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REVIEW

The pathophysiology of chronic subdural hematoma revisited: emphasis on aging processes as key factor

Ralf Weigel · Lothar Schilling · Joachim K. Krauss

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Abstract Chronic subdural hematoma (CSH) affects mostly elderly subjects. Previously, pathophysiological concepts suggested that CSH is secondary to degradation of subdural collections of blood and its products exerting merely a mass effect on the underlying brain. During the last decades, however, new insights into the pathogenetic mechanisms urge us to reconsider such a simplistic view. Here, we critically review novel pathophysiological, imaging, interventional, and medical treatment aspects and establish an integrative concept of the pathogenesis of CSH stressing the role of age as key factor. Trauma is considered a trigger event that unleashes a cascade of immunological and angiogenic age-dependent responses. These are associated with hypervascularization of the outer hematoma membrane, rebleeding, and exsudation which are crucial determinants for further development and propagation of CSH. Neurosurgical evacuation of the hematoma has long been thought the only viable treatment option, and it is still the method of choice in the majority of cases. Only more recently, embolization of the middle meningeal artery has been introduced as an alternative to surgery, and pharmacological treatment options are being investigated. Persons with advanced age trauma and other trigger events encounter a repair system with characteristics of senescence. This repair system implies a dysfunctional secretory phenotype of senescent cells and results in an insufficient repair process including chronic inflammation and fibrosis. Increased knowledge about the pathomechanisms of CSH will inform future studies and open new perspectives for its treatment and possibly also for its prevention.

Keywords Chronic subdural hematoma · Pathophysiology · Age · Rebleeding · Exsudation · Hypervascularization

R. Weigel · J. K. Krauss
Department of Neurosurgery, Medical School Hannover, MHH, Hannover, Germany

R. Weigel (✉)
Department of Neurosurgery, Sankt Katharinen Hospital Frankfurt, Seckbacher Landstraße 65, 60389 Frankfurt am Main, Germany
e-mail: weigel@neurochirurgie-katharinen.de

L. Schilling
Department of Neurosurgery and Division of Neurosurgical Research, University Hospital Mannheim, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany

Introduction

Chronic subdural hematoma (CSH) affects mostly the elderly with increasing relevance due to aging of the population both in Western and Asian countries [1]. Apart from the mechanistic view that CSH is simply a posttraumatic subdural collection of blood and its degradation products becoming symptomatic because of its space-occupying effect, new insights including

molecular-biological aspects are increasingly gaining acceptance. The latter indicate that immunological and angiogenic mechanisms are pivotal for CSH development and enlargement which is fundamentally different from the pathophysiology of acute subdural hematoma [2–9].

The diagnosis of CSH is of utmost clinical importance as it is a treatable entity affecting the elderly and manifesting with various neurological symptoms and dementia [10–12]. In fact, it is one of the most common disorders seen in neurosurgical practice [13]. The typical CSH patient is a male in his seventh decade. Obviously, age may predispose to the development of CSH in a multifaceted fashion: older patients suffer falls more often [14], they are frequently under anticoagulation treatment [15], and brain atrophy—an independent risk factor for CSH—is correlated with advanced age [16–19]. However, it becomes evident that various other factors need to be considered which have been neglected or underestimated thus far. On closer inspection, CSH is not just the chronic version of an acute subdural hematoma. Trauma is not the single leading cause of CSH [20, 21] and acute subdural bleeding is not an indispensable prerequisite for the development of CSH (Fig. 1) [4, 22–24]. Only a minority of acute subdural hematomas turn into the chronic form [4, 25–27] and CSH is not an obligatory transient phase during the healing process after an acute bleeding. In contrast, CSH constitutes a unique entity and both trauma and bleeding can be seen as triggering events which are followed by a cascade of immunological and angiogenic responses.

The clarification of these mechanisms is currently considered the most promising approach to develop non-surgical treatment modalities. Such treatment options would be desirable since mortality rates and unfavorable functional outcomes are still relatively high after surgery, most probably associated with the advanced age of the patients [28–30]. Therapeutic options had not changed substantially for decades until recently [13] with the introduction of embolization of the middle meningeal artery evolving as a new therapeutic concept for patients with CSH (for review, see Haldrup et al. [31]). Treatment by embolization is based directly on the angiogenic concept of CSH development and propagation [2, 32–35] and may serve as further evidence for the relevance of new insights.

Moreover, the age profile of CSH patients strongly points to age-dependent alterations of the involved physiological immune responses and angiogenic pathways which may involve genomic instability, epigenetic defects, dysregulation of metabolic pathways, increased cell senescence, impaired cell regeneration, increased reactive oxygen species by mitochondria, and loss of proteostasis [36]. A closer look at these issues may yield crucial rationales for future research. Therefore, we here aim to shed light on age-dependent cellular and molecular particularities of immune responses and angiogenic

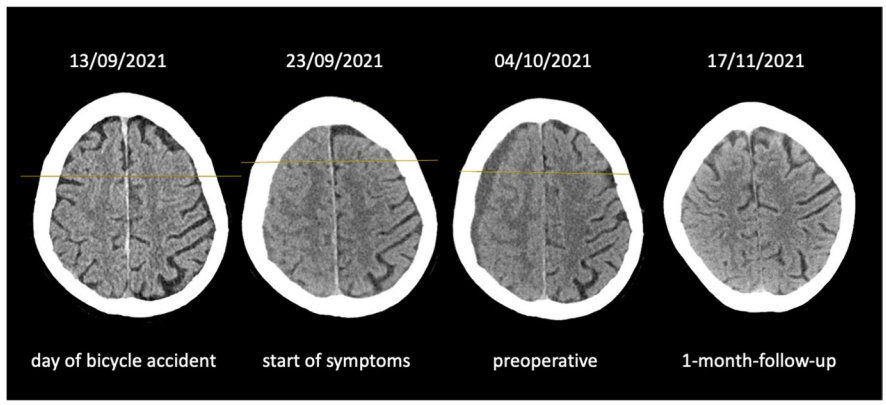

Fig. 1 CT scans of an 85-year-old woman. **A** Few hours after a bicycle accident without loss of consciousness. There is not any intracranial lesion. **B** Ten days after the accident slight speech disturbance is noted. **C** Twenty-one days after the accident. The patient suffers from continuous headache, mild hemiparesis on the left, and psychomotor slowness. **D** One month after surgery the patient has recovered completely

mechanisms in older patients and we will unravel possible relationships between experimental findings in CSH and age-associated alterations.

Methods

To provide a critical review of pathophysiological, imaging, interventional, and medical treatment aspects of CSH concerning immunological and molecular-biological processes, a systematic literature search was performed using the PubMed database. The following keywords were applied in combination with the term chronic subdural hematoma: "pathophysiology," "etiology," "computed tomography," "CT," "magnetic resonance imaging," "MRI," "inflammation," "inflammatory," "angiogenesis," and "angiogenic."

As a second step, research and review articles on CSH were screened for additional references.

All original articles were screened for content concerning the topics under investigation in the present review. Findings were attributed to the following categories: imaging studies, molecular factors involved in the pathogenesis of CSH, and non-surgical treatment studies.

Results

Imaging studies

CT morphology

Contemporary CT- and MRI-based imaging quality allows detection of a CSH in clinically suspected cases with a near 100% sensitivity. Because of its broad availability, the short acquisition time, and its relative insusceptibility for movement artifacts in potentially noncompliant patients, CT-based imaging is still the primary method of choice [37]. In cases of intracranial hemorrhage, fresh blood with its high content of cell nuclei and protein is hyperdense compared to brain tissue. With ongoing degradation of these elements, the appearance becomes iso- and finally hypodense. However, these characteristics of intracerebral hemorrhages cannot simply be seen as equivalents of fluid accumulation in CSH. Obviously, there are mechanisms involved in CSH that can cause different chronological scenarios paralleling encapsulation of the hematoma, rebleeding, and exsudation [38].

Ito and colleagues had demonstrated in the 1980s that high and mixed density hematomas represent recent rebleeding [39] whereas Kao showed that hematomas of the layering type have a high tendency to rebleed [40]. Different attempts have been made to categorize the appearance of CSH cases in order to estimate the extent of rebleeding or exsudation. Both may influence the need for surgery due to hematoma enlargement or the risk of recurrence after decompression. Nomura et al. used a classification that differentiated 5 types of CSH: hyperdense, isodense, hypodense, mixed, and layering type. They found that in mixed density hematomas and in the layering type the tendency to rebleed was highest. Additionally, the layering type had a higher fibrinolytic activity. According to their findings, they draw the conclusion that enlargement of the hematoma is the result of both rebleeding and plasma exsudation [41]. It had already been shown before that the concentration of the plasmin α_2-plasmin inhibitor complex reflecting local hyperfibrinolysis was highest, also in the latter type of hematomas [42]. Subsequently, it was shown that hematomas of the layering type have a higher tendency to recur [43, 44]. In contrast to this, Nakamura et al. showed that hematomas which resolve spontaneously are hypodense [45]. Tokmak and colleagues demonstrated that the exsudation rate is related to CT appearance and was highest in hyperdense and mixed density hematomas including hematomas from the layering type. On the basis of Nomura's CT classification, our group showed that the exsudation rate was significantly correlated with the concentration of vascular endothelial growth factor (VEGF) in the hematoma [38]. A similar correlation was found also on the basis of a MRI classification [46]. High rates of VEGF were found to be combined with high rates of exsudation and leaky vessels.

Another classification postulated 4 different types of CSH according to the internal architecture of the hematomas. Based on serial imaging of a series of 18 patients, Nakaguchi and colleagues draw the conclusion that CSH evolves from a so-called homogenous type of hematoma and matures via a laminar type to a separated type and finally to a trabecular type. Spontaneous resolution of hematomas would occur in the trabecular stage. The lowest rate of recurrence

was found in this group of hematomas. Subsumed in the homogenous type of hematomas are those with homogenous hypodense or isodense appearance [44]. This is in line with the descriptions of Lee and colleagues who reported that up to 58% of hygromas (a watery collection of fluid in the subdural space without encapsulation) evolve into CSH [47]. The highest rate of recurrence was seen in the separated type that corresponds to the layering type of Nomura.

MRI morphology

The physical background of MRI is much more complex and the prediction of resolution of the CSH or its recurrence is much more challenging [43]. The image characteristics of CSH are dependent on the magnetic properties of its content. It seems that the appearance of hematoma fluid is mainly a function of hemoglobin and its degradation products. Oxygenated hemoglobin is diamagnetic, appearing hypointense on T1- and hyperintense on T2-weighted images. With deoxygenation after bleeding, it becomes hypointense on T1 and T2. Thereafter, deoxyhemoglobin is degraded to methemoglobin which appears hyperintense on T1 and hypointense on T2. After lysis of cells, methemoglobin accumulates extracellularly and causes a hypertense signal in T1 and T2. Finally, hemosiderin deposits are superparamagnetic and are hypointense in T1 and T2 [48]. MRI may help to distinguish CSH from hygromas which have properties similar to CSF and show low signal intensity on proton weighted images whereas the high protein content of CSH results in a high signal intensity [43]. It was found that T2*-gradient-echo sequences (GRE) are highly sensitive to the susceptibility effects of the paramagnetic and superparamagnetic properties of hemoglobin and its breakdown products [48]. They allow showing even small bleedings in brain parenchyma which was confirmed by histological studies [49]. Imaizumi and colleagues described a black band corresponding to the inner membrane of the hematoma as a characteristic finding in T2* images [50]. They suggested that it would indicate deoxyhemoglobin or hemosiderin deposits within macrophages. The band vanished in cases that resolved spontaneously and in those who healed after decompression whereas continuance of the band was indicative of recurrence. From a histological point of view, these findings are difficult to explain because the inner membrane is not well vascularized and is probably not the location of major bleeding.

Tsutsumi et al. described 5 different types of hematomas according to their characteristics on T1-weighted images [43]. Low intense or isointense hematomas would reflect recent rebleeding and had the highest rate of recurrence. They indicated that a higher concentration of methemoglobin would correlate with a higher intensity of the hematoma and with a longer period since the last rebleeding. Consecutively, they concluded that high intense hematomas reflect the lowest risk for rebleeding. On serial images, Kaminogo et al. confirmed that rebleeding was an important factor in hematoma enlargement and neurological deterioration [51]. At 1.5 Tesla, fresh rebleeding appeared as low-density lesions on T1 and high-density lesions on T2. A recent metanalysis on the importance of low signal intensity in T1-weighted images seems to confirm an increased recurrence rate in these cases [52]. Moreover, Hua and colleagues correlated the concentration of VEGF and matrix metalloproteinase (MMP) 2 and 9 [53] which are important proangiogenic factors that trigger an angiogenic switch in an otherwise quiescent vascular bed [54, 55]. They used a MRI classification that considered T1 and T2 characteristics of hematomas. Hematomas with low intensity on both sequences indicated a high risk of rebleed and were significantly related to a high concentration of VEGF. High concentrations of VEGF however were paralleled by high concentrations of MMP-2 and MMP-9 which may confirm the notion that VEGF is an important factor for hematoma enlargement due to rebleeding and exsudation [38].

Molecular factors involved in the pathogenesis of CSH

Inflammatory pathways

Chronic subdural hematoma had originally been described as an inflammatory disorder under the name pachymeningitis hemorrhagica interna [56]. Subsequently, several direct and indirect markers of inflammation were found to be locally elevated within the hematoma compared to serum including fibrinogen degradation products [57], platelet activation factor (PAF) [58], tissue plasminogen activator (tPA) [59], bradykinin [60], tumor necrosis factor

(TNF) [61], VEGF [35, 62], interleukin 6 (IL-6), and IL-8 [61]. Infiltration of inflammatory cells has been described early in histological studies, especially the high number of eosinophils in the outer membrane awakened interest [63–67]. Eosinophils can secrete plasminogen and induce fibrinolysis which starts the cascade that ends with wound healing or fibrosis [66]. These cells are considered to be important effector cells of fibrosis in eosinophil-associated allergic diseases like asthma [68], idiopathic pulmonary fibrosis [69], obstructive nephropathy [70], and pediatric eosinophilic esophagitis [71] by releasing transforming growth factor β (TGF-β) and activating the TGF-β/Smad pathway. More recently, Osuka et al. found that eotaxin 3, an eosinophil-specific chemoattractant, is present in high concentrations within the hematoma [72]. Eosinophils are also the source of TGF-β, the concentration of which is also elevated in hematoma fluid. Furthermore, the Smad pathway was shown to be activated in fibroblasts of the neomembranes [72].

In previous studies, Osuka et al. had described activation of the JAK/STAT pathway in fibroblasts of the outer membrane which is an activator of transcription and is also related to pathological fibrosis activated by IL-6 [73]. Both IL-6 and IL-8 are potent agents of the inflammatory response and are found in hematoma fluid in high concentrations [6, 61, 74–78]. Even more important is the fact that concentrations are higher in those patients who suffer recurrence [6, 74]. The proinflammatory cytokine IL-6 modulates cell–cell contacts by enlarging gap junctions and increasing vascular permeability [79]. It is part of the acute phase reaction during inflammation. IL-8 (nowadays called CXCL-8) is a chemotactic chemokine which has an impact on migratory immune cells. It supports angiogenesis and is involved in angiogenesis-dependent processes like formation of granulation tissue and wound healing [80]. Bradykinin, thrombin, and PAF fuel secretion of IL-6 and IL-8 from fibroblasts, endothelial cells, and immune cells within the neomembranes [6].

Comparing the concentration of proinflammatory and anti-inflammatory cytokines in the hematoma, there is an imbalance to the disadvantage of the latter which has led to the speculation of a poorly coordinated innate immune response within the hematoma [77].

Angiogenic pathways

Knowledge about the molecular mechanisms of angiogenesis has increased tremendously during the last 30 years [81]. The sequential steps of vessel branching are well orchestrated by various types of biological factors which are also active in CSH development. Remarkably, the majority of processes involving angiogenesis are strictly related to inflammation. When quiescent vessels sense an angiogenic stimulus like VEGF, bFGF, or ANG 2, pericytes liberate from the shared basement membrane by proteolytic degradation. This process is mediated by MMPs. Its histological characteristics have already been described for formation of the neomembranes in CSH in publications in the 1970s [82–86]. In line with this, we detected specific patterns of growth factor distribution within the hematoma with increases in VEGF and bFGF and a decrease in platelet-derived growth factor (PDGF) [62]. In addition to elevated concentrations of VEGF within the hematoma [35, 74, 87, 88], also synthesis of VEGF within the neomembranes was described [89]. However, since the concentration of VEGF within the hematoma can be excessively high, it is doubtful whether there is just a simple secretion from the neomembranes. Furthermore, the occurrence of postoperative cures despite the presence of relatively high residual amounts of diluted fluid within the hematoma cavity in postoperative imaging studies may indicate that healing is not primarily a problem of hematoma volume but rather of content. Cells floating within the hematoma could be additional sites of synthesis. Also, the ANG1/ANG2 ratio was shown to be indicative of ongoing angiogenesis [90]. As outlined, the involvement of MMPs was described both in the formation of neomembranes [91] and in the development of hematoma itself [53]. Tissue inhibitors of MMPs (TIMP) as well as plasminogen activation inhibitors (PAI) inactivate MMPs and cause the deposition of a basement membrane. The latter is a prerequisite for competent vessels and indicates maturation of newly sprouted vessels. Remarkably, the concentration of PAI was shown to be highest in low-density hematomas which are considered to have the lowest rate of rebleeding; hence, the neomembranes are maturated and have the lowest angiogenic activity [92].

Placental growth factor (PlGF) is another potent stimulus for induction of angiogenesis which in contrast to VEGF is exclusively associated with pathological angiogenesis [93]. It has been found in high concentrations within the hematoma [88]. In this context, it is of interest that the ratio of PlGF to its counterpart, the soluble VEGF receptor 1 (sVEGFR-1), is decreased in the hematoma fluid compared to serum. High concentrations of VEGF and PlGF but low concentration of sVEGF-1 lead to vessel overgrowth [94], which might explain the vascular characteristics of the neomembranes. The proangiogenic properties of hematoma fluid are underlined by the fact that they activate the mitogen-activated protein kinases (MAPK) which transduce the signals generated from growth factors, cytokines, and stressor agents [95]. Under laboratory conditions, for example, the extracellular signal-regulated kinase complex (MEK/ERK) was activated within 5 min in the endothelium of vessels from the neomembranes by the hematoma fluid. Blocking VEGF or IL-6 interrupted activation of MEK/ERK [96]. Since VEGF increases vascular permeability via this pathway [97], it may explain exsudation which is one of the main mechanisms of hematoma enlargement.

PI3/Akt/mTOR is another important signaling pathway for the control of cell cycle and proliferation that is activated in the ECs of hematoma membranes [98]. To date, this pathway is considered to play a role in different organ cancers [99]. Under physiological circumstances, extravasation of plasma constituents provides a provisional extracellular matrix (ECM) which changes to an angio-competent milieu by liberating angiogenic molecules from extracellular stores via proteases like MMPs [81].

One of the intriguing questions is which factors turn on the angiogenic switch in CSH. Local hypoxia might be an important candidate since it induces the secretion of IL-6, TNF-α, Cox-2, and hypoxia-inducible factor (HIF). When tissue sensors detect hypoxia, the heterodimeric transcriptional factor HIF is induced which mediates the expression of VEGF on the transcriptional level [100]. HIF-1α is oxygen labile and degrades under aerobic conditions. Throughout the neomembranes, it is constantly expressed in conjunction with VEGF and it has been suggested that HIF is one of the main inducers of VEGF expression in CSH [101]. Other potential candidates for VEGF induction or VEGF release from extracellular matrix stores in CSH include IL-6 [6, 61, 75, 77], TNF [76], COX2/PGE2 [102, 103], bFGF [2], and MMPs [91, 104].

A prerequisite for maturation of branching vessels is covering the EC lines with pericytes and deposition of a basement membrane. This is in part mediated by the release of platelet-derived growth factor (PDGF). However, compared to serum, the concentration of PDGF is reduced within the hematoma [2].

Non-surgical treatment studies

Interventional

New insights into the pathophysiology of CSH suggest that exsudation and rebleeding from the outer membrane are important factors for recurrence and probably for hematoma enlargement, too. According to these angiogenic theories, the constituents of the hematoma and the outer membrane interact within a vicious cycle. Reduction of blood supply to the outer membrane via embolization of the middle meningeal artery (EMMA) should interrupt this vicious cycle. First success of this concept was documented in a case report in 2000 [105]. Since then, several small case series but also randomized controlled trials (RCT) evaluated the impact of EMMA within nonoperative and operative treatment algorithms (for review, see Srivatsan [106]). Further studies are under way and may suggest additional treatment options in the near future at least in oligosymptomatic or asymptomatic patients who actually follow a watch-and-wait or wait-and-scan policy [107].

Pharmacological

As CSH is significantly influenced by inflammatory and angiogenic mechanisms, the use of corticosteroids appears to be a logical consequence. Steroids inhibit IL-6 and IL-8 and reduce the expression of VEGF [108–111]. Indeed, back in 1976, Glover and Labadie demonstrated under laboratory conditions that dexamethasone inhibits the formation of a neomembrane [112]. However, the animal model used was based on the assumption that CSH derives from chronification of an acute hematoma which did not prove true. A few case series or retrospective series in patients with CSH followed since then [113–118]. Several national surveys on the treatment

of CSH, however, revealed a controversy about its use [119–122]. Overall, two strategies of cortisone treatment were recognized: (1) cortisone as a monotherapy as part of a non-surgical treatment and (2) cortisone in addition to surgery in order to prevent recurrence (for review, see Berghauser Pont et al. [123]). Preliminary results of a prospective study with dexamethasone could not find any beneficial effect of standalone cortisone treatment but revealed more serious side effects in the verum group [124]. A recent prospective randomized trial of dexamethasone as an adjunct to surgery demonstrated a beneficial effect concerning the number of recurrences but an increased number of adverse events and an overall reduced outcome [125]. The authors therefore did not emphasize the regular use of dexamethasone. On the basis of the available evidence that corticosteroids can reduce VEGF concentrations in certain entities and that VEGF concentration is highest in the layering type of hematomas which corresponds to the very high recurrence rate in this type of hematoma, its use may be justified especially in this subgroup of hematomas [126]. Further controlled randomized trials are currently underway to clarify some of the issues [127].

Since PAF has been shown to be a potent mediator of inflammation and is thought to be involved in the formation of the neomembranes [128], the PAF receptor antagonist etizolam deserves interest. There is evidence that treatment with etizolam reduces the risk of recurrence [129], and it is negatively correlated with the need for surgery [130].

Atorvastatin is another possibly attractive pharmacon for conservative treatment of CSH with its anti-inflammatory properties having been demonstrated in vitro and in vivo [131, 132]. In a rat model of acute subdural hematoma, atorvastatin modulated the inflammatory reaction and fueled shrinkage of hematomas. The authors ascribed the positive effects of the statin to reduction of the concentration of inflammatory cytokines and maturation of newly sprouted vessels of the neomembrane [133]. In a small size retrospective analysis, atorvastatin given as an adjunct to surgery reduced significantly the rate of postoperative recurrence [134]. A prospective trial demonstrated that atorvastatin in adjunct to surgery significantly reduced the risk for recurrence and prolonged the time to recurrence [135]. Unfortunately, the manuscript reporting the trial was retracted from publication because of irregularities in follow-up in one of the collaborating centers. Recently, a beneficial effect of atorvastatin on recurrence and also on outcome was confirmed by a meta-analysis according to PRISMA criteria including six original publications [136].

Angiotensin-converting enzyme (ACE) inhibitors [90] have been shown to interfere with tumor angiogenesis [137] and attenuate pathological angiogenesis in diabetic retinopathy [137, 138]. We have shown previously that ACE inhibitors used for the treatment of arterial hypertension reduced the risk of recurrence if not the overall occurrence of CSH [90]. Furthermore, a reduced concentration of VEGF in the hematoma fluid was found in patients with ACE inhibitor treatment. This indicated that elevation of VEGF could be a causative factor in CSH. However, neither a prospective randomized study with the ACE inhibitor perindopril could demonstrate an advantage regarding recurrence or residual hematoma size 6 weeks after surgery [139] nor two retrospective studies [140, 141].

Furthermore, COX-2 inhibition was tested in a prospectively designed multicenter study [102]. The synthesis of VEGF and other proangiogenic factors is dependent on COX-2 mediated eicosanoids like prostaglandins and thromboxanes. Selective COX-2 inhibition revealed anti-angiogenic effects in vivo and in vitro [142, 143]. Although theoretically attractive, the study was discontinued due to recruitment problems.

A different treatment concept was tested using tranexamic acid which interrupts fibrinolysis through inhibition of plasmin synthesis. Preliminary results from 5 RCTs suggest both reductions of hematoma volume when used in a non-surgical treatment concept and lowering of recurrence rates when used as an adjunct to surgical treatment (for review, see Edlmann et al. [144]).

Finally, cure from recurrent CSH in a patient with rheumatic arthritis was anecdotally reported after the patient started treatment with infliximab, a TNF-α inhibitor [145].

Discussion

Since the first description of a case of CSH by Johann Jacob Wepfer in 1675 [146], different theories on the

pathophysiology of CSH have emerged (for review, see Weigel et al. [147]). Historically, Virchow had favored an inflammatory condition [56] whereas Gardner had postulated an osmotic gradient as the driving force for CSH development and growth [148]. Later on, Ito and coworkers developed a theory of local hyperfibrinolysis [149] and demonstrated repetitive bleeding episodes inside the hematoma cavity with labeled erythrocytes [39]. Furthermore, pathological vascularization of the outer membrane was studied in more detail [85, 150, 151], and exsudation was identified as an important mechanism of hematoma enlargement [7, 152]. Subsequently, it was postulated that CSH can be interpreted as an angiogenic disorder [2]. The limited body of scientific research provides evidence in support of each of these aspects [3, 6, 41, 42, 61, 74–76, 78, 87–89, 104, 152–156]. Until recently, no valid experimental model was available to test former and current disease concepts and therapeutic approaches in the laboratory [157]. Only in 2021, an encouraging new animal model using old Sprague Dawley rats showing the typical features of CSH in humans was published [158].

Integrative concept of the pathogenesis of CSH

The subdural space is not present under physiological conditions. In the following, we summarize the pathophysiological mechanisms according to current knowledge. Shear stress even from a minor trauma dissolves the loosely connected border cells of the inner layer of the dura. This constitutes also a signal for fibroblast growth. A cascade of cellular angiogenic and inflammatory responses follows which results in the formation of a richly vascularized external neomembrane. The subdural space is filled with blood, blood degradation products, and extravasation fluid. Chemotaxis of immune cells occurs and is driven by fibrinogen degradation products, eotaxin, PAF, and CXCL-8 (IL-8). Increased levels of IL-6, HIF, TNF-α, and Cox-2 might induce VEGF secretion. Additionally, proteases like MMPs liberate angiogenic molecules stored in the provisional extracellular matrix (ECM). In parallel oversecretion of TGF-β activates intracellular messenger systems like Smat, which sensitizes cells for external stimulation via growth factors and other cytokines. High levels of VEGF and PlGF and overexpression of ANG-2 within the neomembranes keep newly sprouted vessels leaky by activation of the MEK/ERK signal transducers. Together with constantly high levels of IL-6 that increase vascular permeability via the JAK/STAT pathway, extravasation of plasma proteins perpetuates and leads to enlargement of the hematoma volume. Finally, anti-inflammatory cytokines like IL-10 and IL-13 or factors that could establish a patent vessel network like PDGF are inadequately represented within the hematoma which facilitates chronification.

The role of age and further perspectives

The immune response in CSH is unrewarding leading to a condition which may best be described as a chronic proinflammatory state characterized by hypervascularization, exsudation, and rebleeding (Fig. 2). The concentrations of proangiogenic and proinflammatory cytokines and chemokines are elevated. In general, a prolonged inflammatory response delays wound healing and probably promotes tissue fibrosis reducing the chance of true regeneration

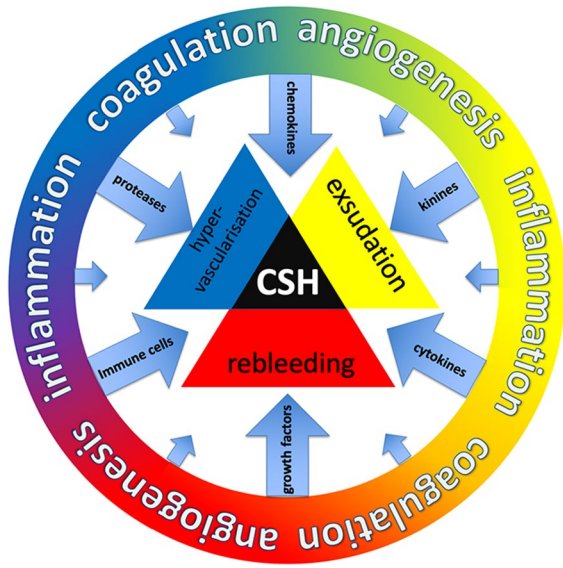

Fig. 2 Schematic illustration of the pathogenesis of CSH. The outer ring represents different biological processes that are involved: angiogenesis, coagulation, and inflammation. Subsequent processes are chemotaxis of immune cells and secretion of growth factors, chemokines, cytokines, kinins, and proteases. The passages between these processes are fluent. They cause exsudation, hypervascularization, and rebleeding. As a result, chronic subdural hematoma (CSH) develops and is maintained

[159, 160]. Increased inflammatory responses are also characteristic features of aging cells and aging tissues [161, 162].

With regard to the data available presented thus far, the demographic background of CSH may suggest a "protective" effect of sex hormones, a dysregulated immune response of the senescent immune system, and a dysregulated angiogenetic response of an aging vascular bed.

It was early discussed in the CSH literature that sex hormones might exert a protective effect in minor head trauma [163]. Meanwhile, it has been demonstrated that estrogen has a potent anti-inflammatory effect [164, 165], it can accelerate wound healing [166], and it can improve systemic as well as cellular immune responses to traumatic injury [167]. Furthermore, estrogen has a vasoprotective effect in women [168]. Overall, it is feasible that there is a positive net effect of estrogen in patients at risk for the development of CSH.

Aging as an important prerequisite for the development of CSH might explain why experimental studies which were conducted with young rodents failed to produce experimental CSH thus far [157]. In general, aged individuals appear to be at higher risk for processes associated with pathological vessel formation. It has been shown that aging impacts virtually every angiogenic pathway identified thus far [169, 170]. With advancing age, endothelial cells have depleted anti-inflammatory and anti-oxidant defense mechanisms. Hence, they are subjected to augmented inflammatory and oxidative stress that impairs their number, morphology, and function [171]. Furthermore, changes in hemostatic function in the aging vasculature may have a profound effect on the induction of new vessels [172]. Angiogenesis in the aged often reveals impairment of maturation and stabilization of newly formed vessels [173] as it is seen also in CSH [82, 84, 85]. Such impaired angiogenesis may also be related to the production of reactive oxygen species (ROS) [174] or advanced glycation end products (AGE) [175]. The role of neither one has yet been elucidated in CSH. Notably, oxidative stress is increased in aging [176], and ROS can induce hyperstimulation of endothelial cells both by inducing VEGF production and by amplifying its intracellular effects [177].

There are several examples of age-dependent cellular and molecular disturbances of the immune response in the elderly (Table 1). In the following, we want to set such findings in perspective to the development of CSH in the elderly. Advanced age affects macrophage function, cytokine and chemokine secretion, infiltration, and wound repair [172]. It was shown that ocular macrophages in aged mice have impaired anti-angiogenic properties leading to pathological hypervascularization as seen in macular degeneration [193]. Furthermore, mRNA expression coding for the proinflammatory cytokines IL-6 and TNF-α has been shown to be increased in macrophages of elderly mice as compared to young animals [194]. Moreover, increased levels of IL-6 in IL-6 knockout mice are characteristic of the age-associated microenvironment of macrophages which play a role in the regulation of age-dependent defects of macrophages [167].

The term "inflammaging" stands for a chronic inflammatory state in elderly patients without an obvious underlying disease [195]. It is characterized by an elevated inflammatory response after trauma associated with increased levels of IL-6 [196]. Remarkably, increased IL-6 levels have been thought to be associated both with increased morbidity and disability [197, 198]. Such mechanisms may also be related to the increased IL-6 levels in CSH [6, 61, 74–77]. Another issue to consider is that in the elderly the number of peripheral eosinophils correlates with elevated serum levels of IL-6 [199]. The exact mechanism of the correlation has not yet been elucidated; however, a similar constellation is present within the neomembranes and the hematoma fluid of CSH patients [63, 64, 66, 200].

Inflammation is part of the wound healing process that induces further steps such as new tissue formation and tissue remodeling. Aging affects both the ability of cells to respond to injury and the physiology of the extracellular matrix (ECM) [201]. It is known that MMPs are involved in the remodeling of ECM and the expression and the activity of MMPs is dysregulated in the aging vasculature. This is a key factor of age-related vascular pathology and includes both excess or deficient activity [172]. Gingival repair is delayed in aged patients, and it has been shown that this is paralleled by an increase in the level of MMPs [202]. It was hypothesized that tissue repair is impaired in aged subjects secondary to increased levels of proteolytic activity [201]. With that regard, it has to be noticed that the involvement of different

Table 1 Mediators that are identified in the pathogenetic process of CSH and possible interference with age

Mediator	CSH	Age
IL-6	Higher concentration in CSH fluid compared to plasma [6]	Increase with age [178]
IL-8	Higher concentration in CSH fluid compared to plasma [6]	No correlation of spontaneous levels with age; increased production in fibroblasts of the elderly after stimulation [179]
Eosinophils	Infiltration of eosinophils in outer membrane [64]	Age impairs effector functions [167]
Eotaxin 3 (CCL26)	Higher levels in CSH fluid compared to CSF [72]	Elevated levels in age- associated Neurodegenerative diseases [180]
TGF	Higher levels in CSH fluid compared to CSF [72]	Impairment of TGF signaling with age; upregulation of TGF-beta ligands [181]
VEGF	Higher levels in CSH fluid compared to plasma [35, 62]	Serum levels positively correlated with age [182]
bFGF	Higher levels in CSH fluid compared to plasma [2]	Expression of bFGF positively correlated with age in a mouse model of wound repair [183]
PDGF	Lower levels in CSH fluid compared to plasma [2]	Expression of PDGF delayed with increasing age in a mouse model of wound repair [183]
PlGF	Elevated levels in CSH fluid compared to plasma [88]	Role of PlGF restricted to pathological conditions [93] elevated in age-related retinal vasculopathies [184]
PAI	Lower levels in CSH fluid of layering and mixed density hematomas [92]	Elevated in the elderly [185]
MMP	Present in neomembranes [91] and hematoma [53]	Relevance in age-associated disorders [186, 187]
Bradykinin	Higher concentration in CSH fluid compared to plasma [60]	Downregulation of receptors in senescent cells [188]
TNF	Lower concentration in CSH fluid compared to plasma [104]	Increase with age [189–191]
tPA	Increased in CSH [59]; correlates with recurrence [92]	Reduced release with age [192]

MMPs in the pathophysiological process of CSH was described both for the neomembranes and also for the hematoma itself [53, 91].

Aging also has been generally associated with increased intracellular levels and activity of the enzyme cyclooxygenase-2 (COX-2) [203]. In contrast to COX-1, it is synthesized on demand in cases of injury, inflammation, or cell proliferation, and it is involved in the induction of angiogenesis [204]. Notably, COX-2 was found in the outer membrane of CSH patients [103]. Furthermore, the concentration of prostaglandin-E2 (PG-E2) which is the product of COX-2 synthesis linearly correlates with the time period which precedes the manifestation of CSH.

While angiopoietin 1/TIE2 (ANG1/TIE2) supports the maturation of vascular structures and has a role in maintenance of vascular integrity through the recruitment of pericytes and endothelial cells, angiopoietin 2 (ANG2) interferes with the ANG1/TIE2 signal and loosens tight cellular connections [205]. Thus, it exposes the endothelium to inducers of angiogenesis like VEGF and other growth factors. The relative ratio of ANG1 and ANG2 is thought to be crucial for the regulation of angiopoietins. It was shown to be stable in a mouse model for aging of skeletal muscles whereas the TIE receptor mRNA was decreased [206]. When expression of the receptor TIE is reduced in aging vascular structures, a relative preponderance of the ANG2 signal will result and the vascular integrity will be reduced [206]. Likewise, it was demonstrated that in the neomembranes of CSH patients, the ratio of ANG1/ANG2 turned towards a preponderance of the ANG2 signal. Both mechanisms might explain the unmatured phenotypic characteristics of the majority of vessels within the neomembranes [3]. Recently, a similar preponderance of ANG2 was verified at the protein level within the hematoma [98].

The expressions of the VEGF receptors fms-like tyrosine kinase 1 (flt-1) and fetal liver kinase 1

(flk-1) also change with aging. In young individuals, there is a preponderance of the flt-1 receptor which plays an essential role in the development of embryonic vasculature, the regulation of angiogenesis, cell survival, and migration, as well as macrophage function and chemotaxis. In aged vessels, the expression of flk-1 predominates. It was shown that in vessels of the neomembranes of CSH, flk-1 is the principal receptor [207]. flk-1 is responsible for transmitting VEGF signals in the vascular endothelium including proliferation, migration, survival, and permeability [208]. With that regard, it is also of interest that tumor growth and diabetic retinopathy are associated with pathological signaling of flk-1 characterized by hyperpermeable neovascularization as it is seen in CSH [85].

Experimental models have demonstrated impairments in the expression and function of the angiogenic factor PDGF in aging [209]. PDGF is an important cytokine during the last step of angiogenesis where the newly sprouted endothelial tubes mature. PDGF steers both coverings of the EC lines with pericytes and deposition of a basement membrane. Compared to the high concentrations of VEGF and to a lesser degree of basic fibroblast growth factor (bFGF) in hematoma fluid, the concentration of PDGF is only marginal which might be another mechanism that hinders newly formed endothelial tubes to mature into patent vessels in CSH patients [2].

A higher expression of TNF-a, in general, is also observed with advancing age [189, 210]. This results in NADPH-dependent free radical production [211] and the biotransformation of NO into tissue-reactive and harmful nitrogenous species including peroxynitrite ($OONO^-$) [212]. Subsequent to NO depletion and upregulation of proinflammatory genes, the vasculature becomes vulnerable to inflammation and fibrosis. Remarkably, TNF-a is a proinflammatory cytokine which is controlled by estrogen [213]. This might be one of the mechanisms why women are more rarely afflicted by CSH than men.

Knowledge of the molecular mechanisms which are involved in the development of CSH has considerably increased during the last decades. While the presence of some of these mechanisms per se indicates a pathological condition, it remains unclear whether or not some findings are truly pathological or they simply represent a physiological process. Nevertheless, also physiological mechanisms can be exaggerated or diminished and as such become pathological. Age probably has an impact on all of these eventualities. It is reasonable to assume that trauma or other trigger events encounter a repair system with characteristics of senescence. This repair system implies a dysfunctional secretory phenotype of senescent cells and results in an insufficient repair process including chronic inflammation and fibrosis. Increased knowledge about the pathomechanisms of CSH may also open perspectives for prevention of its occurrence in the future.

Author contribution R.W. and L.S. had the idea for the article. R.W. performed the literature search and the data analysis. R.W. and L.S. drafted the first manuscript. J.K.K. critically revised the work. All authors read and approved the final manuscript.

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