Management of Chronic Subdural Hematoma: Part I—Pathogenesis and Diagnosis
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Learning Objectives: After participating in this CME activity, the neurosurgeon should be better able to:
1. Describe the pathophysiology of chronic subdural hematoma.
2. Diagnose chronic subdural hematoma using appropriate clinical judgment and imaging modalities.

This is the first of 2 parts

Chronic subdural hematoma (CSDH) is a common condition in neurosurgical practice. A CSDH is defined as an “old” collection of blood and blood breakdown products in the subdural space, developing over a period of longer than 14 days. CSDH has a high prevalence, ranging from 1.72 per 100,000 in the general population to 58 per 100,000 in the elderly (≥65 years). Because of an aging global population, the prevalence of CSDH is expected to increase. Moreover, the use of anticoagulants and antiplatelet treatment for cardiovascular problems, which is an important risk factor for developing CSDH, is increasing. Although CSDH is well treated with burr-hole craniostomy or conservative modalities in selected cases, the mortality rate after 1 year is as high as 32%. Therefore, early diagnosis and adequate treatment are essential. In part I of this review, we discuss the pathophysiology and diagnosis of CSDH. In part II, we present treatment options and the most important determinants of disease outcome in patients with CSDH.

Pathogenesis and Risk Factors
There are various theories as to how CSDH develops. According to one theory, the cause is rupturing of bridging veins that leak fluid into the subdural space, whereas another theory suggests that the appearance of microtears in the dura–arachnoid border layer, with subsequent leakage of cerebrospinal fluid (CSF) in the newly created space, creates an inflammatory reaction.

Various conditions are associated with CSDH, minor trauma most commonly. Minor trauma can trigger subdural leakage and hematoma formation. Brain atrophy in the elderly population is an important contributing factor to development of CSDH. This makes the bridging veins prone to tear. In elderly patients, the “virtual” subdural space is much larger compared with a nonatrophic cerebrum. Coagulopathy is another important risk factor for CSDH. This correlates with a rise in incidence related to contemporary anticoagulant use. Coagulopathy may also
be caused by alcohol abuse and liver failure, which are less frequent. In a previously published study, anticoagulant/antiplatelet use was present in 50% of 500 surgically treated patients.

As mentioned, CSDH may develop from an acute subdural hematoma. CSDH is often surrounded by an inner and an outer membrane. These membranes probably arise as a proliferation reaction from a rupture of the dural border layer. We explain this in the next section.

Pathophysiology
A Coagulopathic State Maintains and Promotes the Subdural Bleeding

Virchow first referred to CSDH in 1857, namely as pachymeningitis haemorrhagica interna. Coagulopathy and hyperfibrinolysis in the subdural fluid expand the hematoma through rebleeding and impaired clotting. In a mature CSDH, it has been demonstrated that the subdural fluid contains low levels of coagulation factors and high levels of coagulation inhibitors. Next to the hypocoagulable state, the outer membrane produces high levels of tissue plasminogen activator (TPA). TPA transforms plasminogen into plasmin, which degrades fibrin. The subdural fluid contains low concentrations of plasminogen activator inhibitor. This tilts the balance in favor of production of TPA. Hyperfibrinolysis causes fibrinogen to degrade into factors that act as anticoagulants and vasodilators. This contributes to maintenance and growth of the hematoma.

Thrombomodulin (TM) levels in the subdural fluid are usually higher than those in peripheral blood. TM is a thrombin receptor that inhibits clotting by forming a complex with thrombin and activated protein C. In case of endothelial thrombin receptor that inhibits clotting by forming a complex usually higher than those in peripheral blood. TM is a maintenance and growth of the hematoma.

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Thrombomodulin (TM) levels in the subdural fluid are usually higher than those in peripheral blood. TM is a thrombin receptor that inhibits clotting by forming a complex with thrombin and activated protein C. In case of endothelial injury such as in CSDH, the TM levels rise. This suggests continuous damage of sinusoidal vessels. TM also inhibits hemostatic thrombus formation in the hematoma, leading to hematoma expansion. The injured blood vessel causes platelet accumulation at the damaged site to form a hemostatic plug. Plasma coagulation proteins are activated to initiate secondary hemostasis. Clotting follows by the extrinsic and intrinsic pathways. The intrinsic clotting system involves factors VIII, IX, XI, and XII, which have been demonstrated to be reduced in the hematoma fluid of CSDH. Activated protein C and antithrombin III are the most important inhibitors of coagulation in blood plasma, and these levels are reduced in subdural fluid as well. The low levels of the latter suggest that decreased levels of clotting factors are caused by rapid consumption, which reflects the attempt at coagulation. The hematoma expands because of defective clot formation within the capsule. Thus, the regulatory mechanisms for coagulation and fibrinolysis are disturbed, which causes uncontrolled hemorrhaging.

Role of Inflammation in Hematoma and Membrane Formation

There are many scientific reports of the presence of inflammatory molecules within hematoma. Among these molecules, the proinflammatory platelet-activating factor (PAF) is important. It stimulates chemotaxis and TPA. PAF increases vascular permeability and causes degranulation of eosinophils. Compared with venous blood, a higher concentration of the proinflammatory interleukins IL-2R, IL-5, IL-7, IL-8, and IL-6 and the anti-inflammatory cytokines IL-10 and IL-13 can be found in the hematoma.

Table 1 lists the function of some important cytokines. The high level of IL-6 is explained by its induction in fibroblasts and epithelial cells by thrombin. The concentrations of the proinflammatory cytokines tumor necrosis factor (TNF)-α, IL-1β, IL-2, and IL-4 are lower in the hematoma than in blood. The cells that produce cytokines (eg, eosinophils, lymphocytes, monocytes, neutrophils, basophils, and mast cells) can be found in hematoma capsules and fluid.
JAK-STAT, Janus kinase-signal transducer and activator of transcription.

The kallikrein-kinin system also plays a role in the pathophysiology of CSDH: prekallikrein in the hematoma is transformed to kallikrein by factor XII. Kallikrein converts high-molecular-weight kininogen into bradykinin, the most potent inflammatory agent in the human body. This agent stimulates vascular permeability leading to more hematoma fluid. In summary, the concentration of proinflammatory cytokines in the hematoma fluid is higher than the concentration of anti-inflammatory cytokines. This leads to a sustained inflammatory reaction.

Membranes

In a mature state, the hematoma is surrounded by an inner and an outer membrane. The inner membrane forms later than the outer membrane, usually when the latter has a thickness of 1 to 2 mm. The inner membrane is not vascularized and does not play an important role in the pathophysiology of CSDH. Its main role is bordering the hematoma on the arachnoid side. Studies suggest that eosinophils proliferate and degranulate inside the membranes and influence the inflammatory process. Because of the presence of immaturely developed blood vessels, smooth muscle, eosinophils, myofibroblasts, and connective tissue, the outer membrane contributes to hematoma maintenance. The neovasculature partially regulates hematoma growth and retention. The membrane exhibits capillaries that are widened (up to 1000 μm) and proliferative. One of the proteins enhancing the proliferation of these fragile vessels is vascular endothelial growth factor (VEGF). VEGF enhances vascular permeability, which results in an increased transfer of plasma components into the hematoma and disrupts endothelial gap junctions. Because of the high permeability of macrocapillaries and the large gap junctions, exudation of intravascular content is possible.

Subdural Hematoma Versus Subdural Effusion

It is important to distinguish between subdural hematoma and subdural effusion. The hematoma fluid originates from blood and has a high concentration of erythrocytes. In patients with subdural effusion however, there is an accumulation of CSF in the subdural space. This is not surrounded by neomembranes. The accumulation is caused by CSF leaks, which in return can lead to CSDH, as described in the pathogenesis section.

Diagnosis

Epidemiology

CSDH has a peak incidence in the sixth and seventh decades of life. This is partly attributable to brain atrophy in elderly people. The space between the brain and skull increases from 6% to 11% of the total intracranial space. Moreover, elderly persons have a higher susceptibility to (minor) trauma, which is a major cause of CSDH. In addition, because of the high prevalence of cardiovascular disease in the elderly population, the use of anticoagulants and antiplatelet therapies is frequent (9%–41%) and is a risk factor for development of CSDH. Patients with bilateral hematomas are more often on antiplatelet or anticoagulant therapy than patients with a unilateral hematoma.

Clinical Presentation

CSDH is often called the “great imitator” because there are no specific symptoms belonging only to this disease. For example, the differential diagnosis of CSDH includes acute stroke in some patients. Whereas anticoagulants are an accepted treatment for stroke, CSDH is a contraindication to use of anticoagulants. This illustrates the importance of excluding CSDH if it is suspected.

The most common symptoms of CSDH are headache, neurologic motor deficits, lowered consciousness level, and an altered cognitive state. Vomiting and symptoms of high intracranial pressure are more common in younger patients. Headache can be accompanied by nausea or vomiting. Nausea, vomiting, headache, and an unsteady gait are more prevalent in bilateral hematomas. Speech disorder is more prevalent in unilateral hematomas, especially on the left side. The neurologic motor deficits and altered cognitive state, which are often present in elderly patients, may mimic dementia or cerebrovascular disease. Therefore, CSDH can easily be misdiagnosed. The motor deficits reported are often mild, but they may become more severe over time. Less commonly, patients with CSDH experience epileptic insults, transient neurologic deficits, isolated neurologic deficits, extrapyramidal symptoms, and frequent falls.

Imaging

Most often, CSDH is diagnosed by use of CT. This is a safe and, compared with MRI, relatively cheap method of imaging. A CT scan in a patient with CSDH can roughly demonstrate one of the following 3 distinct forms: (1) a hyperdense hematoma; (2) an isodense hematoma; or (3) a hypodense hematoma. Hyperdense hematomas are usually relatively recent hematomas, with active (re)bleeding components because fresh blood with high protein exudation rates has a high density on a CT scan. Hypodense hematomas are older hematomas. From 2 to 4 weeks onward, hematomas have been demonstrated to become less dense than the brain parenchyma. Older hematomas with components pertaining to rebleeding may appear as mixed dense or isodense. The problem with patients with the latter form of hematoma is that the diagnosis of CSDH is easily missed.

Table 1. Effect of Cytokines on the Pathophysiology of Chronic Subdural Hematoma

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Effect</th>
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<tbody>
<tr>
<td>IL-5</td>
<td>Stimulates growth and differentiation of eosinophils that secrete plasminogen, contributing to fibrinolysis</td>
</tr>
<tr>
<td>IL-6</td>
<td>Influences immune and inflammatory response and mediates the acute phase reaction</td>
</tr>
<tr>
<td></td>
<td>Causes enlargement of gap junctions and increases vascular permeability</td>
</tr>
<tr>
<td>IL-8</td>
<td>Induces chemotaxis of lymphocytes and neutrophils and stimulates angiogenesis</td>
</tr>
<tr>
<td>IL-10</td>
<td>Deactivates inflammation and is involved in the regulation of the JAK-STAT pathway</td>
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Help to maintain the balance between cytokines in the fluid.
Figure 1 shows 5 CT scans with different presentations of CSDH. CT scans with enhanced ion concentration are highly sensitive for diagnosis of isodense hematomas. MRI can detect CSDH that appears isodense on CT, even in patients without midline shift. On MRI, septa within the hematoma can also be visualized, which can be important for treatment. In general, CSDH appears hyperintense compared with normal brain tissue on both T1-weighted and T2-weighted MRI sequences.

Conclusion

The incidence of CSDH is increasing because of the aging population and common use of antithrombotic therapies. Therefore, it is important to be alert for this condition when patients, especially older patients, present with headache or other nonspecific neurologic symptoms. Part II of this series will discuss surgical and conservative treatment options for patients with CSDH.

Readings


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To activate your online access, click “Register” at the top right corner of the website.
1. Use of anticoagulant and antiplatelet treatment for cardiovascular conditions is an important risk factor for the development of CSDH.
   True or False?

2. CSDH is frequently associated with minor trauma.
   True or False?

3. CSDH is frequently associated with brain atrophy in older patients.
   True or False?

4. The effect of IL-8 on the pathophysiology of CSDH is stimulation of growth and differentiation of eosinophils that secrete plasminogen, contributing to fibrinolysis.
   True or False?

5. In CSDH, the regulatory mechanisms for coagulation and fibrinolysis are disturbed, which causes uncontrolled hemorrhaging.
   True or False?

6. Compared with venous blood, a higher concentration of the proinflammatory interleukins IL-2R, IL-5, IL-7, IL-8, and IL-6 and the anti-inflammatory cytokines IL-10 and IL-13 can be found in the hematoma.
   True or False?

7. It is important to distinguish between subdural effusion and subdural hematoma. In patients with subdural effusion, there is an accumulation of CSF in the subdural space. Hematoma fluid, however, originates from blood and has a high concentration of erythrocytes.
   True or False?

8. Nausea, vomiting, headache, and an unsteady gait are more prevalent in unilateral hematomas, especially on the left side. Speech disorder is more prevalent in bilateral hematomas.
   True or False?

9. On CT, hyperdense hematomas are usually relatively recent hematomas, and hypodense hematomas are older. In older hematomas, components pertaining to rebleeding may appear as mixed dense or isodense.
   True or False?

10. In general, CSDH appears hypointense compared with normal brain tissue on both T1-weighted and T2-weighted MRI sequences.
    True or False?