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Original Article

Cerebrospinal fluid leak as a driving factor in chronic subdural hematoma formation: A histological study

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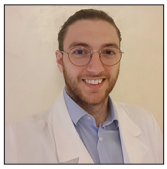

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ABSTRACT

Background: Chronic subdural hematoma (CSDH) represents the most common neurosurgical disease. Given the demographic shift toward an aging population, the overall incidence of this condition is increasing. Nevertheless, clarity in the pathophysiological process is yet to be made. Several etiological mechanisms have been proposed to initiate and consequently promote fluid collection in the subdural space. Traumatic injury of the bridging veins has long been considered the primum movens of the pathology but increasing evidence shows that trauma is not the only factor involved. Along with recent advances we sought to understand the role of the cerebrospinal fluid (CSF) in the buildup of the intense inflammatory reaction that characterizes CSDH.

Methods: In the present study, we examined histological features of reactive membranes secondary to extracranial CSF leakage with CSDH-related membranes. Similarity and differences between the specimens were examined by means of light microscopy.

Results: Histological similarities were consistently found between CSDH membranes and reactive membranes secondary to CSF leakage in the extracranial space. Activated histiocytes were highlighted in all specimens along with an intense inflammatory reaction.

Conclusion: CSDH is most likely the result of a complex interaction among different pathophysiological events resulting from both traumatic and inflammatory etiologies. In the present work, we highlight how CSF leakage could be an early factor that leads to a cascade of events that culminates in CSDH formation.

Keywords: Cerebrospinal fluid, Chronic subdural hematoma, Dura mater, Inflammation, Subdural hygroma

INTRODUCTION

Chronic subdural hematoma (CSDH) is a pathological collection of fluid in the subdural space. It is recognized as one of the most frequently encountered neurosurgical diseases,[15,31] yet pathophysiological drivers are not thoroughly understood. It generally occurs in the elderly with an average age of 79 years, and its prevalence is increasing due to the demographic shift toward an aging population.[29] A recent observational study of the Finnish population reveals a growing incidence from 8.2 to 17.6 per 100,000 persons per year in 25 years.[23] Similarly, data derived from our institution showed an incidence rate of 25 patients per year per 100,000 people with 153 admissions in the past 3 years (median age: 78 years).

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Traumatic injury was first suggested as the main cause of CSDH formation, linking the tearing of the bridging veins to the accumulation of venous blood layered between the arachnoid and dura mater.[14,19] Notwithstanding the major importance of mechanical injuries, the precise pathway with which trauma induces CSDH is debated. Recent evidence indicates that a slow venous hemorrhage would accumulate in far less time than the usual onset period of CSDH, becoming symptomatic early on.[26] Other possible pathophysiological mechanisms explaining the fluid collection have been proposed.[5,8,11,22]

The scope of the present study was to examine histological specimens derived from reactive membranes secondary to cerebrospinal fluid (CSF) leakage in the abdominal wall and CSDH-related membranes found in patients treated with burr hole surgery.

MATERIALS AND METHODS

Patient selection

During the months of March and July 2021, two cases of ventriculoperitoneal shunt malfunction associated with CSF leakage in the abdominal wall were admitted to our institution. Both these patients were previously treated for idiopathic normal pressure hydrocephalus. At 1-month follow-up fluid in the subcutaneous adipose tissue was noticed, indicating that shunt had pull out of the subperitoneal space. During surgical revision, reactive membranes were obtained.

In the same period, two cases of post-craniotomy subgaleal CSF collection were identified. Revision surgery for dural fistula allowed the collection of subcutaneous reactive membranes caused by CSF leakage. These patients were not treated for CSDH and came to our attention due to primary CNS tumors managed with surgery.

Between August and November 2020, five patients were admitted with the diagnosis of CSDH. The first three patients presented with clinical and radiological evidence of CSDH and were thus admitted and treated with single burr hole surgery. The fourth and fifth patients exhibited evidence of subdural hygroma (SDHy) on computed tomography (CT) scan and were managed with a "wait and watch" strategy as most of these patients usually improve over time. After initial improvement, all patients came back in 2021 with worsened symptoms, and an evacuative craniotomy was performed. Reactive membranes were obtained during surgery.

The patients enlisted in this study did not show any relevant neurosurgical condition in addition to those for which they were treated, and their characteristics are summarized in [Table 1]. Written informed consent to participate in the study was obtained from all the patients before surgery was performed.

Histological analysis was carried out using light microscopy. Independent and comparative evaluation of the nine membranes allowed the identification of similarities. Different areas of each membrane were evaluated to exclude possible sampling bias.

RESULTS

Histological examination of the membrane tissue revealed a substantial non-specific inflammatory reaction in both reactive and CSDH-related specimens. In each type of membrane, collagen fibers and different layers of fibroblasts were noticed along with neutrophils and dural histiocytes [Figure 1]. Highly permeable capillaries lacking pericytes and smooth muscle cells were also noticed in line with other reports [Figure 2]. Differences among the 5 hematoma-derived specimens were noticed but were imputed to the different stages of scar formation. Interestingly, further analysis of the reactive membranes secondary to extracranial CSF leakage showed the presence of activated histiocytes similar to the ones seen in CSDH membranes [Figure 3].

DISCUSSION

From trauma to drama

CSDH has been recently reconsidered as part of an intense and sustained inflammatory reaction rather than a post-traumatic injury alone.[5,8,22] Although trauma plays a major role in the pathogenesis of this condition, the mechanisms by which this progresses to CSDH are not yet fully understood. For instance, the way that fluid commonly accumulates spanning the cerebral convexities is inconsistent with the bridging vein source theory.[1,13] This evidence prompted to focus on more functional aspects of the process rather than mechanical drivers only. Inglis[8] described how a persistent

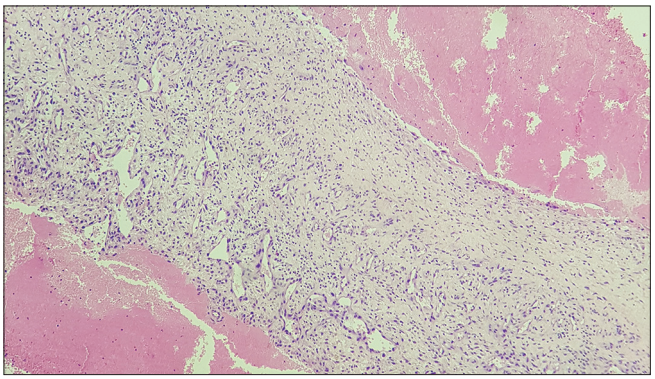

Figure 1: Histologic specimen obtained during burr hole surgery in a patient with chronic subdural hematoma. Evidence of inflammatory reaction of the external membrane of the hematoma, with presence of activated fibroblasts, collagen fibers, and dural histiocytes (Hematoxylin and eosin staining).

Table 1: Patient Demographics, Initial Diagnosis and Histological Specimens Examined.

Age	Sex	Initial diagnosis	Surgical Treatment	Histological specimen
67	F	Idiopathic normal pressure hydrocephalus	Ventriculoperitoneal shunt	Reactive membrane secondary to subcutaneous CSF leakage
72	M	Idiopathic normal pressure hydrocephalus	Ventriculoperitoneal shunt	Reactive membrane secondary to subcutaneous CSF leakage
57	F	WHO-2021 meningioma of the falx	Interhemispheric approach through a midline crossing craniotomy	Reactive membrane secondary to subgaleal CSF collection
67	F	WHO-2021 Glioblastoma, IDH-wildtype	Parietal craniotomy followed by gross total resection	Reactive membrane secondary to subgaleal CSF collection
72	F	CSDH	Single burr hole drainage	External membrane of CSDH
81	M	CSDH	Single burr hole drainage	External membrane of CSDH
79	M	CSDH	Double burr hole drainage	External membrane of CSDH
67	F	SDH progressed to CSDH	Single burr hole drainage	External membrane of CSDH
80	M	SDH progressed to CSDH	Double burr hole drainage	External membrane of CSDH

CSDH: Chronic subdural hematoma, CSF: Cerebrospinal fluid

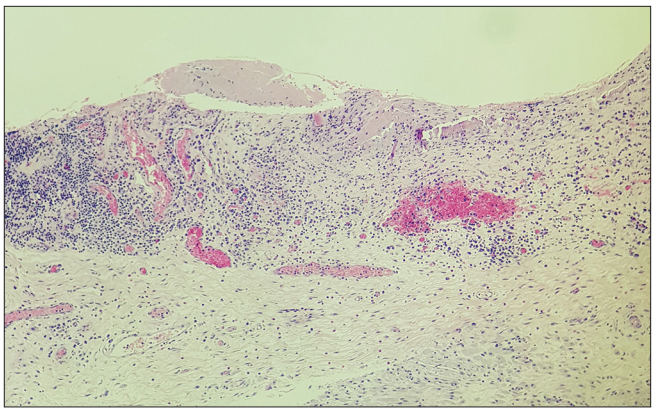

Figure 2: Microphotography of the dural membrane in a patient surgically treated for chronic subdural hematoma, showing the presence of highly permeable capillaries lacking pericytes and smooth muscle cells (Hematoxylin and eosin staining).

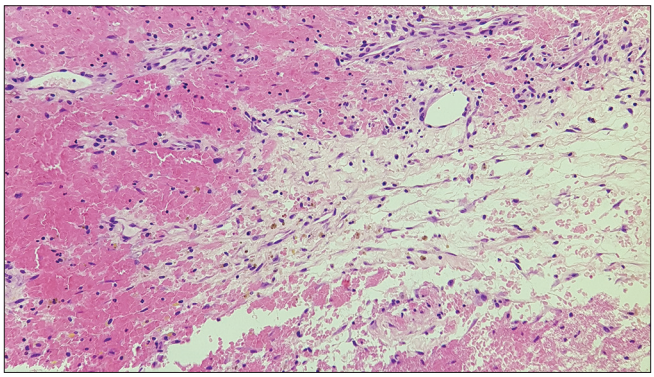

Figure 3: Reactive membrane obtained from subcutaneous cerebrospinal fluid leakage revision surgery. Similarities with the chronic subdural hematoma reactive membranes were noticed, including reactive histiocytes and newly formed blood vessels (Hematoxylin and eosin staining)

inflammatory response could damage a specialized subset of dural cells termed "dural border cells," which ultimately leads to reactive membranes and "leaky" vessels formation. Following the pathological delamination of the dural border cells, two membranes are formed, encapsulating the new subdural cavity. Evidence of high concentration of type 1 and type 3 procollagen and vascular endothelial growth factor (VEGF) and VEGF receptor in the subdural fluid suggests a general activation of the pro-inflammatory branch of the immune system.[6,7,10,12] This process ultimately leads to the activation of fibroblasts and the synthesis of collagen fibers, resulting in membranes formation which enclose the newly formed subdural cavity. For instance, contiguous with the dura mater is the external membrane of the hematoma, which is considered to be crucial in driving CSDH growth. Indeed, it contains numerous highly permeable capillaries lacking smooth muscle cells and pericytes. This membrane also shows progressive changes over time with evolutionary scarring processes.[16]

Mediators involved

Bleeding hosts a central role in the pathogenesis of CSDH and recently several angiogenic mediators have been identified to be involved in the formation of the reactive membranes. The concentration of VEGF and its receptor is reported to be more than 28 times higher in the subdural fluid collection than that found in serum.[25] The source of this growth factor is debated with some studies suggesting it may be produced by neutrophils infiltrating the CSDH fluid.[17] VEGF activates several signaling pathways, but one of the most relevant is the phosphatidylinositol-3-kinase-serine/threonine kinase pathway[3] This pathway is involved in the production of nitric oxide and monitors cell proliferation. A consequent

excess of vascular permeability may contribute to the ongoing rebleeding implicated in CSDH growth.[25] Persistent bleeding could also be explained by hyperactivation of the fibrinolytic process. Several studies have found high levels of fibrinogen degradation products (FDPs) in CSDH fluid.[9,18] This evidence suggests that the dysregulation of the balance between coagulation and fibrinolysis can initiate and promote CSDH formation. Nomura *et al*.[18] found that levels of fibrin and FDPs in the subdural fluid collection correlate with CSDH subtypes, indicating different bleeding frequencies over time. Indeed, radiological evidence suggests the presence of various hematoma subtypes which ultimately correlate with clinical presentations. More mature membranes are associated with more hypodense and hence chronic hematomas, whilst more immature membranes show hyperdensity due to more bleeding and are more frequently seen in the patients with a worse clinical state.

Role of CSF leakage

Recent evidence shows how CSF leakage in the subdural space could be associated with CSDH formation.[11,30] Arachnoid tearing secondary to even minor trauma could allow CSF to leak from the subarachnoid space and to accumulate under the pachymeninx, and this has been proposed to result in SDHy.[32] In their study, Kristof *et al*.[11] found higher levels of beta trace protein (βTP) in CSDH, indicating the presence of CSF in the pathological collections. They then looked for evidence of progression from SDHy to CSDH and found consistently higher βTP concentrations in either condition. Edlmann *et al*.[2] found that 54% of patients presenting with CSDH not associated with acute hemorrhage at baseline imaging also showed evidence of SDHy. Therefore, a correlation between the two conditions has been proposed but to our knowledge, no histological evaluation is available in the literature.[20,21]

In the present work, we speculate that CSF leakage into extracranial sites could initiate a similar inflammatory reaction to the one associated with CSDH formation, therefore indicating that reactive membranes could be secondary to a non-specific inflammatory reaction associated with the subdural CSF leakage. Findings of similarities between reactive and CSDH-related specimens suggest that CSF could be an underestimated factor in the formation of the membranes. The presence of activated histiocytes could also indicate a common mechanism underlying the two processes. If this is confirmed by future research, CSF leakage in the subdural space could not only be associated with hygroma but also, under certain conditions, cause progression to CSDH.

Future treatment perspectives

Knowledge of the pathophysiological dynamics of CSDH is crucial for optimizing surgical and pharmacological treatment options. Operative treatment has long been considered the main solution for the patients presenting neurological deterioration and radiological evidence of CSDH.[24] Nonetheless, recent data suggest that conservative treatment with corticosteroids could improve patients' condition by avoiding surgery. Dexamethasone shows good safety profiles in these patients with very low rates of subsequent surgical evacuation need.[4] In their prospective case study, Thotakura and Marabathina[27] showed how 4 mg every 8 h for 72 h could critically improve the clinical condition of patients presenting with lower grades of CSDH. Acknowledging the role of inflammation in CSDH is critical for establishing new patient-oriented treatment options.[11,28]

CONCLUSION

CSDH is likely the result of a complex interaction among various biomolecular pathways induced by both traumatic injury and inflammatory dysregulation. In rare cases, it can result from an SDHy progressed the most of the time with no clinical evidence. The role of the immune system and particularly histiocytes is still debated. In the present work, we found evidence of non-specific inflammatory reaction associated with extracranial CSF leakage and speculate that the histological similarities seen with the CSDH-related membranes could indicate an underlined common pathophysiological mechanism.

Further research is necessary to better understand phlogistic reactions caused by CSF leakage in the subdural space and how these could influence pharmacological therapy.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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