Chronic subdural hematoma (CSDH) is prevalent among elderly populations worldwide, and its mysterious pathogenesis has been discussed in the literature for decades. The issues remaining to be solved in regard to CSDH include the initiating events; the bleeding into the subdural space and the formation of the outer and inner membranes, its development; increase and liquefaction of hematoma, the optimal treatments, and the natural history. The pathophysiology is becoming more clear due to recent findings from computed tomography studies and human models of CSDH. In this work, we review previous studies on CSDH and present a new integrated concept about the development of this common condition after head injuries.

Key words: subdural fluid collection, chronic subdural hematoma, inflammation, neomembrane, head injury, craniotomy, unruptured cerebral aneurysms

Introduction

Chronic subdural hematoma (CSDH) is defined as a cystic unclotted hematoma with the outer and inner membranes in the subdural space. A common disease in the elderly, CSDH usually develops within one or two months after a minor head injury. In the computed tomography (CT) era, many clinicians described the clinical process by which CSDH develops after persistent subdural fluid collection in the weeks following a minor or moderate head injury. However, the time gap between the collection of subdural fluid and the development of CSDH has not been described in detail, mainly because there has been no suitable experimental model for examining it. Today, new knowledge has changed the thinking about CSDH — namely, it has become clear that CSDH is occasionally encountered in elderly patients after a craniotomy for an unruptured cerebral aneurysm. We think this finding that CSDH can arise as a sequela of craniotomy will have a significant impact on research into the disease. Here, we review previous studies on CSDH and present a detailed description of the mechanism of this common disease after head injury.

Historical review of studies on CSDH before the CT era

CSDH and its causal mechanism, pathophysiological processes, natural history and treatment methods have been studied for over 150 years, as this disease is very common in the elderly around the world. Hundreds of papers about CSDH have been published. There were once etiological disputes regarding the "pachymeningitis theory" proposed by Virchow in 1857 and the "trauma theory" proposed by Trotter in 1914. A connection between these two theories was established through the work of several Japanese researchers, including Nakamura, who examined their clinical patients with CSDH in 1966. Sakaki et al., who clinicopathologically studied 31 patients with CSDH in 1972, and Ito et al., who studied autopsy cases of CSDH pathologically in 1974. In those studies, the researchers all assumed that a thin posttraumatic subdural hematoma played an important role in the development of an inflammatory granulation-like neomembrane as the early stage of
CSDH. It was not until Watanabe et al.\textsuperscript{15} published their findings in an animal study in 1972 that the subdural collection of cerebrospinal fluid (CSF) mixed with blood became a focus of attention in terms of the development of CSDH.

Watanabe et al. developed an experimental animal model of CSDH by mixing blood clots with CSF and inoculating the resulting solution into the subdural space of dogs and monkeys, where the clots grew to form an encapsulated subdural hematoma that was comparable to human CSDH.\textsuperscript{16} Although Watanabe et al. were the first to take note of CSF in the subdural space in the development of CSDH, and stated that the fibrin that was formed on the surface of the clot in the presence of CSF would be essential to induce the capsule formation, they had no further explanation for the development of the hemorrhagic membrane.\textsuperscript{15} In 1974, Appelbaum et al.\textsuperscript{17} repeated similar experiments in the cat and stated that CSF was not necessary to produce such special clots, contrary to the conclusions of Watanabe et al.\textsuperscript{16} The issue remains unresolved today.

As described above, the consensus of opinion in the 1970s was that a neomembrane formed by a dural inflammatory reaction to the presence of subdural blood or subdural fluid collection is the origin of subdural and cystic liquefied hematomas. Based on their studies, Sakaki et al.\textsuperscript{13} and Ito et al.\textsuperscript{14} speculated that multiple bleedings occur inside the neomembrane from abundant sinusoidal channels, and that the neomembrane splits into the outer and inner membranes. Thus, we can frame the hypotheses as follows:

1. A neomembrane can be formed from CSF mixed with blood (as Watanabe et al.\textsuperscript{16} indicated).
2. Bleeding occurs inside the neomembrane to form a cystic hematoma (as Sakaki et al.\textsuperscript{13} and Ito et al.\textsuperscript{14} suggested).

CT studies of CSDH

In the 1980s, in conjunction with the advent of CT imaging, numerous papers were published on the development of CSDH after head injury (Fig. 1).\textsuperscript{1,4} Follow-up CT after head injuries clearly showed that CSDH developed as a consequence of posttraumatic subdural fluid collection. Periodical CT scans precisely captured the developing course of CSDH after head injury. In 1979 Yamada et al. reported three cases in which CSDH developed following traumatic subdural fluid collection.\textsuperscript{1} In a previous study, we reviewed the cases of 43 consecutive patients who had traumatic, bloody subdural fluid collection out of 715 patients who underwent CT scans because of a recent head injury.\textsuperscript{18} Twenty of the 43 patients developed CSDH between 18 and 126 days after the head injury and the mean density of the subdural fluid collection in these patients upon admission was 27.1 ± 6.7 Hounsfield units. Our previous CT study showed that CSDH usually develops as a consequence of traumatic subdural fluid collection, and that nearly 50% of patients with asymptomatic subdural fluid collection might develop CSDH.\textsuperscript{18}

Thus, the knowledge that CSDH requires a precondition of persistent subdural fluid and that this condition causes inflammatory change to the inner surface of the dura mater is most likely due to CT findings.\textsuperscript{18,20} It is conceivable that, as a sequel to traumatic head injury, the brain contusion is accompanied by an outflow of bloody CSF into the subdural space from the subarachnoid space in moderately injured victims, and it seems probable that an arachnoid tear around a bridging vein causes the subdural collection of slightly bloody CSF in patients with a minor head injury. A good experimental model for CSDH would be able to test this hypothesis. It is thus noteworthy that we have encountered more than a few patients with a CSDH that developed after they had undergone a craniotomy as treatment for an unruptured cerebral aneurysm.

Model of CSDH following craniotomy for unruptured cerebral aneurysms

CSDH has been confirmed as a complication of craniotomy in elderly patients with unruptured cerebral
Komatsu et al. first reported on three cases (0.3%) of CSDH among 1,000 craniotomies for ruptured aneurysms before the CT era, and stated that such CSDH was extremely rare. It is notable that these three patients underwent direct surgery in the chronic stage more than two weeks after rupture. Tanaka et al. also observed postoperative subdural fluid collection in 52% of their 147 patients with intracranial aneurysms after craniotomy, including 19 patients with unruptured aneurysms, and reported that the subdural fluid collection transformed to symptomatic CSDH in three patients. This problem rarely occurs in the treatment of ruptured aneurysms, probably because the brain is swollen in the acute stage.

We retrospectively investigated the cases of 76 patients with unruptured cerebral aneurysms who underwent neck clipping by craniotomy from 1997 to 2010. The study protocol was approved by the ethical committee of Tokyo Medical and Dental University Hospital (No.1398, Tokyo, Japan). Eighty-six unruptured cerebral aneurysms (80 craniotomies) in 76 consecutive patients ranging from 42 to 85 years old (average age: 61.5 ± 7.6) with single or multiple aneurysms were treated by craniotomy. Four patients had two craniotomies. Written informed consent for the use of data was obtained from all patients and their next of kin before the surgery. CSDH developed in 10 patients (12.5% of 80 craniotomies) ranging from 59 to 72 years old as shown on CT scans. There was a significant difference (p=0.032) in age between the 66 patients without CSDH (average age: 60.7 ± 7.7) and the 10 patients with CSDH (average age: 66.2 ± 5.2) by Student’s t-test (by manual calculation). Six of the 10 patients (60%) were male. Five of the 10 patients with CSDH became symptomatic and were treated with a burr hole with irrigation. In all 10 of the patients the CSDH was eventually resolved without neurological deficits.

After the neck clipping in the 76 patients, subdural fluid composed of CSF usually accumulated postoperatively, due to sinking of the brain following the removal of CSF. CT scans were taken in 78 of the 80 craniotomies postoperatively, mostly on the 1st and around the 7th postoperative day. Postoperative follow-up CT in 74 of the patients revealed an enlarged subdural space in 64 craniotomies, compared to the preoperative CT findings. The enlargement of the subdural space gradually disappeared with time in most of these patients. No CSDH was observed in 50 craniotomies without or with subdural fluid collection of a thickness not more than 4 mm based on CT scans taken on the 4th to 12th day after surgery. However, CSDH developed in 10 (35.7%) of 28 craniotomies with subdural fluid collection thicker than 4 mm in CT scans within the same date range after surgery (Fig. 2 and 3). In particular, 9 (50.0%) of the 18 craniotomies with subdural fluid collection thicker than 5 mm developed CSDH. Thus, this retrospective study shows that the development of CSDH is associated with the thickness of the postoperative enlarged subdural space and is caused by the persistent accumulation of subdural CSF slightly contaminated with blood cells. Such a craniotomy for unruptured aneurysms can be a type of clinical model for CSDH, which is comparable to what Watanabe et al. intended to produce experimentally.

Another concern is why CSDH did not develop in...
all patients who underwent craniotomy and incision of the arachnoid membrane. The degree of arachnoid injury after craniotomy was much larger than that in cases of minor head injury. However, the incidence rate of CSDH after craniotomy was not unusually high. A possible explanation is that re-expansion of the brain after surgery prevented enlargement of the subdural space. This could also explain why elderly patients more frequently suffer from CSDH (brain atrophy) and SAH patients do not exhibit CSDH (brain swelling).

**Integrated consideration of the pathomechanism of CSDH based on various findings to date**

The incisions to the arachnoid membrane during craniotomy produce conditions similar to those seen in head injuries. CSF with a small number of blood cells, including inflammatory cytokines, collects in the subdural space in cases with postoperative sinking of the brain. That is, craniotomy for unruptured aneurysms is a kind of surgical trauma to the brain and may therefore be identical to minor head injury, as Komatsu et al. pointed out.7 Such fluid collection mixed with a blood cell component persists for a certain period, causing inflammatory changes in the dura mater (pachymeningitis haemorrhagica interna according to Virchow15) and could form a neomembrane on the inner side of the dura mater. In previous studies, the development of a neomembrane attached to the inner surface of the dura mater was recognized around CSDH in autopsy cases of CSDH14 and as pachymeningitis hemorrhagica interna with chronological changes in autopsy cases after craniotomy.20 We consider that the discussion about the causes of neomembrane formation (our hypothesis (1)) is resolved, and that the formation can be attributed both to the presence of a subdural collection of CSF contaminated with a small number of blood cells and blood-derived factors20 and to the dural inflammatory reaction. Our data demonstrating that the development of CSDH was significantly more frequent in older than younger patients are also suggestive of a close relationship between age and the development of CSDH after minor head injury.

The next question is how the inner membrane is formed after the development of a neomembrane above the arachnoid membrane. In other words, does the hemorrhage go from sinusoids in the neomembrane into the subdural space directly, or does it go inside the neomembrane? Sakaki et al.13 and Ito et al.14 proposed a hypothesis (the same as our hypothesis (2)) that a subdural “primary neomembrane” adjacent to the inner side of the dura mater splits into the inner and outer membranes by frequent hemorrhages inside the neomembrane and turns into a cystic hematoma.13,14 We must also consider the other possibility, that the hemorrhage may occur directly into the subdural space. However, CSDH is liquefied without clotting and with the inner membrane usually localized over the frontal and parietal lobes.13 If the hemorrhage from the neomembrane goes directly into the subdural space, it should spread widely over the cerebral hemisphere and it is inexplicable how the smooth inner membrane is formed so soon. Kawano et al.19 performed an ultrastructural examination of the outer and inner membranes of CSDH in 23 patients, and suggested that CSDH was an intradural hematoma which is formed within the split dural border cell layer; the outer membrane consisted of thick granulation tissue; and a few dural border cells on the underlying arachnoid membrane formed a thin fibrous inner membrane. Thus, the formation mechanism of the inner membrane would favor the hypothesis of Sakaki et al.13 and Ito et al.14 Based on the clinical studies of Takahashi et al.9 and Tanaka et al.,8 the pathological studies of Ito et al.,14 Schmidt and Neidhardt,20 and Kawano et al.,19 and our own findings, we induced a chain of developing process of CSDH as shown in Fig. 4. Although there have been many reports about CSDH following craniotomy and also about the causal mechanism of CSDH after head injury, as discussed above, to the best of our knowledge, this is the first publication that correlates the CSDH after craniotomy with that after minor head injury.

CSDH is well known to occur in patients with other conditions, such as renal failure with blood dialysis,21 intracranial hypotension syndrome22,23 including the patients with CSF shunt, and coagulopathy.24 Some
mild head injury is suspected to contribute to the development of CSDH in these patients. Formation of the neomembrane in such cases seems to be due to a mechanism similar to that after head injury.

Growing and resolving course of CSDH and treatment

Our research interest has focused on the local activity of various activated substances in the outer membrane of CSDH.25-27 This outer membrane is a source of tissue plasminogen activator and inflammatory cytokines.28-32 Therefore, CSDH can be studied as a type of inflammatory phenomenon. In our previous work, we analyzed the concentrations of inflammatory cytokines such as interleukin (IL)-6 and IL-8, vascular endothelial growth factor (VEGF), and prostaglandin E₂ in hematoma fluid.25 The results showed that there was a linear and significant relationship between the prostaglandin E₂ concentration in the hematoma fluid and the interval from the trauma to the initial surgery. We came to the conclusion that cyclooxygenase-2, which is an enzyme involved in the synthesis of prostaglandin E₂, might play a crucial role in the development of CSDH.

What we knew in the CT era about the natural history of CSDH is that some CSDHs continue to increase in size to become symptomatic and require aspiration of the hematoma and others resolve spontaneously. Nagahori et al. pointed out, based on a comparison of the density of hematoma on CT and the histological findings of outer membranes, that exudation from inflammation is involved in the early stage of hematoma formation, and that inflammation and hemorrhage are involved in the subsequent stage of hematoma enlargement.33 Based on the histological findings reported by Sakaki et al.13 and Ito et al.,14 there was a natural history from vascular-rich to regressive periods in the neomembrane, which might lead to an increase in the size and the spontaneous resolution of the hematoma. Naganuma et al. reported four CSDH cases that were followed from head injury to spontaneous resolution of hematomas on CT scans.34 The intervals for resolution were 78, 174, 231 and 326 days after the development of CSDH. In our previous CT study, 7 (35%) of 20 patients who developed CSDH following...
subdural fluid collection resolved spontaneously. In our present study as well, the CSDHs of 5 (50%) of the 10 patients resolved spontaneously and the duration from the appearance to the disappearance of CSDH on CT in these 5 patients was 121.8 ± 77.7 days (Fig. 2). Therefore, we think that the spontaneous cure of a CSDH is associated with the healing process of the outer membrane — namely, the eradication of the sources of bleeding.

There have been various treatment methods for CSDH such as total removal of the outer and inner membranes with hematoma, trephination, two burr holes with irrigation, one burr hole with irrigation, solely aspiration of the hematoma, and nonsurgical drug therapies. Total removal of the membranes with a hematoma occasionally resulted in serious complications and came to be used very infrequently. At the time of this writing, one burr hole and saline irrigation is the most common CSDH treatment in Japan. At our hospital, 210 patients with CSDH who were treated with one burr hole and irrigation under local anesthesia between 2006 and 2010 all improved neurologically and were considered to be cured. Repeat operations were done in six patients without any complications. One burr hole with irrigation thus seems to be a safe treatment of choice for CSDH at present. In addition, this procedure is thought to be effective to speed the healing process of the vascular-rich membrane. The postoperative incidence of seizures after burr hole treatment is low and similar to that previously reported for minor head injury. Therefore, the routine use of antiepileptic prophylaxis is not necessary in patients with CSDH caused by minor head injuries or other causes and who are treated by burr hole when there are no additional lesions present on CT scans.

It is important to take measures to prevent the transformation of a subdural fluid collection to CSDH, though more than 50% of patients with subdural fluid collection after head injury or craniotomy became free from the collection spontaneously, according to the results of our previous CT studies and the study of unruptured aneurysms (the percentage was even higher among younger patients). This complication after craniotomy for unruptured aneurysms provides a model for further elucidating the causal mechanism of CSDH and for investigating preventive measures such as drug prophylaxis to decrease the subdural fluid collection commonly seen in elderly patients after head injury.

Conclusion

We proposed a new integrated concept to describe the pathogenesis of CSDH, one of the most common conditions requiring neurosurgical treatment in the neurosurgical field. The starting point is a subdural collection of CSF with blood cells which occurs due to tears in the arachnoid membrane following contusion of the brain or slight bleeding from a bridging vein. The next step is the formation of a primary neomembrane with a rich vasculature following an inflammatory reaction by persistent and somewhat bloody subdural fluid collection. Gradual bleeding with exudation including various cytokines and activating substances occurs inside the neomembrane, and the unclotted hematoma increases in size as an encapsulated hematoma with a thick outer membrane and thin inner membrane above the arachnoid membrane, although some hematoma resolves spontaneously. Natural healing of the hematoma membrane may occur as part of the regression of the inflammatory process. A burr hole with irrigation is thought to be effective to speed this healing process of the vascular-rich membrane.

Disclosures

The authors have no conflicts of interest to disclose, and the study was approved by the Conflict of Interest Committee of Tokyo Medical and Dental University.

References


