Original Article

New histopathological evidence for the relationship between hydromyelia and hydrocephalus following subarachnoid hemorrhage: An experimental study

ABSTRACT

Objectives: Subarachnoid hemorrhage (SAH) is a serious pathology with a high death and morbidity rate. There can be a relationship between hydromyelia and hydrocephalus following SAH; however, this subject has not been well investigated.

Materials and Methods: Twenty-four rabbits (3 ± 0.4 years old; 4.4 ± 0.5 kg) were used in this study. Five of them were used as the control, and five of them as the SHAM group. The remaining animals (n = 14) had been used as the study group. The central canal volume values at the C1-C2 levels, ependymal cells, numbers of central canal surfaces, and Evans index values of the lateral ventricles were assessed and compared.

Results: Choroid plexus edema and increased water vesicles were observed in animals with central canal dilatation. The Evans index of the brain ventricles was 0.33 ± 0.05, the mean volume of the central canal was 1.431 ± 0.043 mm^3, and ependymal cells density was 5.420 ± 879/mm^2 in the control group animals (n = 5); 0.35 ± 0.17, 1.190 ± 0.114 mm^3, and 4.135 ± 612/mm^2 in the SHAM group animals (n = 5); and 0.44 ± 0.68, 1.814 ± 0.139 mm^3, and 2.512 ± 11/mm^2 in the study group (n = 14). The relationship between the Evans index values, the central canal volumes, and degenerated ependymal cell densities was statistically significant (P < 0.05).

Conclusions: This study showed that hydromyelia occurs following SAH-induced experimental hydrocephalus. Desquamation of ependymal cells and increased cerebrospinal fluid secretion may be responsible factors in the development of hydromyelia.

Keywords: Hydrocephalus, hydromyelia, intraventricular hemorrhage, subarachnoid hemorrhage

INTRODUCTION

Blood vessels in the subarachnoid space tear as a result of different pathophysiological factors and lead to subarachnoid hemorrhage (SAH).[1] In humans, strokes are caused by SAH in between 5% and 10% of cases;[2] nevertheless, it has disastrous consequences. Intraventricular hemorrhage and hydrocephalus can occur with SAH; hence, SAH is a complex illness, and a large portion of its pathophysiology is yet unknown. Currently, there are reports that COVID-19 infection may be a predisposing factor for SAH.[3] There is a correlation between SAH and hydrocephalus.[4] The central canal of the spinal cord is the continuation of the cerebral ventricles in the spinal cord. Blood in the ventricular system induces hydrocephalus.[5,6] Stripped ependymal cells and ruptured subependymal basement membrane fragments can cause

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an occluded aqueduct[7] and lead to hydrocephalus following SAH.[7] There have been used many terms for hydromyelia, such as "central canal syrinx," "syringohydromyelia," and "idiopathic localized hydromyelia." Those lesions are cavities within the spinal cord.[8] These cavities can be divided into communicating and noncommunicating forms. Meanwhile, a focal dilatation of the central canal is called hydromyelia.[9] Some hydrocephalus can be associated with hydromyelia.

Technological breakthroughs have been observed in the current medical practice.[10] In intracranial SAH, blood reaches the spinal central canal and spinal subarachnoid distance due to cerebrospinal fluid (CSF) circulation, and despite advances in medical technology,[11] the pathogenesis of hydromyelia associated with hydrocephalus following SAH is still not clear. Investigating the relationship between hydrocephalus and hydromyelia following experimental SAH was the aim of this study.

MATERIALS AND METHODS

The study was approved by the local Ethical Committee. Twenty-four rabbits (3 ± 0.4 years old; 4.4 ± 0.5 kg) were used in this study. Five of them were used as control and five of them were SHAM groups. The remaining animals (n = 14) were injected with autologous blood into their lateral ventricles and had been decapitated after 4 weeks of follow-up. Then, the brains of all animals were examined histopathologically.

Experiment protocol

Before performing surgery, 0.2 mL/kg of the anesthetic mixture (ketamine hcl, 150 mg/1.5 mL; xylazine hcl, 30 mg/1.5 mL; and distilled water, 1 mL) was subcutaneously injected. Anesthesia was produced with isoflurane administered using a face mask. Animals in the study group had autologous blood (1 mL) drawn from the auricular arteries and injected using a 22-Gauge needle over a minute into the lateral ventricles through the occipital horns. In the SHAM group, 1 mL of serum saline was injected into the lateral ventricles. After being followed for 21 days, the animals were sacrificed as in the study by Celiker *et al*.[12] The brains and cervical spinal cords of all animals were removed and examined histopathologically.

Histopathological procedures

Because stereological techniques are helpful for extrapolating three-dimensional structural volumes from planar measurements on two-dimensional slice pictures, they were applied in this investigation.[13] It was evaluated according to the previously published study.[14] All brains were sectioned coronally at the levels of the biparietalconus to calculate the Evans index, the ependymal cell density of the ventricular surfaces of the aqueducts, and the aqueduct volumes. To estimate the Evans index, the figures of animals were taken on the prepared forms of glass lamellae, and bifrontal cornual indexes were calculated using mini-squared papers. The brain ventricles in a rabbit of the control group and the Evans index estimation method are shown in Figure 1a-A. The changes in an animal of the SHAM group in Figure 1b-B and the study group in Figure 1a-C are seen. Figure 1a-D shows the left brain ventricles of an animal of the control group. For the central canal volume and ependymal cell estimation calculation, longitudinal sections were done at the C1-2 levels. Then, these sections were embedded in paraffin blocks. They were stained with the hematoxylin and eosin method and glial fibrillary acidic protein method and sectioned of 5 mm consecutively in the numbers of 20–50. The cylinder method was used to evaluate the volumes of the central canal. Tissue samples were cut into several parallel pieces from one side of the aqueduct to the other, and volumes were determined using the cylinder method according to the formula, $V = h\pi\,[(x + y + z)/3]^2$ [Figure 1b], as in the study by Yolas *et al*.[7]

Statistical analysis

The differences in the values in the control, SHAM, and SAH groups were statistically compared using SPSS® Statistical Software Package version 21 (IBM Corporation, Somers, NY, USA). All data were reported as the mean standard deviation. The Mann–Whitney *U*-test was used for data analysis, and

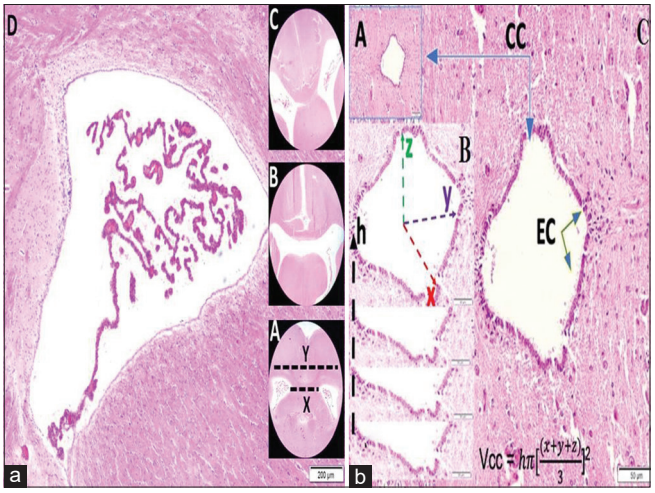

Figure 1: (a) shows the brain ventricles in a rabbit of the control group and the Evans index estimation method (ligth microscopy (LM), H and E, ×2/A), SHAM (LM, H and E, ×2/B) study animals (LM, H and E, ×2/C). (D) The left brain ventricles of an animal of the control group (LM, H and E, ×4/D). (b) Histopathological appearances of the spinal cord and central canal (LM, H and E, ×4/A), radius (r = (x + y + z)/3/B) of the central canal, central canal surface/volume estimation formula (LM, H and E, ×20/C) in an animal of the control group. CC: Central canal, EC: Ependymal cell, Vcc: Central canal volume. H and E: Hematoxylin and eosin

nonnormal distribution was detected. At $P = 0.05$, differences were deemed significant.

RESULTS

In the histopathological evaluation of the spinal cord and central canal, there was no central canal enlargement in normal animals, while minimal central canal dilatation was observed in the SHAM group and advanced central canal dilatation in the study group [Figure 2a]. Although minimal central canal enlargement in the SHAM group animals has occurred, ependymal cell desquamation and subependymal basal membrane rupture were not observed [Figure 2b]. In the animals in the study group, the findings of advanced central duct dilation, ependymal cell desquamation, and subependymal basal membrane rupture were noted [Figure 3].

Numerical results

In this study, the Evans index of the brain ventricles values, central canal volumes, and degenerated ependymal cell densities were evaluated. The Evans index of the brain ventricles was 0.33 ± 0.05, mean volumes of the central canal was 1.190 ± 0.114 mm^3, and ependymal cells density was 5.420 ± 879/mm^2 in the control group animals ($n = 5$); 0.35 ± 0.17, 1.431 ± 0.043 mm^3, and 4.135 ± 612/mm^2 in the SHAM group animals ($n = 5$); and 0.44 ± 0.68, 1.814 ± 0.139 mm^3, and 2.512 ± 11/mm^2 in the study group ($n = 14$) [Table 1]. The statistically significant difference observed between the control and SHAM groups was $P < 0.005$ and between the SHAM and study groups was $P < 0.0005$, control/study: $P < 0.00001$. Ventriculomegaly was defined as radiographic evidence of progressive ventricular dilatation. The Evans index, the relationship between central canal volumes, and degenerated ependymal cell densities were found to be significant between the SHAM and study groups.

DISCUSSION

Key results

This study indicates that hydromyelia can occur following SAH-induced experimental hydrocephalus. The upper cervical central canal dilatation, desquamation of ependymal cells, destruction of the subependymal basement membrane, and accumulation of blood cells in the subependymal basement membrane were observed in animals with hydrocephalus secondary to ventricular hemorrhage.

Central canal and ependymal cells changes following hydrocephalus secondary to subarachnoid hemorrhage

It is assumed that hydrocephalus following SAH occurs by three main pathways: (1) anatomic obstruction or block of

Table 1: The Evans index of the brain ventricles values, central canal volumes, and degenerated ependymal cell densities in the control, SHAM, and study groups

	Evans index of the brain ventricles	Mean volumes of the central canal (mm^3)	Ependymal cells density (/mm^2)
Control group	0.33±0.05	1.190±0.114	5.420±879
SHAM group	0.35±0.17	1.431±0.043	4.135±612
Study group	0.44±0.68	1.814±0.139	2.512±11

Statistical results were shown. The difference was significant between Control and SHAM: ($P<0.005$), SHAMand study ($P<0.0005$), Control and study ($P<0.00001$)

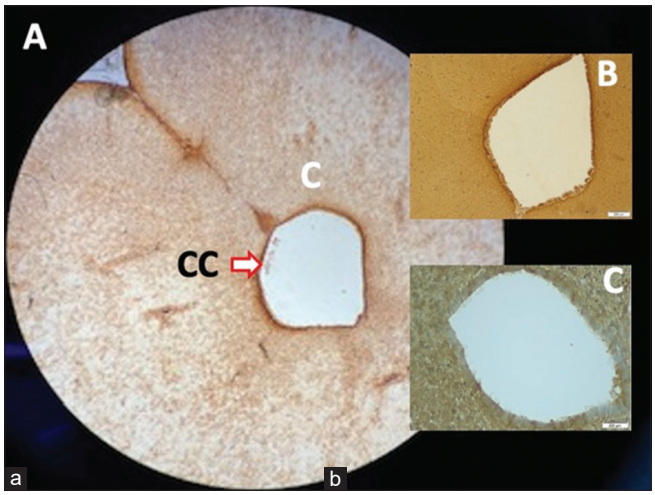

Figure 2: (a) The central canals of the three groups are seen in an animal of the control group, (A) partially dilated in the SHAM, (B) and dilated in the study group (C) (LM, glial fibrillary acidic protein, ×4). (b) Histopathological appearances of the spinal cord and central canal (LM, H and E, ×4/A), EC (LM, H and E, ×20/B) in a SHAM animal. H and E: Hematoxylin and eosin. CC: Central canal, EC: Ependymal cell

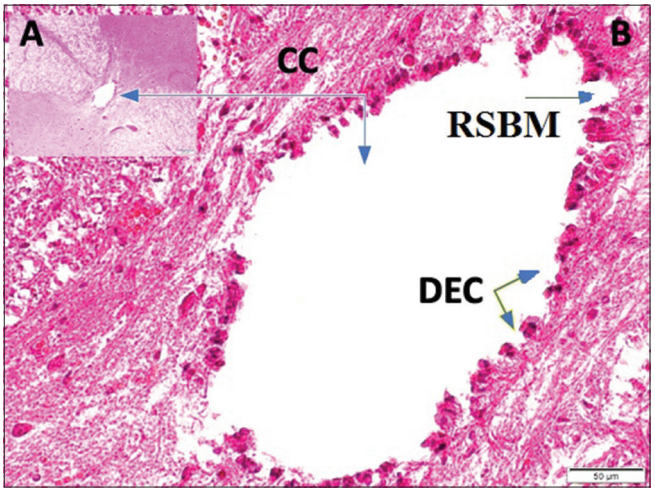

Figure 3: Histopathological appearances of the spinal cord and dilated central channel (LM, H and E, ×4/A), degenerated-desquamated ependymal cells (DEC), and ruptured subependymal basal membrane (RSBM) of the central canal (LM, H and E, ×20/B) in the spinal cord in an animal with SAH. H and E: Hematoxylin and eosin. DEC: Degenerated-desquamated ependymal cells, RSBM: Ruptured subependymal basal membrane. CC: central canal

the path of CSF-like aqueduct by hemorrhage, (2) reduced absorption from impaired arachnoid granulations,[15,16] and (3) increased secretion of CSF.[5] All of these events may occur following ventricular hemorrhage. Ventricular hemorrhage may occur after SAH. In ventricular hemorrhage, the blood may obstruct the aqueduct, and hydrocephalus may occur. According to reports, subarachnoid blood can cause arachnoiditis and arachnoid scarring; both of which can result in hydrocephalus. Intracranial hematoma volume is a factor that impacts postoperative results and the prognosis of patients.[17] Intraventricular blood following SAH causes dangerous changes in the choroid plexus (CP).[5,6,18] The CP has numerous important functions.[18] The CPs are the main source of CSF[19] and are highly vulnerable to damage in SAH.[18] SAH may lead to choroidal artery vasospasm.[18] The consequence of these changes is the obstruction of the aqueduct and hydrocephalus.[7] Ischemic damage of the ependymal occurs following SAH.[7] In Figure 3, the central canals in an animal of the control group (A), partially dilated in the SHAM (B) and dilated in the study group, are seen. It is well-known that a dilated central canal or hydromyelia may result in spinal cord atrophy.

Spinal subarachnoid hemorrhage and central canal dilatation

The anatomy of the human spinal column is intricate.[20] SAH may impair the flow of blood to the spine,[21] and cause bloody CSF, and the bloody or highly proteinous CSF may lead to neural degeneration,[22] spinal arachnoiditis,[23] and spinal cord ischemia.[24] Neuronal loss and glial cell reactivity may be occurred by spinal cord ischemia.[25] These ischemic changes may be responsible for developing changes in the spinal cord. The neuronal injury occurs by the blood in the subarachnoid space and hemoglobin degradation products[26] because disruption in neural signal processing and transmission may occur after SAH.[27] Maintaining normal spinal cord activity and tissue integrity requires constant oxygen delivery and CO_2 clearance.[25] The balance between cell death and cell growth is essential for all tissues, particularly for the nervous system,[28] spinal cord, and nerves.[25] Spinal cord movement and cord systolic expansion also produce significant local CSF flow, which can be disturbed in a patient with syringomyelia or hydromyelia. In Chiari malformation, altered CSF circulation at the foramen magnum leads to instantaneous pressure disequilibration between the intracranial and spinal subarachnoid space. This situation may be responsible for the initiation of syringomyelia formation.[29] Many patients with Chiari malformation develop syringomyelia; however, central canal dilation or hydromyelia may also occur. It was previously suggested that there is a huge plastic potential in the human nervous system.[30] There are some cases with syringomyelia caused by arachnoiditis secondary to SAH in the literature.[31] Central canal dilatation may be associated with intracranial hydrocephalus. This study shows that central canal dilatation may occur by disruptions in the ependymal cell in animals with hydrocephalus secondary to SAH. Following SAH, the developing hydrocephalus and syringomyelia require an understanding of the physiology and anatomy of the CSF and water pathways between the brain and spinal cord. Figure 3 shows the histopathological appearances of the spinal cord and dilated central channel (LM, H and E, ×4/A), degenerated-desquamated ependymal cells, and ruptured subependymal basal membrane of the central canal (LM, H and E. ×20/B) in the spinal cord in an animal with SAH. The present study has importance because currently, the epidemic of COVID-2019 (SARS-CoV-2) is a big problem in the world. SAH may also occur after COVID-19 infection.[32]

Limitations

It is not possible to detect the cellular and histopathological changes following SAH in the human spinal cord; the experimental animal studies show the cellular[33] and histopathological changes; however, the experimental studies may not accurately represent the human diseases.[34] In this study, the radiologic and clinical evaluation of animals was not performed. Intracranial pressure and cerebral perfusion pressure values in the animals were not evaluated. Statistically significant differences were observed between the control and SHAM groups ($P < 0.005$); we think that saline injection in the SHAM group can, sometimes, be harmful.[35] Figure 2b shows a minimal central canal enlargement in the SHAM group animals. The sample number is limited in this study. A statistician needs more cases to conduct statistical analysis.[36] The animals of each group are not equal in this study. Equal sample sizes can give a greater power to detect differences.[37] Given the limited access to the vital human spinal cord cells,[38] we think that the findings of the animal study such as present are valuable.

CONCLUSIONS

Knowledge of the condition and its implications is essential for successfully managing the patient with SAH. Scientific concepts serve as a framework for our clinical practice.[39] The treatment of patients with hydromyelia requires an understanding of CSF pathways between the brain and spinal cord. The finding of this study is interesting, and little is known about spinal consequences after ventricular hemorrhage. Our study provides indirect evidence that increased CSF flow occurs from an intracranial area into the central canal, following hydrocephalus with SAH. This increased CSF flow may be the impetus for the expansion of the central canal to

produce hydromyelia. The main pathological findings may be disruption of the ependymal layer. The enlarged central canal may be related to the increased flow of CSF from the cerebral subarachnoid space into the central canal. If we consider the nervous system as a great orchestra,[40] the impairment of cerebral autoregulation or orchestral situations may occur in SAH. Our study suggests that ependymal cell disruption following hydrocephalus-induced SAH may have a role in the pathogenesis of central canal dilation. Its dilatation likely due to increased intraspinal pressure was observed. The mechanism we found in our study based on the desquamation of ependymal cells and subependymal membrane rupture has not been published in the literature. The brain and spinal cord are inseparable parts of the central nervous system that should be considered together in SAH. In hydromyelia development secondary to hydrocephalus following SAH, desquamation of ependymal cells, subependymal basement membrane destruction, and blood cell accumulation in the subependymal basement membrane seem to have a role. More studies are required.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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