The Pathogenesis of Chronic Subdural Hematomas: A Study on the Formation of Chronic Subdural Hematomas and Analysis of Computed Tomography Findings

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■ BACKGROUND: **The origin of chronic subdural hematomas (CSDH) and the pathophysiology of its enlargement remain unknown. The chemical fluid composition of CSDH, the contribution of cerebrospinal fluid (CSF) to its enlargement, and the relationship to its appearance on computed tomography (CT) also are not entirely clear.**

■ METHODS: **In this prospective study, 58 samples in 41 patients treated surgically for CSDH were analyzed. CSDHs were evaluated for the presence of CSF via β-2 transferrin and substances related to cell breakdown and hemolysis. These were compared with normal value of those substances in the serum and the CT appearances of the CSDH.**

■ RESULTS: **In this study, 24% of the samples contained β-2 transferrin, which was statistically significant. Total protein, lactate dehydrogenase, total bilirubin, and red blood cells also were statistically different when compared with their normal serum concentration, indicating an active process of rebleeding and hemolysis rather than plasma ultrafiltration; however, their concentrations did not correlate with specific CT scan appearance. The absence of CSF in CSDH in 76% of cases did not support the theory that most CSDHs originate from subdural hygromas. The presence of hemolysis and cell breakdown, byproducts supports the hypothesis that the primary enlargement of CSDH develops through neomembrane and neovascular formation, rebleeding, and inhibition of the blood coagulation process. Our study did not test for serum transudation as a component of the enlargement of CSDH.**

■ CONCLUSIONS: **Our study confirms that the origin and enlargement of CSDH is multifactorial, but the contribution of individual factors and condition under which it occurs still remains unclear. CT scan findings do not correlate with the chemical composition or the presence of CSF in the CSDH.**

INTRODUCTION

Chronic subdural hematoma (CSDH) is one of the most common neurosurgical disease of elderly patients. With advances in medical care, the elderly population will continue to increase and will remain more active, with therefore a potential increase in incidence of CSDHs. Currently, the overwhelming treatment modalities of fully developed CSDH are various forms of surgery, addressing its mass effect, but ideally, early medical treatment could prevent the formation of CSDH and avoid surgical procedures. The main obstacle to developing a more rational treatment of CSDH is our poor understanding of its origins, particularly the pathophysiology of its enlargement, despite the large body of literature dealing with this subject.[1-26]

In 1826, Bayles ascribed the pathophysiology of CSDHs to "chronic rebleeding." Virchow went on to further classify subdural hematomas (SDHs) in 1857 with the initial description of pachymeningitis hemorrhagica interna.[3,9]

It was believed that CSDHs develop initially as acute SDHs after presumed trauma,[21] but experience shows that in most instances small acute hematomas reabsorb spontaneously. Although recent research by Lee et al.,[5,6] supported by Nakaguchi et al.,[14] suggests that traumatic subdural hygromas may be the major

Key words
- Beta-2 transferrin
- Chronic subdural hematoma
- Computed tomography
- Fluid analysis

Abbreviations and Acronyms
β_2T: β-2 transferrin
βTP: β-trace protein
CSDH: Chronic subdural hematoma
CSF: Cerebrospinal fluid
CT: Computed tomography
DBC: Dural border cells
LDH: lactate dehydrogenase
RBC: Red blood cells
SDH: Subdural hematoma

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Citation: World Neurosurg. (2017) 107:376-381.
http://dx.doi.org/10.1016/j.wneu.2017.07.108

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

source of its transformations into CSDH, there are questions about the methodology of their studies and their conclusions, as pure subdural hygromas are quite rare. Lee[5] in fact admits that the distinction between subdural hygromas and CSDH is difficult and often impossible.

Just as the several theories of the origin of the CSDH are not entirely satisfactory, so are the many theories of its enlargement. An early hypothesis by Gardner in 1932[3] was based on the hypothesis that SDHs grow in volume because blood components break down with time into smaller molecules, thereby increasing the osmotic pressure within the hematoma. This in turn pulls water into the hematoma "sac" from the cerebrospinal fluid (CSF), thereby causing a progressive expansion of the clot. Weir[23] measured osmotic activity in the CSDH and serum and found them to be same and suggested that this theory alone cannot explain the enlargement, although its methodology is now being questioned.

Studies in which the authors used radioisotopes, however, found the presence of serum albumin in the subdural fluid, suggesting that plasma ultrafiltrate leaking through poorly developed microvasculature of the neomembranes may contribute to the CSDH enlargement.[27] Another hypothesis suggests that the CSF leak into the hematoma is the primary cause of the enlargement through a disruption of the arachnoid membrane. Kristof et al.,[4] using β-trace protein (βTP) as an indicator of CSF presence, reported that CSF was present in CSDH in 93% of their patients.

Whatever the initial step in development of CSDH, it currently is accepted that the next step is the migration of inflammatory cells derived from the dural border cells (DBCs) followed by fibroblasts along the dura and the development of outer membrane. In this membrane, there is a growth of fragile sinusoidal vessels with poorly developed endothelial cell junctions containing thrombomodulin, which is one of the factors that prevent the blood in the CSDH from clotting.[13] These vessels are thought to be the source of repeated multifocal bleeding,[11] which is accompanied by clotting prevention and hemolysis. This process currently is considered to be the main causative factors in the enlargement of CSDH.

We attempted to determine whether CSF leak into the hematoma in fact plays a significant role in the enlargement of CSDH and whether a different concentration of the products of hemolysis between CSDH fluid and serum may elucidate whether there is an active process versus plasma ultrafiltration. i.e., rebleeding/clot prevention. We further tested whether the chemical composition of the CSDH and/or CSF presence contribute the different appearance of CSDH on computed tomography (CT) scans. We analyzed the CSDH for the presence of CSF using beta-2 transferrin (β_2T). Total protein, lactate dehydrogenase (LDH), total bilirubin, red blood cells (RBC), glucose, and K+ in both CSDH and serum also were measured.

MATERIALS AND METHODS

After approval from institutional review board was obtained, samples were collected by a single investigator from consecutive patients older than the age of 18 years presenting for drainage of CSDH who were treated at Saint Barnabas Medical Center, a 597-bed regional hospital, from November 2006 to July 2008. Bilateral subdural collections, repeat drainage samples, and partial fluid analysis were included.

Each patient had at least one noncontrast head CT on admission and one more postsurgery. The studies were interpreted by the radiologist on call and the operating surgeon. A blinded neuroradiologist later evaluated all of the admission CT scans using a modified classifications reported by Fujisawa et al.[2] The hematomas were classified into low density, isodensity, mixed, and layering types, omitting the high-density type more common to acute SDH. The chemical content of the CSDH, its hemolytic products, and the presence of CSF were then correlated with the findings.

The subdural fluid was obtained immediately after the dura and membrane was broken, with no gross violation of the arachnoid membrane. Five milliliters of the initial egress of subdural fluid was collected for biochemical analysis. This fluid was immediately sent to the pathology department for analysis the same day or stored in the pathology department at 4°C for analysis the next day. The subdural fluid was analyzed for the presence of β_2T.[28] This test was performed at the Mayo Laboratories (Rochester, Minnesota, USA). All the other studies, i.e., total protein, LDH, total bilirubin, RBC, glucose, and potassium, were performed at our institution.

A 2-proportion Z test was performed for both the presence and absence of β_2T in CSDH. A 2-tailed Student t test was used to compare the components of the content of CSDH with the normal value of that component reported in serum, with obvious unequal variance. If a particular component was determined to be statistically significant, it was further analyzed with a 2-tailed Student t test. The values for each component were correlated with the 4 CT appearances. A one-way analysis of variance was used to determine statistical significance for each component with respect to the 4 independent groups of CT appearances.

RESULTS

There were 41 patients with 58 total samples. The median age was 79 years, ranging from 41 to 96 years; 63% of the total patients were male. The results are shown in Table 1.

Twenty-seven samples were obtained from the right side, and 31 were obtained from the left side. Of these, 13 samples were bilateral. Four samples, 7% of total, were redrained. The results are shown in Table 2.

There were incomplete samples due to hemolysis of the sample or laboratory error. There are 8 patients with only valid β_2T values, 4 in each the isodense mixed and isodense layered groups. One patient in the hypodense group had only valid β_2T and RBC values. There was one patient in the isodense homogeneous group with

Table 1. Demographics of Patient Population

Demographics	Number of Samples	Percentage
Total patients	41	
Male	26	63%
Female	15	37%