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Publication Date

2017-12-01

DOI

10.1016/j.wneu.2017.09.063

Peer reviewed

HHS Public Access

Author manuscript

World Neurosurg. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

World Neurosurg. 2017 December ; 108: 954–958. doi:10.1016/j.wneu.2017.09.063.

Chronic Subdural Hematoma: a Perspective on Subdural Membranes and Dementia

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Abstract

Chronic subdural hematoma (cSDH) is a common intracranial pathology, and a leading cause of reversible dementia. cSDH is projected to affect at least 60,000 new individuals in the United States annually by 2030. This can result from mild to moderate head trauma that leads to hemorrhaging in the dura-arachnoid interface. The short and long-term effects of cSDH and the subdural membrane on the pathogenesis of dementia and the newly discovered dural lymphatics is a topic of increasing importance. This manuscript aims to review the complex pathogenesis of the subdural membrane, and the link between head trauma, dementia, and dural lymphatics.

Keywords

chronic; subdural; hematoma; neurosurgery; membrane; trauma; lymphatics; dementia

Introduction

Chronic subdural hematoma (cSDH) is a relatively common and debilitating pathological entity that affects 1–5.3 per 100,000 individuals annually. [1, 2] Notably, cSDH is particularly prevalent in elderly males, with over 50% of cSDH cases in patients over 60, and the highest incidence (7.35 cases per 100,000) in adults aged 70–79. It is projected to affect 60,000 Americans over the age of 65 annually by 2030. [3, 4] Reasons for this lie in the increased risk factors, such as falls or anti-coagulants, in the elderly, coupled with age-related cortical atrophy that distends small cerebral vessels and bridging veins. [5–9]

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Financial interests: None

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

cSDH commonly develops, over the course of 3 or more weeks, following mild to moderate head trauma coupled with a chronic inflammatory reaction.[10] Following cSDH development, natural physiological sequelae lead to a gradual enlargement of the cSDH, primarily through the formation of a subdural neomembrane. [11] This subdural membrane is composed of an inner and outer layer [Figure 1], which release anti-thrombotic and fibrinolytic molecules to liquefy the hematoma to prevent clot formation and facilitate cSDH reabsorption. [12, 13] However, in cases where reabsorption is impaired or absent, the cSDH can expand and result in mass effects, blood flow impairment, and metabolic disturbances in the underlying cortex. [14] The presence of blood alone in the subdural space is not adequate to induce cSDH; rather, chronic inflammation and other contributing factors, such as cerebral atrophy, may be the true etiological factors underlying cSDH. [15] In the following sections, we will provide a brief overview of subdural membrane formation, and discuss potential links between cSDH, dementia, and intracranial lymphatic systems.

Subdural Membrane Formation

The subdural membrane is an important contributor to the pathogenesis and clinical symptomatology of cSDH. It consists of an inner and outer layer that forms within the dura-arachnoid meningeal interface. [16] This interface creates a “potential” space, termed the “subdural space,” that consists of a tight group of cells known as the interface layer., This layer lines the inner dural border and forms the outermost arachnoid barrier. These two cellular components fuse within the interface layer and form a tight attachment. [17] This dura-arachnoid interface is structurally weak since it lacks collagenous reinforcement, has extracellular cisterns between dural border cells, and has few intercellular contacts. The dural border cells where the cSDH initially develops have two essential roles: phagocytosis, and proliferation into fibrous connective tissue; the latter of which is implicated in cSDH neomembrane development.[15, 18]

During cSDH formation, the hematoma itself forms within a sheet of torn dural border cells rather than within a pre-existing compartment; thus, this cavity only opens under pathological conditions. Following hematoma formation, epithelial cells that line the inner dural surface proliferate and form an inner, surrounding membrane. [11] cSDH presence results in a local inflammatory response that forms granulation tissue known as the external or outer membrane. [19] This membrane contains permeable macro-capillaries. Exudation from these capillaries contributes to the enlargement of the hematoma. [20] The inner membrane contributes to liquefaction of the hematoma, while the outer membrane contributes to hematoma enlargement, particularly with subsequent head trauma. The subdural membranes are maintained by activation of the clotting cascade and generation of thrombin within the hematoma, followed by anticoagulant and fibrinolytic activity. [13] The outer membrane contains vessels that are extremely porous and contribute to the slow expansion of the hematoma. The outer membrane may also be formed, in part, by increased production of extracellular matrix (ECM) by the meninges. [21]

Histopathology

The inner cSDH membrane contains multilayered tiers of flattened cells with increased ECM between the cells and tiers. [16] These cells have characteristics of dural border cells in the human dura-arachnoid interface, while cells adjacent to the hematoma contain indented nuclei, a prominent nucleolus, abundant enlarged rough ER, glycogen granules, lipid droplets, and caveolae. The layer of cells interacting with the arachnoid surface showed cellular organelle disintegration and nuclear chromatin dissolution. The increased ECM between the cells was composed of collagen fibrils, elastins, and finely granular material intermingled with blood pigments or fibrins. This study concluded that initial extravasation of blood within the dura-arachnoid interface layer might dislodge several tiers of dural border cells, which can surround the inner hematoma surface, proliferate, and eventually form the inner membrane.

Both cSDH membranes are populated with thin-walled permeable capillaries that are mostly free of basement membrane and pericytes. [22] Moreover, many gap junctions facilitate the transfer of blood from these capillaries to the SDH cavity. [22, 23] The internal membrane has little role in the advancement of cSDH because of its collagenous and fibroblast nature, on the other hand, the external membrane's inflammatory features such as the presence of lymphocytes, macrophages, neutrophils, and eosinophils make it an important contributor to cSDH progression. [23, 18–21] The external membrane's expression of aquaporin-1 has also been implicated in playing an additional key role in cSDHs fluid growth. [24]

When dura border cells are injured and separated, the newly formed membranes are filled with fluid that is rich in type 1 (PICP) and type 3 (PIIINP) procollagens, fibrous proliferating processes that go beyond tissue repair and form new membranes. [25] As summarized by Edlmann et al., the inflammation is driven by external membrane's pro-angiogenetic factors Ang-2 and VEGF, tissue plasminogen activator (tPA), and thrombomodulin. [13, 26, 27] Edlmann et al. suggests that when damaged, dural border cells recruit inflammatory cells and the proliferation process not only forms new membrane, but its pro-angiogenic nature also gives birth to leaky subdural vessels, leading to further subdural micro-hemorrhage. [15]

Angiogenesis is important in the pathophysiology of cSDH since the newly developed vasculature can serve as a fragile source of blood for the chronic hemorrhage. In cSDH, the outer membrane is reported to increasingly express Ang-2 mRNA, an angiogenesis growth factor that potentially leads to continuous formation and destabilization of membranous vessels. [27] Angiogenesis is also driven by VEGF which is upregulated in cSDH and may play a crucial role in disrupting external membrane gap junctions and vascular permeability, all contributing to the lasting nature of cSDH. [28–31] In addition to angiogenesis and vascular permeability, inflammation is a key factor in the pathophysiology of cSDH. The inflammatory response is mediated by cytokine-induced macrophages, neutrophils, lymphocytes, and eosinophils. Further research on the exact involvement of various cytokines can potentially lead to enhanced targeted treatments for cSDH. [15, 31–34]

The outer membrane results from granulation tissue and can be further delineated into four distinct histological subtypes based on the maturity and intensity of the ensuing

inflammatory reaction and intramembranous hemorrhaging. [19, 20] These four subtypes [Figure 2] are (I) noninflammatory, (II) inflammatory, (III) hemorrhagic inflammatory, and (IV) scar inflammatory membranes. The noninflammatory subtype contains immature fibroblasts, collagen fibers, sparse cellular infiltration, and neocapillaries. The inflammatory subtype consists of a single sheet of immature connective tissue with marked cellular infiltration and vascularization. The hemorrhagic inflammatory subtype consists of two or three sheets of connective tissue, and is associated with cellular infiltration and moderately-sized capillaries. The hemorrhagic inflammatory subtype also contains many thin new vessels adjacent to the hematoma cavity. Sometimes, this membrane consists of only collagen fibers and fibroblasts, and hemorrhage into the membrane is often observed. Finally, the scar inflammatory subtype contains inflammatory cell infiltration, neovascularization, and hemorrhage.

A study conducted by Gandhoke et al. correlated hematoma membranes with functional outcomes in 156 patients with histopathological classification of the membrane into one of the previously described subtypes. Each patient was assigned GCS scores in accordance with clinical presentation and radiological features. Specimens were fixed with formalin and stained with hematoxylin and eosin. Upon histopathological analysis of the outer hematoma neomembranes, there were no type I cases, 42.3% type II cases, 34.6% type III cases, and 23.1% type IV cases. Patients with a GCS <13 only had type II membranes, suggesting that patients with more severe functional loss lacked the non-inflammatory outer membrane subtype. Although the ramifications of these findings warrant further investigation, the study underscores the heterogeneity of cSDH.

A separate study examined the ultrastructure of 23 outer cSDH membranes and two inner membranes via electron microscopy. [21] The outer membrane contained granulation tissue from multiple mesenchymal cell origins, and was composed of fibroblasts, myofibroblasts, smooth-muscle cells, blood vessels, blood-born cells, and dural border cells. The inner membrane was composed of spindle cells mainly comprised of fibroblasts with some dural border cells. The study suggested that cSDH is an “intra” dural hematoma formed within the split dural border cell layer rather than in between the dura-arachnoid interface. The subdural membrane is increasingly being recognized as a proliferation and excessive thickening of the normal layer of dural border cells, which contrasts with the traditional view of cSDH pathogenesis and should be reevaluated. Friede et. al. suggests that there is no compelling reason to believe that proliferation always and exclusively develops secondary to traumatic hemorrhage. The authors suggest a vicious cycle: minimal trauma triggers bleeding into a thin neomembrane which then leads to proliferation of the dural border cells, forming more neomembranes. [17] With the emergence of a better understanding of the effects of traumatic brain injury (TBI) on dementia, chronic traumatic encephalopathy (CTE), and the recent emergence of dural lymphatics as a key player in intracranial homeostasis, the role of cSDH and the subdural membrane on clinical outcomes may have broader implications than previously anticipated. [35,36]

Linking cSDH to Dementia and Dural Lymphatics

The clinical effects of treated and untreated cSDH have been broadly explored and overshadow the physiological effects of cSDH on the underlying brain parenchyma. In addition to overt mass effect, the presence of a large cSDH can alter cerebral blood flow and result in ischemia and deleterious metabolic changes within the neuroparenchyma. [37] cSDH evacuation has been shown to improve cerebral blood flow (CBF) and cognitive function in patients.

Although the exact extent of the adverse physiological effects of cSDH on the brain remain to be elucidated, the link between TBI (a classification into which cSDH falls under) and dementia has been steadily uncovered. [38] TBI is a significant problem in adolescents and young adults, but is most prevalent in the elderly over the age of 65. [39, 40] TBI and dementia can influence one another. For instance, TBI is often the result of motor vehicle accidents and falls, situations that can be precipitated by dementia. [41–43] TBI itself can also cause deficits in attention, memory and executive functioning. Thus, while dementia is a risk factor for TBI, the opposite is also true - TBI is a risk factor for the ultimate development of dementia.

cSDH mimics dementia clinically, particularly in elderly patients, and is considered a reversible cause of dementia since hematoma evacuation frequently results in improvement of mental status and cognitive abilities. [44, 45] Left untreated, cSDH can be confused with Alzheimer's disease (AD), which is associated with the gradual deterioration of mental faculties.[46]

Meta-analysis data of case-control studies show that TBI is a risk factor for development of AD, one of the most common types of irreversible dementia. [47, 48] This association is particularly strong in males, and may be due to the protective effects of estrogen in females, or due to the different frequencies of traumatic events between the sexes. [49, 50] Though the evidence linking TBI and AD is not entirely consistent, meta-analyses report a relative increase in risk for developing AD in patients with a history of TBI, suggesting that TBI may be a predisposing factor in the development of AD long after acute TBI symptoms have subsided. [47] There are several proposed mechanisms by which TBI may lead to AD. First, TBI has been shown to modulate hippocampal synaptic plasticity and lead to amyloid precursor protein (APP) accumulation in damaged axons. [51, 52] Second, severe TBI can cause accumulation of cerebrospinal Aβ-peptide in humans. [53] In mice, it increases glial protein immunoreactivity and results in atrophy of the hippocampus. [54] Third, TBI may, through other unknown mechanisms, decrease total cognitive reserve or lead to slow-onset cognitive impairment - mimicking hallmark signs and symptoms of AD. Thus, cSDH may also impact the development of dementia, or exacerbate a pre-existing dementia through unknown mechanisms, though the role of lymphatic vessels in the dura are only recently being interrogated as a potential causal explanation for this phenomenon.[57]

The existence of a lymphatic system within the dura mater has been suggested to exist for some time, but has recently gained more traction.[55] With this, the possibility that TBI causes disruptions in dural lymphatic function and may underlie the development of dementia

warrants investigation. Several studies have highlighted the manner by which this may occur; cSDH causes an increase in intracranial pressure (ICP), which impedes dural lymphatic outflow. [56, 57] Convective cerebrospinal fluid (CSF) flow works concurrently with dural lymphatic outflow to clear toxic metabolites from neuroparenchymal tissue. [58] If the efflux of lymphatic fluid is disrupted in any manner, there is a possibility that convective interstitial fluid flux through the neuroparenchyma is perturbed, and subsequently, the brain's circulatory filtration system may malfunction. This may contribute to cognitive deterioration that is a hallmark feature of neurodegenerative disorders such as AD. Moreover, alterations in lymphatic drainage may reduce the efficacy of cerebral autoregulation, or the brain's ability to maintain consistent perfusion of tissue despite abrupt pressure changes, and may further contribute to dementia-like symptoms. [59] Another possible mechanism linking TBI and cSDH to dural lymphatics would be the potential blockage of lymphatic channels due to inflammatory processes, age-related changes such as dural calcifications which can hinder lymphatic flow, or changes at the level of the aquaporin 4 (AQP4) channel which can be impeded by blood breakdown products and is a critical element of normal lymphatic clearance. [60, 61] AQP4 is readily expressed perivascular astrocytic endfeet in a polarized manner, and AQP4-dependent bulk flow facilitates influx of CSF through the para-arterial pathway in order to allow for ISF clearance along the paravenous route. This ultimately facilitates clearance of interstitial solutes from neural parenchyma. [57] Regardless of the mechanism, the potentially intermingled roles of TBI, cSDH, and dural lymphatics offer an exciting new platform for discovery and paradigm reevaluations of the clinical treatment of cSDH.

Conclusion

Chronic subdural hematoma (cSDH) results from head injuries and is a type of TBI that effects 1–5 per 100,000 individuals each year. cSDH is a leading cause of reversible dementia, in that surgical evacuation can lead to symptomatic improvement, yet multiple treatment options exist. Furthermore, an increasingly greater emphasis must be placed on the short and long-term effects of cSDH and the subdural membrane that accompanies it on the pathogenesis of dementia and the mechanistic role of newly discovered dural lymphatics.

Acknowledgments

Source of funding: RS is funded in part by an MSTP Grant from the NIH (T32-GM08620)

Abbreviations

cSDH	Chronic Subdural Hematoma
ICP	Intracranial Pressure
CSF	Cerebrospinal Fluid
ECM	Extracellular Matrix
tPA	tissue Plasminogen Activator
TBI	Traumatic Brain Injury

CTE	Chronic Traumatic Encephalopathy
CBF	Cerebral Blood Flow
APP	Amyloid Precursor Protein

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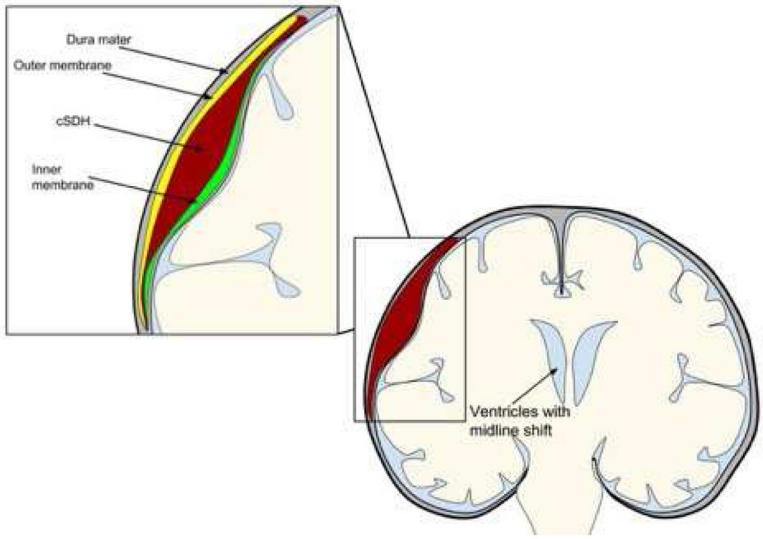

Figure 1.
Diagram illustrating a chronic subdural hematoma (cSDH) between the dura-arachnoid interface (coronal view) and the associated inner/outer membranes.

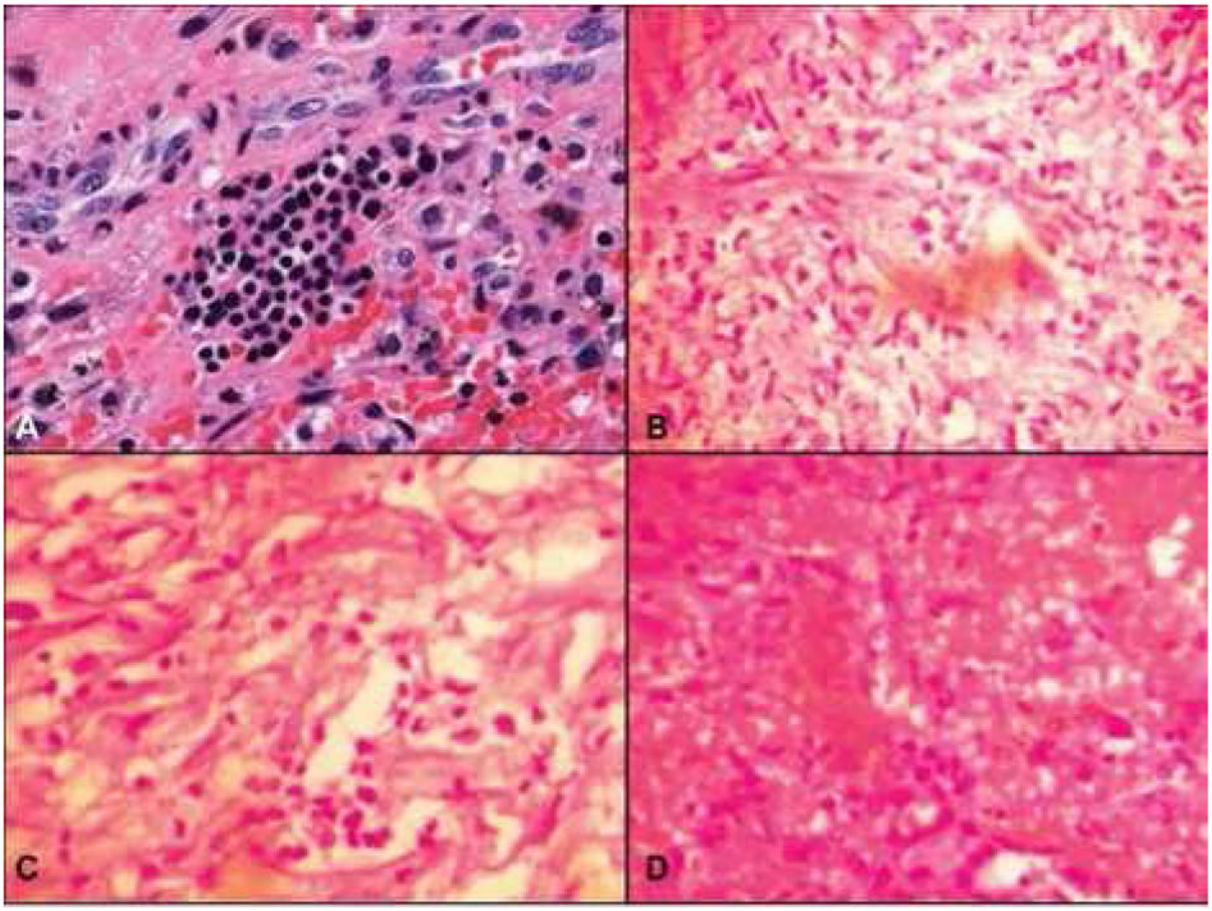

Figure 2.

Histological classifications of the outer chronic subdural hematoma membrane depicting A) a Type I noninflammatory membrane which contains immature fibroblasts and collagen fibers. B) Type II inflammatory membrane consisting of a single layer of immature connective tissue and associated with marked vascularization and cell infiltration. C) Type III hemorrhagic inflammatory membrane which consists of 2–3 layers associated with large diameter capillaries and marked cell infiltration with proliferation of new vessels accompanied by hemorrhage into the membrane. D) Type IV scar inflammatory membrane depicting inflammatory cell infiltration, hemorrhage, and neovascularization. Adapted, with copyright clearance, from Nagahori et al., 1993.[19]