Pathophysiology and Nonsurgical Treatment of Chronic Subdural Hematoma: From Past to Present to Future

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Key words
- Angiogenesis
- Chronic subdural hematoma
- Corticosteroids
- Head trauma
- Inflammation
- Pathophysiology

Abbreviations and Acronyms
ACE: Angiotensin-converting enzyme
BHC: Burr-hole craniostomy
CSDH: Chronic subdural hematoma
COX-2: Cyclooxygenase 2
CSF: Cerebrospinal fluid
CT: Computed tomography
IL: Interleukin
PGE_2: Prostaglandin E_2
t-PA: Tissue plasminogen activator
VEGF: Vascular endothelial growth factor

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BACKGROUND: **Chronic subdural hematoma (CSDH) is one of the more frequent pathologic entities in daily neurosurgical practice. Historically, CSDH was considered progressive recurrent bleeding with a traumatic cause. However, recent evidence has suggested a complex intertwined pathway of inflammation, angiogenesis, local coagulopathy, recurrent microbleeds, and exudates. The aim of the present review is to collect existing data on pathophysiology of CSDH to direct further research questions aiming to optimize treatment for the individual patient.**

METHODS: **We performed a thorough literature search in PubMed, Ovid, EMBASE, CINAHL, and Google scholar, focusing on any aspect of the pathophysiology and nonsurgical treatment of CSDH.**

RESULTS: **After a (minor) traumatic event, the dural border cell layer tears, which leads to the extravasation of cerebrospinal fluid and blood in the subdural space. A cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis is set in motion. The most commonly used treatment is surgical drainage. However, because of the pathophysiologic mechanisms, the mortality and high morbidity associated with surgical drainage, drug therapy (dexamethasone, atorvastatin, tranexamic acid, or angiotensin-converting enzyme inhibitors) might be a beneficial alternative in many patients with CSDH.**

CONCLUSIONS: **Based on pathophysiologic mechanisms, animal experiments, and small patient studies, medical treatment may play a role in the treatment of CSDH. There is a lack of level I evidence in the nonsurgical treatment of CSDH. Therefore, randomized controlled trials, currently lacking, are needed to assess which treatment is most effective in each individual patient.**

INTRODUCTION

As one of the more frequent pathologic entities in daily neurosurgical practice, chronic subdural hematoma (CSDH) is a major topic in neurosurgical literature. Moreover, CSDH is a public health issue with an estimated 1-year incidence of 5–58/100,000, the highest in elderly patients.[1-7] Because it is expected that the proportion of elderly citizens will double in 2030, the CSDH incidence will likely increase.[8]

The first authentic description of a clinical case that seems to describe CSDH, came from Johannes Wepfer in 1657. He described a "bloody cyst," which he discovered post mortem in the subdural space of an elderly man. The man, just before he died, had an apoplectic stroke with aphasia and hemiplegia.[9]

The first description of a craniectomy for a CSDH was published almost a century later by James Hill in 1751. He described the injury and treatment of a girl who fell off a horse. For the first few days, she had no complaints except amnesia, but in the weeks to follow, she experienced progressive headaches, nausea, and vomiting. After 5 weeks, a trepanation was performed in which 'black liquid blood' appeared from under the dura. She recovered immediately after surgery.[10]

Houssard was the first to describe the CSDH as a clot surrounded by developing membranes in 1817. Bayle also described these membranes in 1826. He stated that the lamination could be caused by recurrent hemorrhages.[11] In 1857, Virchow formulated CSDH as "pachymeningitis hemorrhagica chronica interna" and

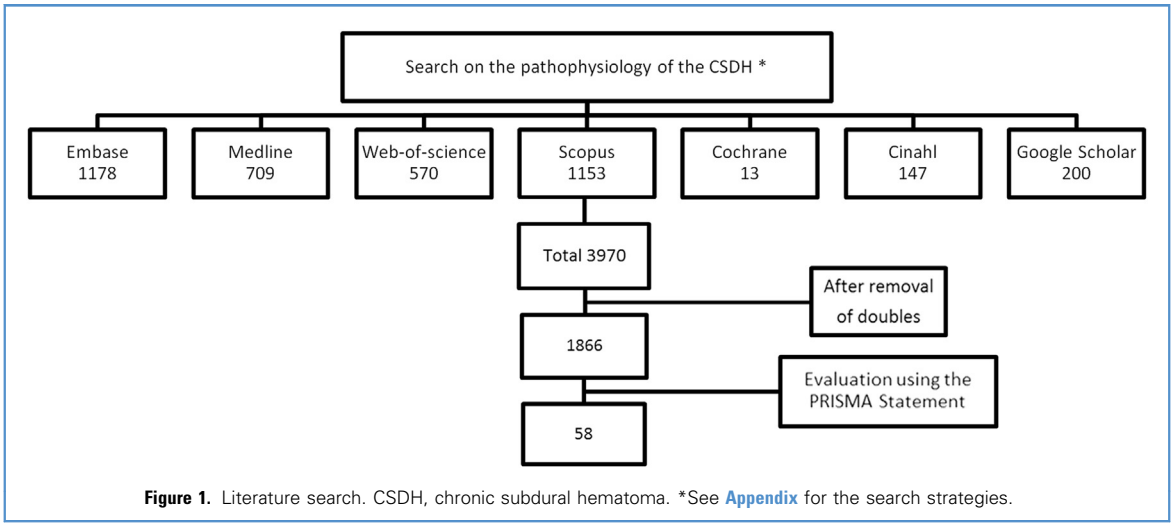

Figure 1. Literature search. CSDH, chronic subdural hematoma. *See **Appendix** for the search strategies.

indicated that CSDH can be initiated by trauma, but the lesion itself was more likely to be caused by chronic inflammation of the dura. He described the histology and formation of (neo) membranes: a process of "chronic inflammation" in the dura followed by fibrin formation and proliferation of capillaries from the dura with extravasation of blood into the subdural space.[12,13] This theory of inflammation of the dura became widely accepted until in 1914 Trotter proposed a traumatic cause of this lesion.[14] Throughout the twentieth century, many different theories came up for the latent interval between trauma and the onset of symptoms in patients with CSDH. The CSDH was proposed as being a chronic or recurrent bleeding,[15] possibly expanded through osmotic pressure[16] or increased as a result of recurrent microhemorrhage after an initial small CSDH.[17,18] The idea was adopted that CSDH is a progressive bleeding that can develop after (mild) trauma, spontaneously, out of an acute subdural hematoma or after a subdural hygroma.[19-23] However, it has been recently suggested that a more complex intertwined pathway of angiogenesis, inflammation, recurrent microbleeds, exudates, and local coagulopathy is involved.[24,25]

The management of CSDH may consist of surgery (burr-hole craniostomy [BHC]), a temporary high dose of corticosteroids as monotherapy or as an adjunct to surgery, or watchful waiting. There is no consensus on optimal CSDH treatment, because none of the available treatment modalities has been evaluated in comparative randomized clinical trials. The fact that its pathophysiologic mechanism has not been fully elucidated further complicates the matter. Consequently, as more research is directed toward this area, the hydra paradox comes into effect: best practice for treatment has not been established and evolving research data raises an increasing number of unsolved questions. Despite the increased research and advances in surgery and technology, little has changed in the management of patients with CSDH in the last decades. The treatment of CSDH is associated with serious morbidity, mortality, and recurrence rates.[1,5,26-33]

This review aims to collect existing data on pathophysiology of CSDH to direct further research questions aiming to optimize treatment for the individual patient.

METHODS

A broad Medline (PubMed and Ovid), EMBASE, CINAHL, and Google scholar search (for gray literature) was performed to review the pathophysiology of CSDH (see **Appendix** for the search strategies). This search yielded 3970 results, 1866 after removal of double references. The results were evaluated using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[34] Fifty-eight papers were included in the review (**Figure 1**).

Original articles and basic, translational, and clinical studies including >10 patients focusing on any aspect of the pathophysiology of CSDH (molecular markers, cytokines, inflammation, or coagulation) were included. Reviews, case reports, and pediatric series were excluded.

Risk of bias assessment was performed by the first 2 authors (V.V. and D.H.) using, among others, the QUADAS-2 tool.[35] For biomarkers, we used no specific tool. The uncertainties were discussed with the senior author (R.D.) and the conflicts were resolved. However, because of the scarcity of evidence and research in this area, no articles were excluded on these grounds. All articles had a relatively high risk of bias given the generally small sample sizes and lack of external validation of results.

Topics of Interest

To discuss all relevant aspects concerning the pathophysiology and treatment of the CSDH, we focus on the following subjects:

1) Anatomic consideration and membranes
2) Inflammatory pathways
3) Angiogenesis and growth factors
4) Coagulopathy and hyperfibrinolysis and exudation
5) Proteome and hormones
6) Nonsurgical treatment of CSDH.

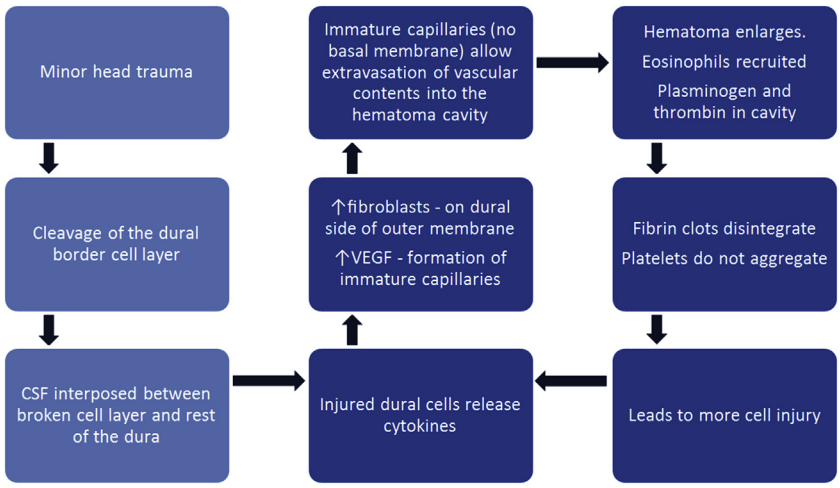

Figure 2. The pathophysiology of chronic subdural hematoma; this cycle perpetuates. CSF, cerebrospinal fluid; VEGF, vascular endothelial growth factor.

RESULTS

Anatomic Consideration and Membranes

The Subdural Space. The subdural space was described in several human and anatomic studies and in a review by Haines et al.[36,37] CSDH was initially regarded as a thin lamina of fluid between the dura mater and the arachnoid mater, a well-accepted theory accepted even in the twentieth century.[38] However, the so-called subdural space is a layer of cells called dural border cells, which have junctions that are less tight than the rest of the properly bound dura and arachnoid mater.[37] In 1936, Munro had already shown in his surgical pathology series that within 24 hours after the event responsible for the initiation of CSDH, fibroblasts lining the underside of the dura, in the vicinity of dural border cells, begin to form an outer membrane that is for the most part fully developed within 1 week.[39] Within 3 weeks, the inner membrane, much thinner, is also fully constituted. These findings were later confirmed through electron microscopy.[40]

The trigger for the chain of events leading to a CSDH with mass effect is likely to be a minor traumatic event that causes tearing of the dural border cell layer and the extravasation of cerebrospinal fluid (CSF) and blood in the now existing subdural space. The mass effect appears because of extravasation of CSF in the subdural space and not as a result of the hematoma itself.[41] The CSF sets a cascade of inflammation, impaired coagulation, fibrinolysis, and angiogenesis (Figure 2). Before discussing these parameters in more detail, we focus on the role of the membranes.

The Membranes. The external membrane has abundant blood vessels, with giant capillaries having a large lumen similar to veins, but without pericyte investment or smooth muscle cells. These capillaries show abnormal permeability through the large gaps and sparse basal membrane permitting the direct spill of vascular contents in the extravascular space.[42] There are also wide gaps, 0.4–1 μm, between adjacent endothelial cells, facilitating the transport of substances and migration of cells as they would from intercellular gaps of venules in inflamed tissue. During the course of disease, vesicles are seen within capillaries pointing toward the evacuation of hematoma contents.[17] Furthermore, the membrane contains active fibroblasts, a large number of collagen fibrils, and migrating cells (Figure 3, Table 1).

The inner membrane contains 4 separate layers, from external to internal: the hematoma surface; the intermediate layer, in which sometimes eosinophils and edematous fluid are found in the dilated extracellular space; the arachnoid surface layer with blood pigments, fibrins, and fibrinoid substance among loosely tied collagen fibrils and elastin; and the final layer, in which the cells scarcely show the tight intercellular junctions such as desmosomes that are to be expected from the arachnoid mater.[43]

Inflammatory Pathways

With progression of disease, fewer cellular and vascular structures and more fibrous tissue are present in the membranes. Fibroblasts are recruited by basic fibroblast growth factor and the release of chemokines. The fibroblasts organize on the dural side of the outer membrane. Some of these fibroblasts become myofibroblasts, which in electron microscopy studies resemble smooth muscle cells. Their presence might be attributable to a physiologic reaction also seen in atheromatous plaques or granulation tissue.[44] Myofibroblasts produce chemokines to recruit inflammatory cells to the inflammation epicenter.[45] The dural border cells organize the inner membrane with help from the arachnoid mater, which becomes adherent to it.

Inflammation in CSDH is a local process, as shown by normothermia and absence of increased/augmented systemic inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. Cytokines, such as the proinflammatory tumor necrosis factor α, interleukin 6 (IL-6), chemokine IL-8, and the antiinflammatory IL-10, are present at higher concentrations in CSDH fluid than in serum.[46] Because CSDH is an encapsulated collection, it is unlikely that CSF may permeate the subdural cavity once CSDH is formed.[46] Therefore, the likely source of cytokines is represented by fibroblasts, endothelial cells, and inflammatory cells found in the membrane, because these types of cells are known to secrete inflammatory markers in response to bleeding.[47]

IL-6 can cause enlargement of endothelial gap junctions with subsequent increased vascular permeability,[48] probably via the JAK/STAT3 (Janus kinase-signal transducer and activator of transcription) pathway,[49] a phenomenon that is also described in the membrane of the CSDH. IL-8 promotes leukocyte recruitment to sites of inflammation or injury by activating integrins and subsequently by promoting migration through

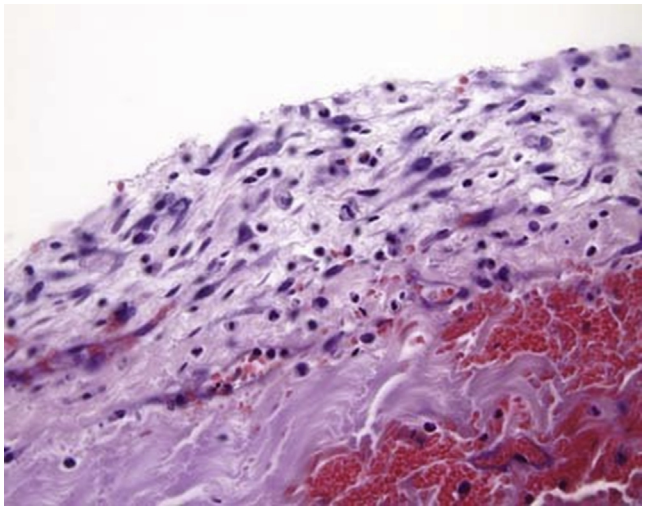

Figure 3. Histologic study of the outer membrane of chronic subdural hematoma. Notice the erythrocytes are inferior and the proliferating fibroblasts are superior. This histologic specimen is dated 7 days after the episode of bleeding. Source: permission received from Jan Leestma, forensic neuropathologist.

the extracellular matrix.[50,51] It is a potent angiogenic factor, which may partly explain why it is significantly increased in the layering type of hematoma.[46]

On magnetic resonance imaging (MRI), T1 hyperintense CSDH showed higher concentrations of IL-6 and IL-8, whereas T2 hyperintense hematomas showed higher concentrations of β-trace protein in the subdural fluid compared with the serum. These findings seem to be associated with recurrences in hyperintense T1 hematomas and CSF admixture in hyperintense T2 hematomas, respectively.[52]

Levels of IL-10 seem also to be increased in CSDH hematoma fluid, even although it is an antiinflammatory cytokine. The patients with increased levels of IL-10 also have higher levels of IL-6 and IL-8,[53] but layering hematomas were correlated with a lower IL-10 level in the fluid.[54] A high level of IL-6 and IL-8 with a high level of IL-10 is indicative of nonspecific inflammation and may suggest that the process can be self-limiting.[53]

The membranes show prominent infiltration of degranulated eosinophils and lymphocytes, whereas within the hematoma, eosinophil counts are only slightly increased.[55] Lymphocytes release chemoattractants, drawing the eosinophils to the site of injury.[56] Most likely, eosinophils promote hyperfibrinolysis by the release of plasminogen, fibrosis in the fibroblasts of the outer membrane, and phagocytosis of metabolites, and even resorption of hematoma products.[57-59]

Another inflammatory pathway is the cyclooxygenase 2 (COX-2)—prostaglandin E_2 (PGE_2) pathway.[60] COX-2 triggers the synthesis of PGE_2, which in turn stimulates the overexpression of vascular endothelial growth factor (VEGF), responsible for induction of angiogenesis. COX-2 is overexpressed in the outer membrane, especially in endothelial cells and in inflammatory cells. Among these cells are numerous CD-68-positive macrophages, which may cause the increased level of PGE_2 in the subdural fluid compared with serum.

Angiogenesis and Growth Factors

VEGF is one of the key angiogenic factors, originally described as a tumor-secreted protein named the vascular permeability factor, which causes substantial vascular leakage.[61] VEGF and the proangiogenic factor angiopoietin 2, create an unstable condition with the continuous formation of new and immature capillaries causing extravasation and recurrent microbleeds.[62]

Also, hypoxia-inducible factor 1α plays an important role in the process of vessel formation. It is induced by hypoxia and strongly present in the outer membrane and correlates strongly with VEGF presence.[63] Levels of VEGF and basic fibroblast growth factor are higher in subdural fluid than in serum and show a strong presence in the neomembrane as well.[61,64]

VEGF is produced by macrophages, plasma cells in the membranes, and endothelial cells of the fragile microcapillaries of the outer membrane. It is suggested that one of the therapeutic aspects of surgical drainage of the hematoma and washing of the subdural space disrupts the cycle of autocrine cell stimulation of VEGF by strongly decreasing its level in the hematoma cavity.[65]

Besides VEGF, which regulates endothelial cell survival through the phosphatidylinositol 3-kinase/Akt/endothelial nitric oxide synthase pathway,[66] 2 other pathways contribute to the CSDH pathogenesis. The Ras/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, activated by IL-6 and VEGF, has a role in endothelial cell proliferation and migration and the transforming growth factor β/activin receptorlike kinase 1 pathway, which is essential for the formation and remodeling of new vessels. These pathways all represent intracellular ways in which VEGF exerts its effects. Further research into the upregulation and downregulation of these pathways, as well as into the factors that influence them, is required to draw the line between normal endogenous repair processes and pathologic VEGF activation and possible halting of its effects.

The exudation rate of VEGF and albumin in the subdural fluid can be related to computed tomography (CT) appearance, using the Nomura classification.[67] Nomura made a subdivision into 5 types of CSDH according to their appearance on CT: high density, isodensity, low density, mixed density, and layering. The mean VEGF concentration was highest in mixed density hematomas.[68,69] There is also a significant correlation between the VEGF concentration and MRI appearance.[70-72]

Coagulopathy, Hyperfibrinolysis, and Exudation

Next to inflammation and angiogenesis, coagulopathy, hyperfibrinolysis, and

Table 1. Factors Involved in the Pathophysiology of Chronic Subdural Hematoma

Inflammatory Pathway	
Fibroblasts	(Myo)fibroblasts produce chemokines
bFGF (basic fibroblast growth factor)	Recruits fibroblasts
Lymphocytes	Release chemoattractants drawing the eosinophils to the site of injury
Eosinophils	Releases plasminogen, promotes fibrosis in the fibroblasts, phagocytosis of metabolites, and resorption of hematoma products
IL-8 (interleukin)	Inflammatory marker; promotes leukocyte recruitment to sites of inflammation or injury
IL-6 (interleukin)	Inflammatory marker; enlarges the endothelial gap junctions, which increases the vascular permeability
IL-10 (interleukin)	Antiinflammatory marker, lower IL-10 in layering hematomas. If IL-6, IL-8, and IL-10 are high, this is indicative of a nonspecific inflammation and suggests a self-limiting process
Janus kinase-signal transducer and activator of transcription pathway	Effector pathway by which IL-6 exerts its pathogenic effects in CSDH
Cyclooxygenase 2 (COX-2)—prostaglandin E_2 (PGE_2) pathway	COX-2 triggers the synthesis of PGE_2 from arachidonic acid, which in turn stimulates the overexpression of VEGF
Angiogenesis and Growth Factors	
HIF-1α (hypoxia-inducible factor 1α)	Transcription factor that regulates VEGF, present in the outer membrane
PGE_2 (prostaglandin E_2)	Stimulates the overexpression of VEGF
VEGF (vascular endothelial growth factor)	Proangiogenic factor, increased in the subdural fluid and neomembrane
MMP-9 (matrix metalloproteinase 9)	Reduced absorption of CSDH because of increased vascular permeability, enhanced inflammation, and reduction of vascular maturation
MAPK pathways (mitogen-activated protein kinase)	Regulates proliferation and migration of endothelial cells, possibly activated by VEGF and IL-6
PI3/Akt/endothelial nitric oxide synthase pathway	VEGF regulates endothelial cell survival through this pathway
Transforming growth factor β/activin receptorlike kinase 1(ALK-1) pathway	Essential for the formation and remodeling of new vessels
Coagulopathy, Hyperfibrinolysis, and Exudation	
Plasminogen	The inactive precursor of plasmin
t-PA (tissue plasminogen activator)	Activates plasminogen, which is converted to plasmin. Activated plasmin degrades coagulation factors V, VIII, and XI
Thrombin	Thrombin catalyzes the conversion of fibrinogen into fibrin
FDPs (fibrinogen degradation products)	Includes fibrin monomer and D-dimers. D-dimers inhibit platelet aggregation and fibrin polymerization
TM (thrombomoduline)	Thrombin receptor on endothelial cells of the capillaries that inhibits blood clotting by binding with thrombin and the activated protein C. It is expressed and increases after vascular endothelial injury
Ang-2 (angiopoietin 2)	Proangiogenic factor that, in combination with VEGF, leads to the formation of immature capillaries
Proteome and Hormones	
TGFβI (transforming growth factor-β-induced protein Ig-H3)	Protein, responds to tissue injury and has a role in wound healing. In CSDH, it plays an important role in the proliferation of the membrane and the meningeal reaction to the subdural collection
PICP (propeptide of type I collagen) and PIIINP (aminoterminal propeptide of type III procollagen)	Increased in the subdural fluid; indicating a long-lasting upregulation of collagen synthesis

CSDH, chronic subdural hematoma; VEGF, vascular endothelial growth factor.

protein exudation play important roles in the maintenance of the hematoma and explain why there is continuous bleeding in the cavity and no clot.

The inflammatory mediators stimulate the vascular permeability and release tissue plasminogen activator (t-PA) from endothelial cells. The level of t-PA in the hematoma fluid was found to be significantly higher than in plasma.[73] These levels correlated with the size of the hematoma and clinical status of the patient: patients with stupor and coma had significantly higher levels of t-PA than did patients with headache or somnolence. The t-PA levels also related to the aspect on the CT scan, on which layering hematomas show higher levels.[73] t-PA activates plasminogen, which is then converted to plasmin. The activity of plasmin in the subdural fluid together with normal plasmatic levels shows local hyperfibrinolytic activity.[74] Moreover, hematoma fluid contains a low amount of plasminogen when compared with serum, because of its ongoing conversion to plasmin, and a higher amount of fibrinogen degradation products, including fibrin monomer and D-dimers. D-dimers inhibit platelet aggregation and fibrin polymerization, whereas the activated plasmin degrades coagulation factors V, VIII, and XI.[75] Thus, the consequences are an impaired platelet function, a defective fibrin clot, and an important hemostatic imbalance.[76] Subdural fluid collected 24 hours after surgery showed reduced t-PA and fibrinogen degradation products levels,[77] signifying the re-establishment of a balance between coagulation and fibrinolysis.

Thrombin also plays an important role in the progression of CSDH. The thrombin-antithrombin III complex and prothrombin fragments 1 and 2 are nonsignificantly increased in subdural hygroma and significantly increased in CSDH, whereas levels of D-dimers, indicating fibrinolytic activity, are only increased in CSDH. Thrombomodulin is expressed and increased after vascular endothelial injury. It is a thrombin receptor on endothelial cells of the capillaries that inhibits blood clotting by binding with thrombin and the activated protein C.[54] It showed higher levels in mixed density hematomas and the highest level in laminar types.[78] The extrinsic clotting system becomes defective in the development of CSDH, and the switch from subdural hygroma to CSDH occurs when fibrinolysis begins to manifest.

Proteome and Hormones

The Subdural Hematoma Proteome. A recent study has characterized the subdural hematoma proteome,[79] in which 1100 proteins were analyzed for differences with serum levels. In total, levels of 11 proteins were increased, most being regulators of coagulation and fibrinolysis. Among those proteins were fibrinogen, corresponding to the state of hyperfibrinolysis and hemoglobin α and β levels, suggesting ongoing erythrocyte lysis. Another protein with increased level is transforming growth factor β–induced (TGFβI) ig-h3,[79] which is associated with tissue injury and wound healing, making it probably responsible for the proliferation of the membrane and the meningeal reaction to the subdural collection.

Complement values were shifted (C3cα) and decreased (C4c), suggesting a role for complement in the inflammatory reaction that characterizes CSDH, but its specific role has yet to be explored.

Two reports stated that propeptide of type I collagen and the aminoterminal propeptide of type III procollagen were 78-fold to 156-fold higher than in serum from the period of 10–85 days after injury, indicating a long-lasting upregulation of collagen synthesis.[80] Moreover, this increase is time dependent in the first 2 weeks and remains high for more than 3 months, whereas in dermal wound healing, these levels normally decline 3 weeks after injury.[81,82] The dural fibrosis reaction stays active even longer than the one observed in subarachnoid hemorrhage, which subsides after a month.

Hormones. An intriguing area of research was proposed in 1977 by observing high urinary estrogen levels in male patients with CSDH, suggesting that this might play a role in the pathogenesis of the disease.[83] In 1984 and later in 1992, positive staining for estrogen and progesterone receptors in the membrane of hematomas was shown. Estrogens might influence the vascularized membranes directly, including stimulating synthesis of t-PA. This characteristic could be more pronounced in men whose vascular system is less adapted to high values of estrogen.[84,85] However, these theories could not be reproduced in a later study.[86]

Nonsurgical Treatment of CSDH

Dexamethasone. Steroids might be an option in the nonsurgical treatment of CSDH. Dexamethasone is known to be antiinflammatory and has antiangiogenic effects. Moreover, it is able to inhibit the formation of new blood vessels. Over the past decades, dexamethasone has been assessed in multiple studies as monotherapy or as an adjunct to BHC.[87-93] Dexamethasone is a noninvasive treatment and might significantly reduce mortality and lead to a better outcome.[94] Also, in some patients, this treatment led to shorter hospitalization, making it more cost-effective compared with BHC.

The downside of dexamethasone use is a higher complication rate such as diabetes, infections, and (temporary) mental changes. The mortality in studies using dexamethasone for treatment of CSDH varies between 0.8% and 4%.[94]

Thotakura and Marabathina identified several variables (female sex, limited midline shift and hematoma thickness, and lower CT attenuation values) that are associated with a good outcome after conservative treatment with dexamethasone.[92] Zhang et al.[95] conclude that in patients with recurrent CSDH, dexamethasone treatment might avoid reoperation. Prospective studies on the role of dexamethasone in the treatment of CSDH are ongoing.[96,97]

Atorvastatin. Besides its role in decreasing levels of low-density lipoprotein cholesterol, atorvastatin has also been widely investigated in the management of CSDH. Some small studies showed atorvastatin to be safe and effective in the treatment of CSDH, leading to a lower rate of BHC.[98-101] In mice models, a low dose of atorvastatin (3 mg/kg/day) was found to have antiinflammatory and antiangiogenic effects.[102]

A proangiogenic effect of atorvastatin in rats was described by Li et al.[103] and Wang et al.[104] A higher dose of atorvastatin (8 mg/kg/day) led to a significantly increased and persistently high level of VEGF and

increased levels of inflammatory factor matrix metalloprotease 9.[104]

Tranexamic Acid. Tranexamic acid might inhibit the fibrinolytic and inflammatory (kinin-kallikrein) systems. In 1 study,[105] it was used as a primary medical treatment, resulting in successful treatment in 18 of 21 patients. In the study of Tanweer et al.,[106] tranexamic acid was administered postoperatively. No increase of hematoma or recurrences were noted. A multicenter randomized controlled trial started in October 2015 in Canada, planning to randomize 130 patients to receive either tranexamic acid or placebo.[107]

Angiotensin-Converting Enzyme Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors decrease VEGF production, possibly resulting in a reduction of new and immature vascularization, a decreased extravasation of fluid into the subdural space, and a reduction of recurrence of CSDH.[108] In a prospective randomized controlled trial,[109] the ACE inhibitor perindopril was tested against placebo; there was no statistically significant effect on recurrence rate. Neidert et al.[110] performed a retrospective case-control study in which they found higher hematoma volumes and a higher frequency of recurrences in patients treated with ACE inhibitors as an addition to surgery. These investigators hypothesize that this situation could be caused by an increase in bradykinin levels, causing increased vascular permeability of the neomembranes in CSDH.

DISCUSSION

Our review shows that, throughout history, different theories on the pathophysiology and treatment of CSDH have been put forward. Using all data from the literature search, we propose a contemporary unifying theory. A minor trauma precedes the formation of a CSDH. Trauma causes cleavage of the dural border cells, after which CSF or CSF with blood or a very small quantity of blood is interposed between the broken cell layer and the rest of the dura. The injured dural cells release cytokines, attracting inflammatory cells, which infiltrate, especially neutrophils and eosinophils. Some of the fibroblasts become myofibroblasts and synthesize chemokines, recruiting more inflammatory cells. Prostaglandins and chemokines induce the expression of VEGF, which in turn recruits endothelial cells in the outer membrane. The immature capillaries without the basal membrane, subjected to high pressure because of lack of drainage on the one side and negative pressure in the newly-formed subdural space on the other side, allow extravasation of all the vascular contents into the hematoma cavity. Progressively more eosinophils are recruited and plasminogen and thrombin are also poured inside the cavity. Fibrin clots are disintegrated, and platelets cannot aggregate. This process produces ongoing cell injury and causes a further increase of inflammatory cells and VEGF production. The cycle perpetuates and the hygroma becomes a CSDH. The membrane is fully constituted and it takes even more damage from the constant pulsating rhythm of the intracranial contents and from changes of position of the head.[111] The CSDH grows until it reaches a size that impairs CBF and metabolism in adjacent brain structures, leading to symptoms such as hemiparesis and/or mental changes.

There is no consensus on the best treatment for the individual patient diagnosed with CSDH. Trephination is internationally considered as the classic standard treatment in symptomatic CSDH. Trephination occurs through BHC, twist-drill craniostomy, or even craniotomy.[112-116] It consists of removing the hematoma by rinsing the subdural space, frequently followed by placing a temporary drain in the remaining cavity. However, surgery is also associated with recurrence, mortality, infection, bleeding, or seizures.[1,5,6,26-32] The operation-related mortality varies between 1.5% and 6% and CSDH recurs in 20%–26% of cases.[29,94,117-120] Because of the mortality, morbidity, and recurrence rates after surgery and also considering the pathophysiologic mechanism of CSDH, other more conservative options in the treatment of CSDH are worth investigating. The stimulation of vessel maturation and antiinflammatory pathways may contribute to the resolution of CSDH and may induce neurologic recovery.[121]

The literature suggests that drug therapy might be useful as a monotherapy or as an adjunct to surgery in patients diagnosed with CSDH. Drugs that might be effective are dexamethasone, atorvastatin, tranexamic acid, and ACE inhibitors. Dexamethasone is believed to intervene in the perpetuating pathophysiologic cycle through its antiinflammatory and antiangiogenic effects. However, properly designed randomized controlled trials need to be carried out to provide high-quality data to enforce clinical decision making. The use of atorvastatin in the treatment of CSDH is questionable, because of the contradictory findings in some studies performed. Tranexamic acid might intervene in the fibrinolytic and inflammatory pathways, but evidence is based on small retrospective studies. It is hypothesized that ACE inhibitors decrease the amount of VEGF and with that decrease, the volume of the CSDH. However, clinical studies have not confirmed this theory. Moreover, a small retrospective study suggests that treatment with ACE inhibitors might increase hematoma volumes and recurrence rate.

CONCLUSIONS

Based on pathophysiologic mechanisms, animal experiments, and small patient studies, medical treatment may play a role in the treatment of CSDH. Medical treatment could be administered as a monotherapy or as an adjunct to the classic surgical treatment, consisting of hematoma drainage. Further research is needed to assess which treatment is most beneficial in each individual patient diagnosed with CSDH. For this purpose, adequately sized multicenter prospective randomized controlled trials on the treatment of CSDH seem most valuable. Moreover, basic research aimed at unravelling the pathophysiology of CSDH is required.

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APPENDIX

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(pathophysiology/de OR angiogenesis/de OR histogenesis/de OR inflammation/de OR 'chronic inflammation'/de OR etiology/de OR pathogenesis/de OR hypocoagulability/de OR fibrinolysis/exp OR 'growth factor'/de OR 'angiogenic protein'/de OR angiopoietin/de OR vasculotropin/de OR 'vasculotropin 121'/de OR 'vasculotropin 165'/de OR pathology/de OR histopathology/de OR 'neovascularization (pathology)'/de OR (pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (('blood clot' OR 'fibrin clot') NEAR/3 lysis) OR fibrinogenol* OR (fibrin NEAR/3 (degradat* OR split*)) OR (growth NEXT/1 factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural NEXT/1 histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*):ab,ti) AND (('subdural hematoma'/de OR 'subdural effusion'/de OR (((subdural* OR subepidur*) NEAR/3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) NEAR/3 pachymening*)):ab,ti) AND ('chronic disease'/de OR (chronic*):ab,ti)) OR (csdh):ab,ti)

Medline (OvidSP)

(pathophysiology.xs. OR "Neovascularization, Pathologic"/ OR inflammation/ OR etiology.xs. OR Causality/ OR fibrinolysis/ OR exp "Angiogenic Proteins"/ OR pathology/ OR pathology.xs. OR (pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (("blood clot" OR "fibrin clot") ADJ3 lysis) OR fibrinogenol* OR (fibrin ADJ3 (degradat* OR split*)) OR (growth ADJ factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural ADJ histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*).ab,ti.) AND ("Hematoma, Subdural, Chronic"/ OR ("subdural effusion"/ AND "Chronic Disease"/) OR (((((subdural* OR subepidur*) ADJ3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) ADJ3 pachymening*)) AND chronic*) OR csdh).ab,ti.)

Cochrane

((pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (('blood clot' OR 'fibrin clot') NEAR/3 lysis) OR fibrinogenol* OR (fibrin NEAR/3 (degradat* OR split*)) OR (growth NEXT/1 factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural NEXT/1 histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*):ab,ti) AND ((((((subdural* OR subepidur*) NEAR/3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) NEAR/3 pachymening*)):ab,ti) AND ((chronic*):ab,ti)) OR (csdh):ab,ti)

Web-of-science

TS=(((pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (("blood clot" OR "fibrin clot") NEAR/3 lysis) OR fibrinogenol* OR (fibrin NEAR/3 (degradat* OR split*)) OR (growth NEAR/1 factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural NEAR/1 histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*)) AND ((((((subdural* OR subepidur*) NEAR/3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) NEAR/3 pachymening*))) AND ((chronic*))) OR (csdh)))

Scopus

TITLE-ABS-KEY(((pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (("blood clot" OR "fibrin clot") W/3 lysis) OR fibrinogenol* OR (fibrin W/3 (degradat* OR split*)) OR (growth W/1 factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural W/1 histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*)) AND ((((((subdural* OR subepidur*) W/3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) W/3 pachymening*))) AND ((chronic*))) OR (csdh))) AND doctype(ar)

Cinahl

(MH Physiopathology+ OR MH "Neovascularization, Pathologic+" OR MH inflammation+ OR MH fibrinolysis+ OR MH "Angiogenic Proteins+" OR MH pathology+ OR (pathophysiolog* OR physiopatholog* OR dysfunctio* OR angiogen* OR Angiopoietin* OR histogen* OR pathogen* OR hypocoagula* OR fibrinoly* OR (("blood clot" OR "fibrin clot") N3 lysis) OR fibrinogenol* OR (fibrin N3 (degradat* OR split*)) OR (growth N1 factor*) OR vasculotropin* OR etiolog* OR aetiolog* OR aetiopatho* OR etiopatho* OR causat* OR causal* OR (natural N1 histor*) OR onset OR patholog* OR clinicopatholog* OR histopatholog* OR neovascular*)) AND ("Hematoma, Subdural, Chronic+" OR (((((subdural* OR subepidur*) N3 (hematom* OR haematom* OR bleed* OR haemorrhag* OR hemorrhag* OR effusion*)) OR ((hemorrhag* OR haemorrhag*) N3 pachymening*)) AND chronic*) OR csdh))

Google scholar

Pathophysiology|angiogenesis|histogenesis|inflammation|etiology|pathogenesis|hypocoagulability|fibrinolysis|"growth factor"|angiogenic|angiopoietin|vasculotropin|pathology|histopathology|physiopathology|dysfunction "chronic subdural hematoma|haematoma"

Literature Search By Wichor Bramer; Information Specialist, Erasmus Medical Centre, Rotterdam, The Netherlands. Search on the Pathophysiology of Chronic Subdural Hematoma

Database	Total	After Removal of Duplicates
Embase.com	1178	1160
Medline (OvidSP)	709	95
Web-of-science	570	161
Scopus	1153	245
Cochrane	13	2
Cinahl	147	88
Google scholar	200	115
Total	3970	1866