDH on the preoperative CT scan. Recurrence was defined as reoperation between 10 days to 1 year postoperatively. Early reoperation before 10 days was considered to be insufficient primary evacuation.

2.3. Collection and analysis of the CSDH fluid

The CSDH fluid was collected peri-operatively by aspiration of approximately 10 mL of CSDH fluid immediately after opening the outer CSDH membrane and before subdural irrigation had been initiated. The fluid was then centrifuged, and 3 mL was pipetted into cryo-tubes, which were put in a freezer at −70 °C until biomarker analysis.

After inclusion of all patients, PEA analysis of the CSDH fluid was conducted using Proseek Multiplex Inflammation 96 (Olink), a panel based on 92 inflammation-associated biomarkers (Olink, 2023). The 92 biomarkers and their classifications are described in Supplementary Table 1. The procedure has been described in detail in previous studies (Svedung Wettervik et al., 2022). The proteins were reported in arbitrary units as normalized protein expression (NPX), which is a log2-scale indicating that an increase in +1 NPX means that the absolute concentration was doubled. The intra-assay coefficient of variance was determined to 4%.

2.4. Statistical analysis

Descriptive data were presented as medians, range, and/or interquartile range (IQR). Differences in CSDH biomarker concentrations were assessed in relation to radiological characteristics (Nakaguchi class and presence of septa below the burr holes) neurological status (Markwalder grade), and medications due to co-morbid conditions using the Kruskal-Wallis or Mann-Whitney *U* test, depending on the data. Adjustment for multiple testing was done using the Benjamini-Hochberg procedure with a false discovery rate at 5%. The analyses were conducted in SPSS version 28 (IBM Corp, Armonk, NY, USA).

2.5. Ethics

The study was approved by the Swedish Ethical Review Authority (Dnr 2019–00014).

3. Results

3.1. Patients

In this cohort of 58 CSDH patients (Table 1), median age was 78 (range 48–94) years, and the male/female ratio was 44/14 (76/24%).

Table 1
Demographics, neurological status, radiological variables, and recurrence.

Patients, n (%)	58 (100%)
Age, median (range)	78 (48–94)
Sex (male/female), n (%)	44/14 (76/24%)
Charlson co-morbidity index, median (range)	1 (0–7)
Medications due to co-morbid conditions	
Statins, n (%)	26 (45%)
ACE-i, n (%)	24 (41%)
Steroids, n (%)	1 (2%)
Markwalder grade, median (range)	1 (0–2)
Uni−/bilateral, n (%)	35/23 (60/40%)
Size (mm), median (range)	25 (12–35)
Nakaguchi type*, n (%)	
Homogeneous, n (%)	17 (30%)
Laminar, n (%)	4 (7%)
Separated, n (%)	11 (19%)
Trabeculated, n (%)	25 (44%)
Burr hole septa* (yes), n (%)	22 (39%)
First time surgery/recurrence, n (%)	57/1 (98/2%)
Recurrence**, n (%)	4 (7%)*

ACE-i = Angiotensin converting enzyme inhibitor. CSDH = Chronic subdural hematoma.

* Radiological scans were unavailable in one case.

** Two more cases were reoperated within 10 days due to insufficient decompression from the first surgery. However, this was considered to be caused by insufficient primary CSDH evacuation.

Most patients had at least one significant co-morbidity, as indicated by a median Charlson co-morbidity index at 1 (range 0–7). Twenty-six (45%) patients were on statins, 24 (41%) on ACE-i, and 1 (2%) was on steroids at the time of CSDH diagnosis due to other co-morbid conditions. Most patients exhibited mild to moderate neurological symptoms due to the CSDH, as indicated by a median Markwalder grade at 1 (range 0–2). The majority had a unilateral rather than bilateral CSDHs (35/23 (60/40%)) and median size of the CSDH that was operated on was 25 (range 12–35) mm. According to the Nakaguchi classification, 17 (30%) had a homogeneous, 4 (7%) a laminar, 11 (19%) a separated, and 25 (44%) a trabeculated CSDH. In addition, 22 (39%) had septa across the inner and outer membranes immediately below the burr holes. Almost all (57/1 (98/2%) patients with a CSDH were operated on for the first time. Four (7%) patients developed a recurrence that required reoperation.

3.2. Inflammatory biomarker panel analysis of the CSDH fluid

Descriptive statistics including median, IQR, and range are reported for the inflammatory biomarkers in Supplementary Table 2. As demonstrated, many variables could be detected, Only IL-2, IL-20, IL-20Rα, IL-22Rα1, IL-24, IL-33, NGF, and NRTN were excluded since >50% of the patients exhibited a value below the limit of detection for these variables.

3.3. Inflammatory biomarkers of the CSDH fluid in relation to radiological variables, neurological status, and medications

In relation to the Nakaguchi classification (Table 2), there was a significant difference in NT-3, GDNF, and IL-8 concentrations depending on the CSDH subtype (q-value <0.002). These biomarkers were more elevated in the trabeculated type of CSDH. In addition, if there were septa in the CSDH immediately below the burr holes (Table 3), the concentrations of GDNF, MCP-3, NT-3, CXCL1, CXCL5, IL-8, and OSM were significantly higher than in cases with no septa. Markwalder grade and medications with statins or ACE-I due to co-morbid conditions were not associated with any of the inflammatory biomarkers. The association between the biomarkers and steroids was not analyzed due to the low number of patients (n = 1) with this medication.

4. Discussion

In this study on inflammatory biomarkers in the CSDH fluid from 58 patients, the main findings were that several inflammatory biomarkers could be detected in this fluid and the concentrations of some biomarkers varied with the maturation of the lesion as measured by the Nakaguchi scale. Particularly, a trabeculated CSDH subtype was associated with increased chemokine levels of IL-8, but also higher levels of the neurotrophic factor GDNF and NT-3. Presence of septa in the vicinity of CSDH collection also corresponded to higher levels of these biomarkers in addition to certain chemokines (CXCL1, CXCL5, and MCP-3) and biomarkers related to fibrosis (OSM). Our findings highlight the presence of local inflammation in the CSDH, a shift in biomarker pattern as the CSDH matures, potentially local differences in biomarker patterns depending on the nearby CSDH characteristics (septa), and that the brain might develop protective mechanisms in case of mature and long-standing CSDHs.

The development and maintenance of a CSDH is thought to involve a local inflammation including formation of an inner and out membrane, recruitment of inflammatory cells, angiogenesis of leaky vessels in the outer membrane, and local coagulopathy (Edlmann et al., 2017; Holl et al., 2018). Consistently, we found elevated levels of several biomarkers related to these processes. Several FGFs (FGF5, FGF19, FGF21) were elevated. The FGF subtypes differ in specific functions to some extent, but they are overall known to recruit and promote fibroblasts (Ornitz and Itoh, 2015), which are crucial for the development of the CSDH membranes (Edlmann et al., 2017; Holl et al., 2018; Hong et al., 2009). FGF2 in the outer membrane, but not in the subdural fluid, has previously been associated with CSDH recurrence after initial surgery (Hong et al., 2009), however, the number of patients with recurrence were too few to proceed with such analyses in this study. Furthermore, OSM mediates a plethora of inflammatory mechanisms. Of particular note, it is known to be involved in fibrosis during chronic inflammation (Stawski and Trojanowska, 2019), which seems compatible with that a higher concentration of OSM was found in the presence of nearby septa.

Furthermore, we found that several cytokines were detected. Specifically, IL-6 was elevated with a median NPX above 10. IL-6 is thought to be a major regulator of inflammation in the CSDH and may contribute to membrane growth and vascular permeability with leaky vessels in the outer membrane (Edlmann et al., 2017, Holl et al., 2018). IL-8 was also elevated to a NPX around 12 in most CSDHs. IL-8 is known to be a pro-inflammatory chemokine that mainly attracts neutrophils (Edlmann et al., 2017; Holl et al., 2018; Kraemer et al., 2022). Frati et al. found that higher IL-6 and IL-8 in the CSDH fluid was more frequent in the layered than the trabeculated CSDH subtype and also correlated with a greater risk of recurrence (Frati et al., 2004). In contrast, another study found IL-6 to be higher in mixed as compared to homogeneous CSDHs (Park et al., 2015), whereas a third study, similar to ours, found no association between IL-6 and the CSDH subtype (Wada et al., 2006). Furthermore, also in contrast to Frati et al. (Frati et al., 2004), we found that IL-8 was more associated with the trabeculated CSDH and we interpret our finding that IL-8 might be important in promoting the more fibrous and capsular trabeculated stage. Some major limitations in all of these studies are the relatively limited cohort sizes and differences in techniques to analyze these biomarkers, which reduce the possibility to compare the results.

In addition, we were able to detect several chemokines in the CSDH, including CCL3, CCL4, CCL11, CCL19, CCL20, CCL23, CXCL1, CXCL5, CXCL6, CXCL9, CXCL10, MCP-1, MCP-2, MCP-3, and MCP-4. All of these are important chemoattractors of inflammatory cells with some

Table 3
Inflammatory biomarkers in relation to presence of septa below the bur hole.

Biomarkers	Septa	No Septa	p-Value	q-Value
GDNF (NPX), median (IQR)	4 (3–5)	3 (2–3)	0.00004	0.00006
MCP-3 (NPX), median (IQR)	8 (7–9)	6 (5–7)	0.0001	0.001
NT-3 (NPX), median (IQR)	4 (3–5)	3 (2–4)	0.0003	0.002
CXCL1 (NPX), median (IQR)	13 (9–14)	8 (7–11)	0.001	0.002
CXCL5 (NPX), median (IQR)	10 (8–12)	8 (6–9)	0.001	0.003
IL-8 (NPX), median (IQR)	13 (13–13)	11 (10–13)	0.002	0.004
OSM (NPX), median (IQR)	10 (8–11)	8 (8–9)	0.003	0.004

CSDH = Chronic subdural hematoma. CXCL1 = Growth-regulated alpha protein. CXCL5 = C-X-C motif chemokine 5. GDNF = Glial cell line-derived neurotrophic factor. IL-8 = Interleukin 8. MCP-3 = Monocyte chemotactic protein 3. NT-3 = Neurotrophin 3. OSM = Oncostatin M.

Table 2
Inflammatory biomarkers in relation to CSDH Nakaguchi classification subtypes.

	Homogeneous	Laminar	Separated	Trabeculated	p-Value	q-Value
NT-3	3 (1–3)	3 (3–4)	2 (2–3)	4 (3–5)	0.0004	0.0006
GDNF	2 (2–3)	3 (3–4)	2 (1–3)	4 (3–4)	0.0006	0.001
IL-8	11 (10–13)	12 (10–13)	11 (9–12)	13 (13–13)	0.001	0.002

CSDH = Chronic subdural hematoma. GDNF = Glial cell line-derived neurotrophic factor. IL-8 = Interleukin 8. NT-3 = Neurotrophin 3.

variations in their preference for specific cell types. For example, CCL3 is known to recruit monocytes, CCL3 to recruit eosinophils, and CXCL1 to recruit leukocytes (Kraemer et al., 2022). Particularly, eosinophils seem to be important in CSDH development as they promote fibrosis of the CSDH membrane and induce local coagulopathy by plasminogen release (Holl et al., 2018). Among the different CSDH subtypes, CXCL1, CXCL5, and MCP-3 were higher in the presence of focal septa in the vicinity of the CSDH collection below the burr holes. CXCL1 is familiar to IL-8 and attracts leukocytes (Kraemer et al., 2022), whereas CXCL5 is more indicative of eosinophils, and MCP-3 of leukocytes (Kraemer et al., 2022), which may all contribute to the membranous growth.

We also detected several angiogenic biomarkers. VEGF-A was very high with a median NPX at 15. This was expected, since VEGF-A is considered to be a major driver of the development of pathological, leaky vessels in the CSDH membrane (Edlmann et al., 2017; Holl et al., 2018). The VEGF-A concentration did not differ among the various radiological subtypes and we speculate that it might be universally expressed to a high degree in all CSDH subtypes. Local coagulopathy and fibrinolysis are important pathophysiological mechanisms in CSDH (Edlmann et al., 2017, Holl et al., 2018). PLAU (urokinase plasminogen activator) was included in this biomarker panel and was elevated in many cases, but also did not differ among the subtypes.

Several growth factors were detected and elevated. TGF-β1 is known to promote membrane formation (Edlmann et al., 2017; Osuka et al., 2014) and was elevated in most cases (median NPX at 9). Two neurotrophic factors, GDNF and NT3, were also elevated in general and more so in case of the trabeculated subtype and in case of septa below the burr holes. GDNF and NT-3 are primarily known to be neuroprotective proteins that are produced within the central nervous system (CNS) (Fielder et al., 2018; Omar et al., 2022). It has been speculated that the membranous capsule isolates the CSDH from the cerebrospinal fluid (CSF), but at the same time the CSF specific protein beta-trace is still usually elevated in the CSDH fluid indicating a communication with the CSF (Edlmann et al., 2017; Holl et al., 2018; Park et al., 2015). It could be speculated that these neurotrophic factors were produced in the CNS as a neuroprotective response to the CSDH and that it might take some time to develop this reaction since it was only evident in case of the most mature CSDH state characterized by trabeculations/septa (Nakaguchi et al., 2001).

Thus, it appears that the most mature CSDH state characterized by trabeculations was associated with biomarkers that are responsible for inflammatory processes (particularly chemokines) and fibrosis. This likely reflects the ongoing formation of granulomatous CSDH tissue. There was no other specific biomarker pattern related to CSDH maturation or neurological grade and we anticipate that these biomarkers were overall generally expressed in the CSDH in most patients. We also did not see any relation between medications and biomarker patterns, possibly due to a lack of effect on CSDH inflammation, variable/too low statin dosage among the patients, or related to the size of the study cohort. Furthermore, the present study was not designed to measure the content of cells participating in the inflammatory reaction, something that could give more information about the origin of the inflammatory proteins.

Considering the frailty of the CSDH patients and the risks of postoperative complications, there is a great interest in developing targeted pharmacological agents that address the pathophysiological mechanisms which contribute to CSDH progression. As outlined in the Introduction, there are some candidates, e.g. steroids to decrease both inflammation and angiogenesis (Hutchinson et al., 2020), angiotensin converting enzyme inhibitors to decrease angiogenesis (Holl et al., 2018; Poulsen et al., 2014), and tranexamic acid to improve the coagulopathic state (Kageyama et al., 2013). However, they are not commonly accepted in clinical practice, mainly because they are not sufficiently effective and/or induce significant adverse effects. Another important consideration would be the timing of these pharmacological agents, since certain biomarkers and pathophysiological mechanisms may follow a certain temporal pattern, as indicated in the trabeculated CSDH type in this study. Ideally, CSDH would be completely prevented by an effective treatment immediately initiated after head trauma for elderly patients at risk of developing this condition. Consequently, future efforts should aim at further improving our understanding of the CSDH disease processes and in parallel find new potential pharmacological agents to increase the therapeutic arsenal for this disease.

4.1. Methodological considerations

There is currently only a limited number of studies on inflammatory processes in CSDH and this study provides further data on a wide array of biomarkers in a relatively large number of patients. Particularly, the advantage of the PEA technology was that it allowed us to analyze a large panel of biomarkers with only a small amount of fluid.

There were several limitations. First, the PEA analyses were semi-quantitative, and it was not possible to translate it into an absolute concentration (e.g. pg/mL). Second, we had no control group, since the analyses were taken directly from the pathology and there is no comparable fluid to analyze in healthy volunteers. An alternative approach would have been to compare the CSDH- with serum-levels to better determine if these biomarkers were more elevated in CSDH than in serum, which has been done in some previous studies (Frati et al., 2004; Stanisic et al., 2012). Third, we excluded the biomarkers for which the concentration was below the limit of detection in >50% of the patients, but there were also some biomarkers with only a few patients with biomarker concentration below the limit of detection. However, data denoted to be below the limit of detection could in fact be detected in most cases, but were in a phase where the log2-scale of NPX is much more unreliable (Olink, 2023). Hence, the absolute concentrations of these data should be interpreted cautiously. However, we still chose to keep these few cases in the statistical analyses since we used non-parametric approaches (Kruskal-Wallis and Mann-Whitney *U* test) which should still be valid since they depend on the ranking of the concentration levels. Fourth, we considered analyzing the time interval from the initial trauma to CSDH surgery in relation to the inflammatory biomarkers. However, the time point of any initial trauma could not be determined in a reliable way in many cases, since e.g. some patients fell repeatedly and others could not remember. Fifth, we restricted the analyses on the relation between the inflammatory biomarkers and medications due to co-morbid conditions to those agents most strongly linked to CSDH pathophysiology (statins, ACE-i, and steroids), although a plethora of many other drugs could have such a link. For example, we did not analyze usage of the antithrombotic and anti-inflammatory agent aspirin in relation to the biomarkers, particularly since this agent had typically been withdrawn >7 days before the surgery to optimize hemostasis before surgery. Lastly, the study was designed as a pilot study with a limited number of patients. The patients' demographic and CSDH characteristics were overall similar to those in a large and complete set of CSDH patients treated at our center (Sundblom et al., 2022), which indicates that our cohort was not skewed.

5. Conclusions

Several inflammatory biomarkers could be detected in this fluid and the concentration for some of the biomarkers varied with the maturation of the lesion. Angiogenic factors were consistently present. Particularly, a trabeculated CSDH subtype was associated with increased chemokine levels of IL-8, but also higher levels of the neurotrophic factor GDNF and NT-3. Presence of septa at the locus of CSDH collection also corresponded to higher levels of these biomarkers in addition to certain chemokines (CXCL1, CXCL5, and MCP-3) and biomarkers related to fibrosis (OSM). Our findings highlight the presence of local inflammation in the CSDH, a shift in biomarker pattern as the CSDH matures, potentially local differences in biomarker patterns depending on the nearby CSDH characteristics (septa), and that the brain might develop

protective mechanisms in case of mature and long-standing CSDHs. However, the usefulness of these CSDH biomarkers in clinical practice to e.g. predict recurrence and influence management remains to be further explored. Future larger studies that also characterize the cellular content in combination with biomarker analyses are necessary to better understand the CSDH pathophysiology in order to potentially develop pharmacological agents that may address these mechanisms better.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2023.578127.

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