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Research Article

Hydrocephalus Mice Model: Choroid Plexus Aquaporin-1 Dynamics Following Cerebrospinal Fluid Drainage

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ABSTRACT

Background: Aquaporins (AQPs) are a family of membrane proteins that act as channels for water, facilitating its movement across the plasma membrane of cells. Aquaporin1 (AQP1), located in the choroid plexus, is thought to be involved in the process of cerebrospinal fluid (CSF) production. **Objective**: The objective of this study is to examine the impact of hydrocephalus and cerebrospinal fluid (CSF) drainage on the expression of AQP1 in a mice model of hydrocephalus. **Material and Methods:** Laboratory experimental study with six groups. Five test groups, one control group, and a rat model of hydrocephalus caused by kaolin were used in the experiment. **Results:** Hydrocephalus in mice model induced by kaolin, and CSF drainage was performed on the 7th and 14th days group. Immunohistochemical analysis was conducted to examine the presence of AQP1 in the choroid plexus using microscopes. The findings revealed a noticeable decrease in AQP1 expression levels in the choroid plexus, which exhibited a semi-quantitative decline in correlation with the duration of hydrocephalus ($p = 0.01$). This decrease was observed when comparing the normal group with the hydrocephalus groups on the 7th, 14th, and 21st days following induction. However, after cerebrospinal fluid (CSF) drainage, there was a significant increase in AQP1 expression ($p < 0.05$). **Conclusions:** This study shows the significant role of AQP1 in CSF production by comparing of AQP1 expression in the *choroid plexus* of hydrocephalus mice model, with and without CSF drainage. AQP1 expression experiences downregulation in hydrocephalus mice model and upregulation after CSF drainage.

Key words: *Aquaporin* 1, AQP1, *Choroid plexus,* Hydrocephalus.

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INTRODUCTION

Hydrocephalus is a medical condition characterized by an anomaly in the production, circulation, and absorption of cerebrospinal fluid (CSF), resulting in disruptions in CSF flow and the enlargement of ventricles and the subarachnoid space. Hydrocephalus can occur as a congenital condition or be acquired due to factors such as infections, tumors, or intraventricular bleeding. In some cases, the cause of hydrocephalus may remain unknown, which is referred to as idiopathic hydrocephalus.[1] In neurosurgery, hydrocephalus is the most prevalent gender-neutral issue.[2] While the precise prevalence of this condition remains uncertain, it is worth noting that over 50% of surgical procedures conducted by pediatric neurosurgeons involve either the implantation or revision of shunts.[3] Meanwhile, hydrocephalus is found in as many as 40% to 50% of medical visits or neurosurgical operations in Indonesia.[4]

The theory of hydrocephalus postulated by Bulat states that changes in fluid in the central nervous system follow the same pattern as a fluid exchange in other parts of the body. This hypothesis relies on the underlying belief that water can permeate the brain parenchyma. The molecular mechanism behind this permeability primarily involves the presence of specific ion channels, specifically Aquaporin channels, which facilitate the passage of water. These channels can provide access to water without any movement of other ions. Aquaporin channel 1 (AQP1) is localized to the apical membrane of the *choroid plexus*.[5,6]

Aquaporins, a group of small integral membrane proteins commonly referred to as aquaporin water channels, are extensively distributed throughout various tissues. The basic structure of aquaporins is the same; the monomer consists of two short helical segments enclosing the cytoplasm and extracellular vestibules and six transmembrane helical segments joined by tiny aqueous holes. The functional identification of aquaporins, first discovered in the late 1980s, was further elucidated in 1992 through complementary RNA expression studies conducted in Xenopus oocytes. The main role of the majority of aquaporins is to facilitate the movement of water across the cell membrane, driven by the osmotic gradient generated by active solute transport. Since it was first discovered, a variety of Aquaporins have been identified in eukaryotic and prokaryotic organisms, totalling 300 species.[7]

Currently, 13 isomers (AQP0 – AQP12) have been found in humans. Aquaporins are classified into two subfamilies: classic aquaporins, which are selective for water, and aquaglyceroporins, which are channels for glycerol. Within the central nervous system, there are eight aquaporins that are expressed, namely AQP1, AQP3, AQP4, AQP5, AQP7, AQP8, AQP9, and AQP11. AQP1 and AQP4 are the primary aquaporins found in significant quantities and perform important functions within the central nervous system. AQP1 is found in the apical membrane of the choroid plexus, and its presence there emphasizes its role in facilitating the passage of water between cells for CSF formation. Because Aquaporin1 is considered to play a role

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in production, it is expected to be a viable target for hydrocephalus therapy. In this study, we explore how hydrocephalus and cerebrospinal fluid (CSF) drainage affect the manifestation of AQP1 in the choroid plexus using a rat model of hydrocephalus.[8]

MATERIALS AND METHODS

The study utilized Sprague-Dawley rats of the *Rattus norvegicus* species as a hydrocephalus model. These rats were aged between 8-10 weeks and weighed 150-200 grams. They were randomly assigned to six groups. The analysis in this study focused on the cerebrum as the examined unit. The normal control group consisted of Sprague-Dawley rats, aged 8-10 weeks, with body weights of 150-200 grams, which were not subjected to kaolin induction. The experimental animals were treated in accordance with the guidelines for maintaining laboratory animals, and they underwent a seven-day adaptation period. Hydrocephalus was induced by administering a sterile kaolin suspension.

Under sedation, the rats' necks were shaved to provide a clear view of the suboccipital region for the Kaolin injection. They were then positioned in a prone position on a 15 cm thick foam pad covered with an underpad. To aid the procedure, the rats' heads and necks were extended beyond the edge of the foam pad, ensuring parallel alignment with the pad's edge and a head flexion angle of around 90 degrees.

Before the injection, an aseptic procedure was carried out at the craniovertebral junction and nape of the neck using a 10% povidone-iodine solution. The neck is flexed until a palpable space between the first cervical vertebra and the occipital bone can be felt. The suboccipital cleft can be located by palpating the region between the occipital bone and the first cervical vertebra. However, one drawback of this method is the possibility of improper neck flexion, which may lead to a gap forming between the second and third cervical vertebrae or even lower. Once accurately identified, a 27G needle was employed to percutaneously administer a sterile kaolin solution (20% suspension in 0.9% saline) into the cisterna magna, with a volume ranging between 20-30 L.

Following the injection, the experimental animals were carefully observed and monitored until they fully recovered from the effects of the anesthetic drug. Once they regained consciousness, they were returned to their respective cages. The animals were subjected to standard maintenance conditions, including maintaining a 12-hour day/night cycle by adjusting the lighting. Adequate amounts of food and water were provided to ensure their well-being. The experimental animals were monitored daily for any physical signs and to ensure sufficient intake, particularly in terms of fluids.

The experimental animals underwent an assessment for hydrocephalus symptoms seven days after the induction of kaolin, which involved monitoring for signs such as alterations in gait, weakness in the hind limbs, and the presence of flattened hind limbs. After it was determined that every experimental animal had displayed physical evidence of hydrocephalus, the experimental units were randomly divided into six groups: the normal group, the hydrocephalus group on day 7, the hydrocephalus group on day 14, the hydrocephalus group on day 21, and the treatment group on day 14 and 21.

The hydrocephalus group was terminated seven days, 14th days, and 21st-days after the kaolin induction, and brain samples were taken to measure the levels of Aquaporin1. The first treatment group's CSF was drained on day seven following kaolin induction, and seven days later, termination and sampling were performed to measure Aquaporin1 levels. The second treatment group's CSF was drained on day 14 after kaolin induction, and seven days later, termination and sample were done to measure Aquaporin1 levels.

Drainage was performed by tapping the CSF with a 27 G needle. The installation location was on the frontal part of the rat in the anterior area of the bregma, according to the estimated coordinates. When using mice as experimental animals, the intended placement for the ventricular drain is 1 cm to the right lateral direction from the skull bone. It should be inserted perpendicular to the skull bone, with a depth of around 1.5 cm. This positioning aims to guide the ventricular tip into the lateral ventricle.

After termination, the samples were decapitated, cutting off the brain tissue and preparing slide preparations with IHC staining.

Brain sample preparation

Conventional methods were employed to prepare paraffin blocks from the excised rat brains. The brains were first wrapped in gauze and then subjected to a dehydration process at room temperature. This process lasted for 60 minutes and involved using a series of graded ethanol solutions, starting from 70% and progressively increasing to 80%, 90%, and finally 100% ethanol. Following the dehydration step, the brains underwent clearing by immersing them in xylol three times for 15 minutes each at room temperature. Following the cleaning procedure, the liquid paraffin infiltration was carried out three times, each taking 60 minutes and in a 60^{0}C incubator. To create a paraffin block, the tissues are submerged in liquid paraffin and chilled to room temperature.

IHC staining protocol

Immunohistochemistry (IHC) staining in this study refers to the method developed by Hsu *et al.* (1981), using the avidin-biotin-peroxidase complex (ABC) method.[9] The primary antibody used was Aquaporin1 polyclonal antibody for rats (SantaCruz Inc., USA). The tissue sections were blocked with endogenous peroxidase activated with 0.3% H_2O_2 in methanol for 30 minutes at room temperature. Non-specific binding of the reagent was blocked with 1% fetal bovine serum in PBS for 30 minutes at room temperature. Tissue sections were incubated with Aquaporin1 primary antibody (1:500) overnight at 4^{o}C. After washing with PBS 3 times, the slides were incubated for 30 minutes at room temperature with a biotinylated secondary antibody, streptavidin-HRP was added for 30 minutes at room temperature and given 3-3 chromogen, diaminobenzidine (DAB) substrate. The slides were washed in running water, given a background stain with haematoxylin, rehydrated, and covered with entellan. The tissues were observed under a light microscope with an objective magnification of 100x in five visual fields.

Statistical analysis

The gathered data underwent coding, tabulation, and entry into a computer system. Data analysis encompassed descriptive analysis and comparative tests. The evaluation of AQP1 intensity was conducted semi-quantitatively, with the choroid plexus AQP1 expression intensity in the normal group serving as a reference point. Statistical analysis of the data was performed using SPSS version 25 software. The normality of the data was assessed using the Shapiro-Wilk statistical test. Statistical test calculations were carried out using the Kruskal Wallis test because the data tested, namely the intensity of aquaporin expression, was in the form of an ordinal scale, namely low, medium, and high. The Mann-Whitney test was utilized to compare the two groups. It is considered significant if the test results have a p-value under 0.05.

RESULTS

This experimental study used 36 Sprague-Dawley rats divided into six groups, each containing six rats. Coding based on day of termination since kaolin induction. There was one normal group without kaolin induction (N), the hydrocephalus group on day 7 (K-7), the hydrocephalus group on day 14 (K-14), the hydrocephalus group on

day 21 (K-21), the treatment group on day 14 (P-14), and the treatment group on day 21 (P-21). These mice observed for signs of hydrocephalus based on the clinical changes, like enlargement of head circumference, back neck bumping, gait distturbance, and limb weakness.

Calculation of aquaporin expression according to the sample was obtained by examining brain tissue preparations, and IHC staining, observed under under a light microscope with a magnification of 100x. A positive Aquaporin1 reaction, characterized by a brownish response, was indicative of the presence of aquaporin expression. (Figure 1-5).

AQP1 expressions and comparisons result

A normality test was performed on Aquaporin1 expression values using the Shapiro-Wilk method, and an abnormal distribution was obtained. The Kruskal-Wallis test yielded a p-value of 0.002 ($p < 0.05$), indicating a significant difference among the six test groups in terms of the intensity value of aquaporin expression (Figure 6).

A comparative test of 6 groups using Mann Whitney compared the normal group with the hydrocephalus on days 7, 14, and 21. Then a comparison test was carried out between the hydrocephalus group day 7 with treatment group day 14 and hydrocephalus group day 14 with treatment group day 21. The test results showed that, in general, there were significant differences between the groups tested with a p-value of <0.05 (Figure 7). The Mann-Whitney comparison test showed that Aquaporin1 expression decreased with increasing age in hydrocephalus (hydrocephalus group days 7, 14 and 21) compared to the normal group. The intensity of Aquaporin1 expression in the group after drainage on day 7 was higher than before drainage on day 7. Aquaporin1 expression intensity in the group after drainage on day 14 was higher than before on day 14.

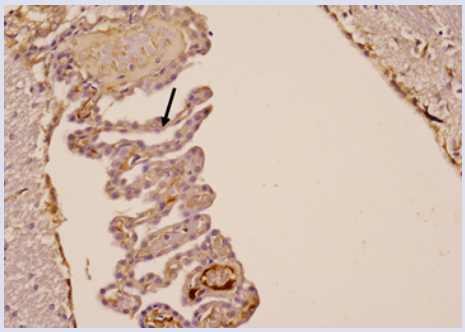

Figure 1: The IHC staining on cross-sections of rats in the hydrocephalus group on day seven was viewed under a microscope with 100x magnification. Black arrows indicate the *choroid plexus*, with brownish colour indicating Aquaporin1 expression.

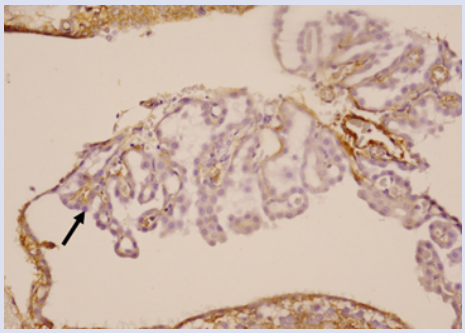

Figure 2: The IHC staining on cross-sections of rats in the hydrocephalus group on day 14 was viewed under a microscope with 100x magnification. Black arrows indicate the *choroid plexus*, with brownish colour indicating Aquaporin1 expression.

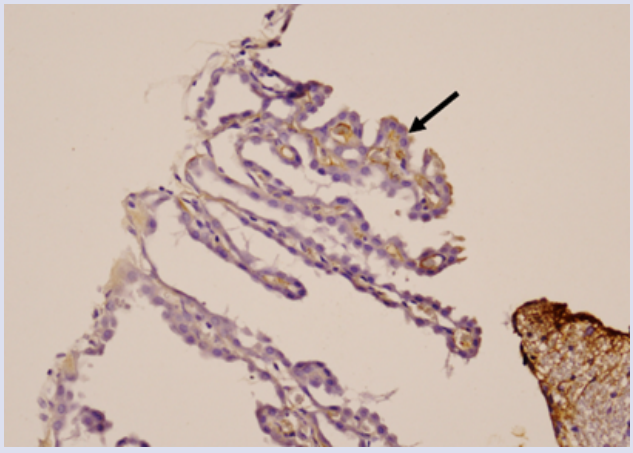

Figure 3: The IHC staining on cross-sections of rats in the hydrocephalus group on day 21 was viewed under a microscope with 100x magnification. Black arrows indicate the *choroid plexus*, with brownish colour indicating Aquaporin1 expression.

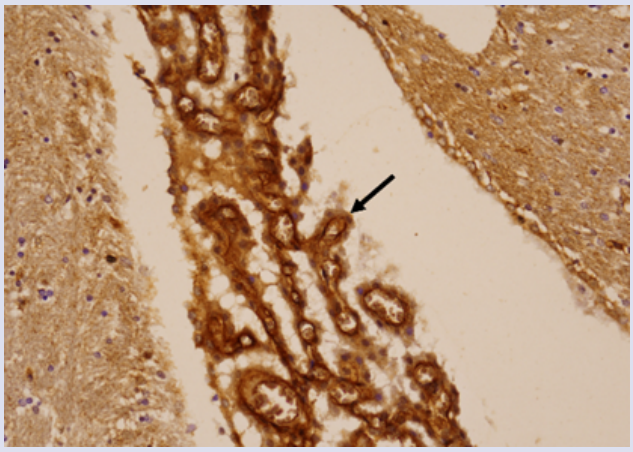

Figure 4: The IHC staining on cross-sections of rats in the treatment group on day 14 was viewed under a microscope with 100x magnification. Black arrows indicate the *choroid plexus*, with brownish colour indicating Aquaporin1 expression.

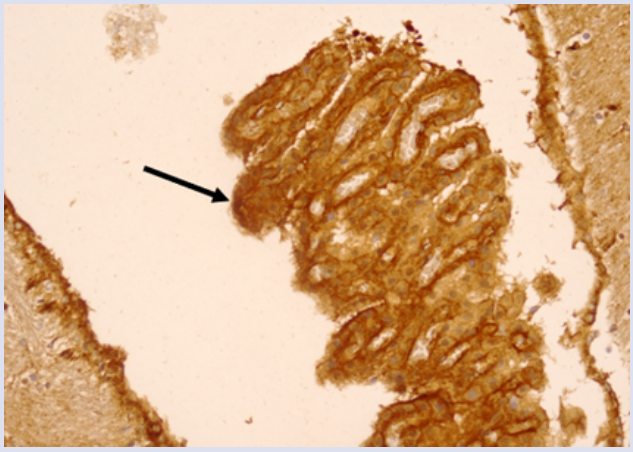

Figure 5: The IHC staining on cross-sections of rats in the treatment group on day 21 was viewed under a microscope with 100x magnification. Black arrows indicate the *choroid plexus*, with brownish colour indicating Aquaporin1 expression.

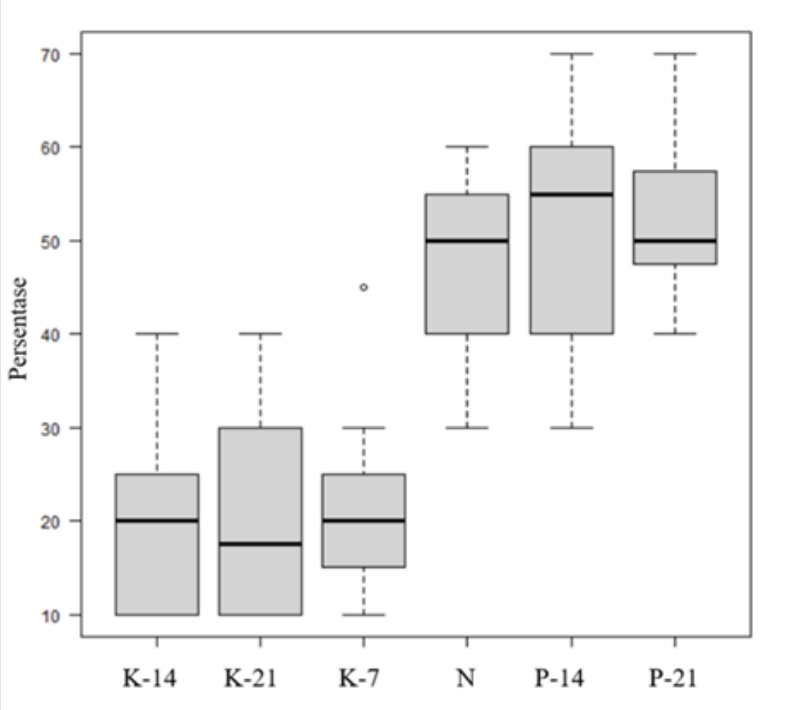

Figure 6: The Kruskal Wallis comparison test with a p-value of 0.002 (p <0.05).

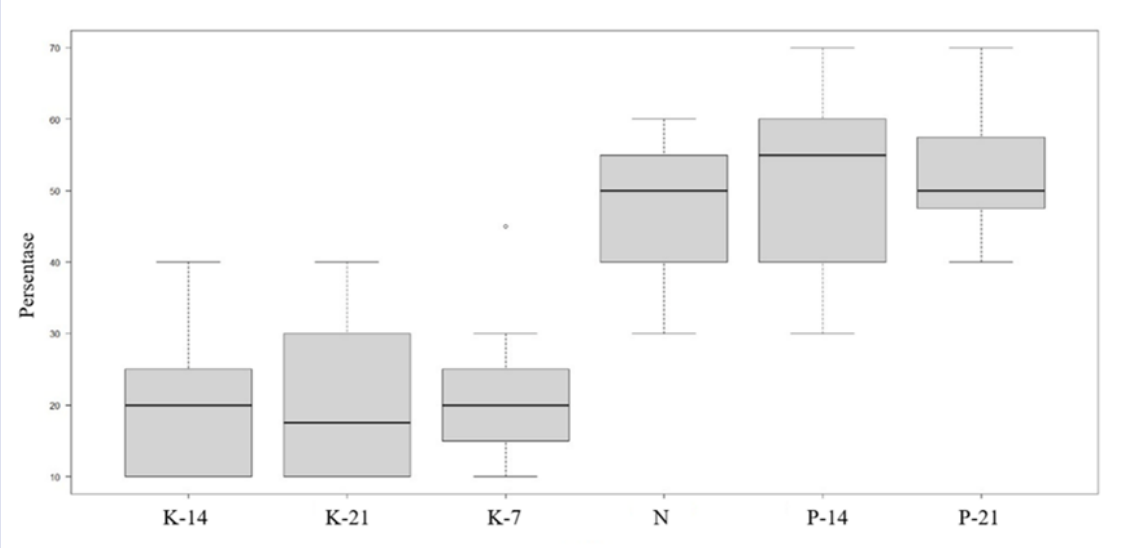

Figure 7: The Mann-Whitney comparison test (p<0.05).

DISCUSSION

This laboratory experiment aimed to investigate the impact of hydrocephalus and cerebrospinal fluid (CSF) drainage on the expression of AQP1 in the choroid plexus. The research involved mice as animal models, which have been reported in several previous studies due to its availability, and accessibility to breed and induced hydrocephalus.[10-12] The kaolin induction technique was chosen due to its simplicity. Kaolin will enter subarachnoid space and create an obstruction in fourth ventricle. Hydrocephalus is going to be obtained, and generally occurred on the 7th day after kaolin administered (mild-moderate), followed by ventricular enlargement macroscopically observed after 14th and 21st days kaolin administration.[13] Hydrocephalus, characterized by enlargement of the ventricles due to the progressive accumulation of cerebrospinal fluid, is a disorder in the CNS that can lead to a decrease in the neurological condition and quality of life of the sufferer.[14] The progression of hydrocephalus, its duration, its duration before treatment, and the structural changes in the CNS brought on by hydrocephalus all affect how quickly neurological problems deteriorate and how well people live their lives.[15] AQP1 specifically resides in the choroid plexus thought, by far, has contribution to the process of CSF production.[16]

The fundamental role of AQPs is to enable the transportation of water across the cellular plasma membrane. Each AQP channel consists of six alpha-helices that span the membrane and form a central pore specifically designed for the transport of water molecules. This pore

exhibits varying levels of permeability to accommodate the movement of water.[17] AQP plays a crucial role in maintaining water balance and facilitating water transport, possessing specialized channels that enable rapid water movement across cellular membranes.[17]

Predominantly found in the central nervous system, AQP1 is primarily located in the apical membrane of the choroid plexus. Its expression becomes evident soon after the development of the choroid plexus in embryonic stages and remains restricted to the apical membrane.[18] Furthermore, with the advancement of age, there is a potential decrease in the quantities of AQP1 within the choroid plexus. Moreover, AQP1 is present in diverse organs such as erythrocytes, salivary glands, myocardium, and renal tissues. When expressed in *Xenopus laevis* oocytes, AQP1 displays remarkably high osmotic permeability, manifesting a twentyfold augmentation in comparison to control oocytes.[18] The mechanism for increasing or decreasing AQP1 expression in hydrocephalus is still unclear. Gaining insights into how AQP1 reacts to alterations in cerebrospinal fluid (CSF) production and the development of hydrocephalus holds significant importance in assessing the potential for hydrocephalus treatment.

In our study, the expression of AQP1 served as an indicator of the activity of cerebrospinal fluid (CSF) production in hydrocephalus, considering its presence in the choroid plexus and its involvement in CSF generation. CSF production comprises both choroidal and extrachoroidal components. The active generation of cerebrospinal fluid (CSF) within the choroid plexus depends on the production and maintenance of an osmotic gradient, which is regulated by carbonic anhydrase and Na/K ATPase. AQP1, situated on the apical membrane, is thought to aid CSF in adhering to the osmotic gradient, thereby maintaining the permeability of the choroid plexus apical membrane. In a study conducted by Oshio *et al*., the focus was on examining how AQP1 contributes to the production of cerebrospinal fluid (CSF) and the regulation of intracranial pressure. The findings revealed that rats lacking AQP1 exhibited a decrease in CSF production by approximately 20% when compared to normal rats. CSF pressure also decreased by 56% compared to normal rats, which is thought to affect the lowering of central venous pressure in rats, although the mechanism cannot yet be fully explained. The contribution of AQP1 to CSF production is well known, but how AQP1 facilitates water transport is still unclear.[19] Another study by Bryan *et al*. related to AQP1 expression in rat models of hydrocephalus by kaolin injection showed no significant change in AQP1 expression compared to controls injected with normal saline.[20]

In this study, we compared the expression of AQP1 in a kaolin-injected mice model hydrocephalus. We grouped them into six groups based on the hydrocephalus induction time and the CSF drainage treatment. One normal group without induction as a comparison, three of induction hydrocephalus without CSF drainage, and two with CSF drainage. In the normal group and the group without CSF drainage, there were differences in the intensity of AQP1 expression, *i.e*., the intensity of expression decreased with increasing time after hydrocephalus induction. We analyzed with the Kruskal Wallis test and showed a significant difference with a p-value <0.05. The age-related decline in the hydrocephalus rat model is reflected in a notable reduction in the intensity of AQP1 expression.

In the group that underwent hydrocephalus induction and CSF drainage, it was found that the AQP1 expression was higher than in the group that induced hydrocephalus without CSF drainage. We analyzed this difference in expression with the Mann-Whitney comparison test and showed a significant difference with a p-value <0.05. These results indicated a significant increase in the AQP1 expression in the *choroid plexus* of hydrocephalus rats after CSF drainage.

The difference of AQP1 expression between hydrocephalus model rats that were not drained of and those that were drained of CSF shows the role of AQP1 in the production of CSF in the *choroid plexus* in hydrocephalus conditions. These results are in line with the study by Brian *et al*., which suggests a role for AQP1 in the production of CSF in the *choroid plexus*. The decreased AQP1 expression in the hydrocephalus model group without CSF drainage indicates the downregulation of AQP1 in hydrocephalus conditions which increases over time. The increased of AQP1 expression in the drained hydrocephalus rat model showed an upregulation of AQP1 expression after intracranial pressure is decreased.[20]

CONCLUSION

This study found significance different response of AQP1 expression in the *choroid plexus* of hydrocephalus mice model, with and without CSF drainage. AQP1 expression experience downregulation in the case of hydrocephalus, which lasted longer, and upregulation after CSF drainage, indicating that the severity of hydrocephalus affects AQP1 expression and the significance of immediate CSF drainage in cases of hydrocephalus. We conclude that due to significant role of AQP1 in CSF production it has potential indicator target in treatment of hydrocephalus.

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