Heliyon 9 (2023) e17621

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Dexamethasone for delayed edema after intracerebral hemorrhage : To be or not to be?

Yongqing Ye [a,b], Jin Xu [a,**], Yuhan Han [a,*]

[a] Department of Neurosurgery, The Affiliated Suqian First People's Hospital of Nanjing Medical University, Jiangsu Province, Suqian 223800, China
[b] Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Heilongjiang Province, Harbin 150000, China

ARTICLE INFO

Keywords:
Delayed cerebral edema
Dexamethasone
Blood-brain barrier
Neuroinflammatory
KLF2

ABSTRACT

The pathogenesis of delayed cerebral edema after intracerebral hemorrhage is still unclear. In this case report, we speculate that the formation of subdural effusion or hemorrhage is associated with delayed cerebral edema. By referring to the treatment plan of chronic subdural hematoma, adding dexamethasone to routine medication, certain therapeutic effect has been achieved. Dexamethasone may maintain the stability of blood-brain barrier by directly increasing the expression of ZO-1, and reduce the neuroinflammatory response caused by NF-κB pathway by upregulating KLF2 expression, ultimately reducing nerve injury through multiple pathways.

1. Introduction

Cerebral hemorrhage is a common and frequently occurring disease in nervous system diseases. It refers to cerebral parenchymal hemorrhage caused by cerebrovascular rupture caused by a variety of reasons. According to the causes of the disease, it can be divided into spontaneous and traumatic. Brain edema is a secondary pathophysiological process of brain tissue caused by a variety of physical damage, biochemical changes and other factors. The pathological manifestations are increased water in brain tissue, increased brain volume, resulting in intracranial pressure imbalance, and in severe cases, increased intracranial pressure, brain line shift, secondary brain hernia and even death. Brain edema is an inevitable pathophysiological process after intracerebral hemorrhage and an important cause of secondary injury after intracerebral hemorrhage [1]. At present, there are in-depth studies on brain edema after ICH, such as brain cell ischemia and hypoxia caused by the mechanical compression of mass effect, which leads to cytotoxic brain edema, or vasogenic edema caused by the damage of blood-brain barrier and the destruction of cell membrane by peroxide reaction. For the treatment of cerebral edema, current clinical guidelines mainly use mannitol, hypertonic saline, furosemide, and albumin alone or in combination to exert dehydration and reduce intracranial pressure [2–5].

For patients with intracranial hemorrhage, the treatment plan is determined according to the volume of hematoma and the site of occurrence. This article mainly discusses the surgical patients. At present, there is no report on the pathogenesis of delayed hematoma after intracerebral hemorrhage. In recent years, some views have suggested that delayed brain edema is associated with inappropriate use of mannitol. As an osmotic diuretic, mannitol's function depends on an intact blood-brain barrier. After the mannitol outflow

* Corresponding author. Department of Neurosurgery, The Affiliated Suqian First People's Hospital of Nanjing Medical University, Jiangsu Province, Suqian 223800, China.
** Corresponding author. Department of Neurosurgery, The Affiliated Suqian First People's Hospital of Nanjing Medical University, Jiangsu Province, Suqian 223800, China.
E-mail addresses: sjwkxj@163.com (J. Xu), hanyuhan1994@163.com (Y. Han).

https://doi.org/10.1016/j.heliyon.2023.e17621
Received 28 December 2022; Received in revised form 22 February 2023; Accepted 22 June 2023
Available online 28 June 2023

through the damaged blood vessels, brain cell osmotic pressure increased, prompting of water seepage of intravascular to normal brain tissue, leading to normal brain tissue edema. Others have suggested that delayed brain edema may be aggravated by the release of toxic products after erythrocyte lysis and extravasation caused by unbalanced pressure at the damaged site. On imaging findings, is different from acute edema (low density edema around the contusion or hematoma), late-onset edema of the lower density change can be far away from the original site or surgery area, present finger edema in hematogenously belt, this kind of phenomenon can cause compression of lateral ventricle, with the sulci structure disappears, the midline to the lateral deviation, severe cases can be produced because of the uneven pressure of cerebral hernia, Endangering the patient's life.

In terms of delayed cerebral edema after intracerebral hemorrhage, the use of dehydrating intracranial pressure lowering drugs could not produce good effects sometimes, and may be due to electrolyte imbalance aggravating the second blow. In clinical work, we found that the postoperative brain tissue expansion is incomplete, and there is a gap between the brain and the dura, which may produce subdural effusion or hematoma, and it may be related to the occurrence and development of delayed brain edema. In the medical record report, we learn the treatment of chronic subdural hematoma, combined with dexamethasone on regular medication, obtained good treatment effect, a significant reduction of cerebral edema on imaging, ventricular pressure disappears, midline shift, and avoid the second operation [6], at the same time to reduce the financial burden of the patients with good prognosis.

1.1. Case description

A 53-year-old female patient was admitted to the hospital on July 30, 2022 due to "right limb weakness with inability to speak for 3 hours". The patient developed right limb weakness and speech inability 3 hours before onset without obvious inducement. The patient also had frequent nausea and vomiting, which was non-ejection, and the vomit was gastric contents. Physical examination: T 36.7 °C, P 72 times/minute, R 17 times/minute, BP 146/80 mmHg, unconscious, GSC score: 6D (E2VDM4), bilateral pupils of equal size and equal circle, about 2.5 mm in diameter, pupillary light reflex exists. Neck is soft. Meningeal irritation is negative. Hemiplegia on the right side, positive pathological signs on the right side. The patient had a history of hypertension for 2 years, received nifedipine orally, and his blood pressure control was unknown. Imaging examination showed cerebral hemorrhage in the left basal ganglia (Fig. 1). CTA cerebrovascular examination showed no vascular abnormalities (Fig. 2).

On July 31, 2022, the patient underwent craniotomy for hematoma removal, and a subcutaneous drainage tube was placed. The dehydrating drugs were mannitol 125 ml q8h ivgtt, 0.9% sodium chloride solution 190 ml plus 10% concentrated sodium chloride 60 ml q12h ivgtt.

On the first day after operation, the patient was intubated with ventilator-assisted breathing, lethargy, speech disorder, unable to follow instructions, limb tingling and retraction, and subcutaneous drainage tube drained 140 ml of hemorrhagic fluid. CT

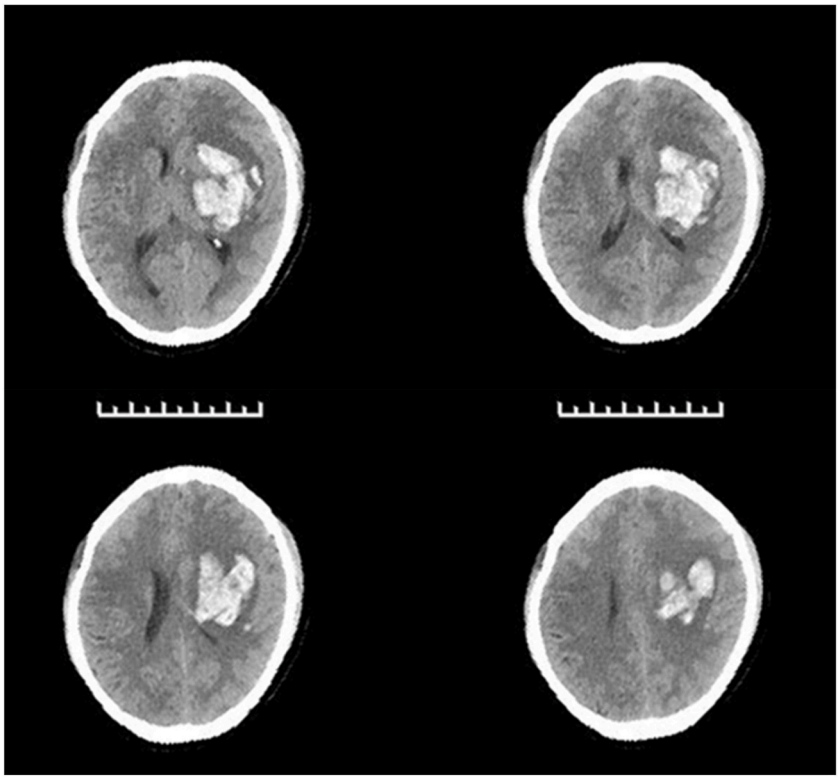

Fig. 1. Preoperative CT craniocerebral examination showed cerebral hemorrhage in the left basal ganglia.

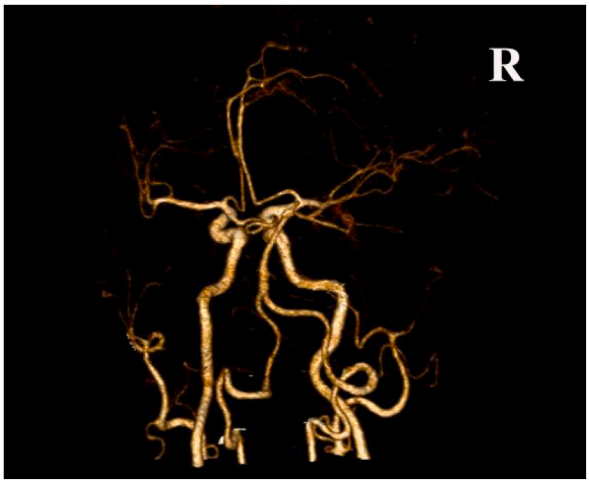

Fig. 2. CTA cerebrovascular examination showed no vascular abnormalities.

craniocerebral examination on the first postoperative day was shown in Fig. 3. On the second day after operation, the patient was lethargic and 50 ml of hemorrhagic fluid was drained by subcutaneous drainage tube, and the drainage tube was removed. On the third day after operation, the dosage of mannitol was adjusted to 125 ml q12h, and concentrated sodium chloride was treated as before. On the sixth day after operation, the patient had dyspnea and the pulse oxygen decreased progressively. A temporary tracheotomy was performed to keep the respiratory tract open and the posterior pulse oxygen gradually returned to normal. Postoperative treatment mainly included dehydration to reduce intracranial pressure, nerve nutrition, blood pressure control, enteral nutrition support and maintenance of internal environment stability, and other programs, and the patient's condition was stable. Imaging examination was performed on the 11th day after operation (Fig. 4).

On the 19th day after operation, the patient was in a shallow coma, and the state of consciousness was aggravated. CT examination showed postoperative changes, brain edema was advanced, adjacent ventricles were compressed, midline shifted to the right, and subdural effusion/hematoma on the left frontal and parietal (Figs. 5–6). The patient's family refused surgery. The patient was dehydrated with mannitol and concentrated sodium chloride, and added with dexamethasone 2.25mg qd. Continue to monitor vital signs and changes in consciousness.

On postoperative day 28, the patient was conscious, with GSC score of 10T (E4VTM6), bilateral pupils of equal size and equal circle, diameter of about 2.5 mm, left limb muscle strength of grade 4, right limb hemiplegia, bilateral muscle tension normal, and right

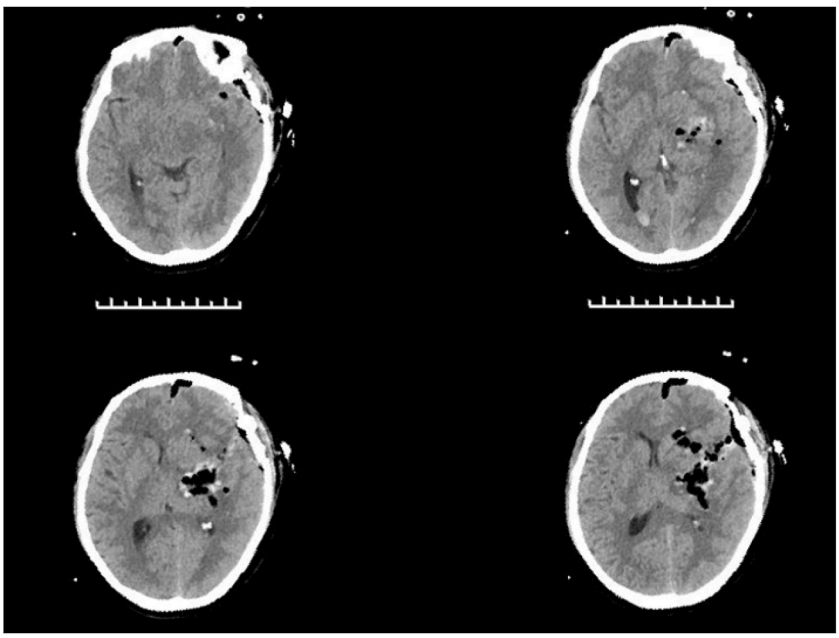

Fig. 3. On the first day after operation, CT craniocerebral examination showed postoperative changes.

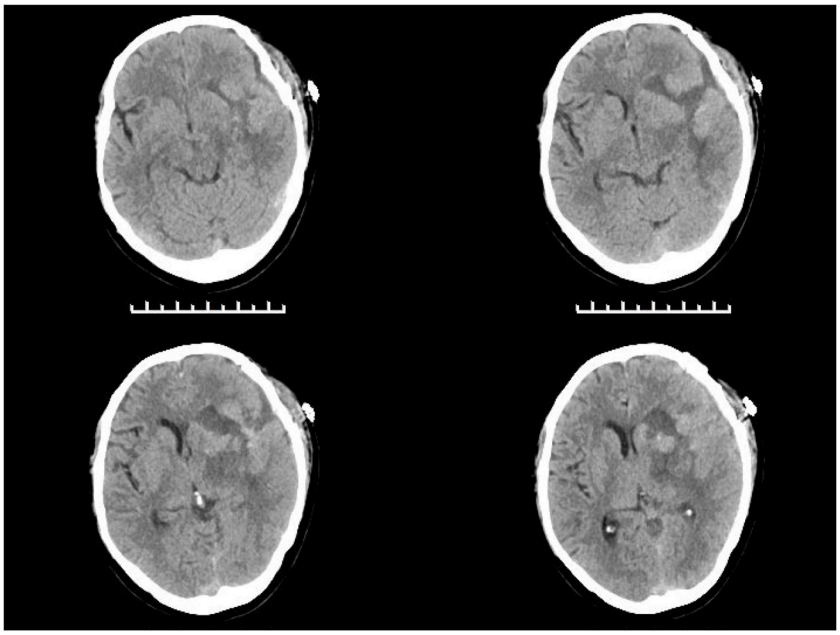

Fig. 4. On the 11th day after operation, imaging examination showed low-density shadow in the operative area and edema progression compared with the anterior image.

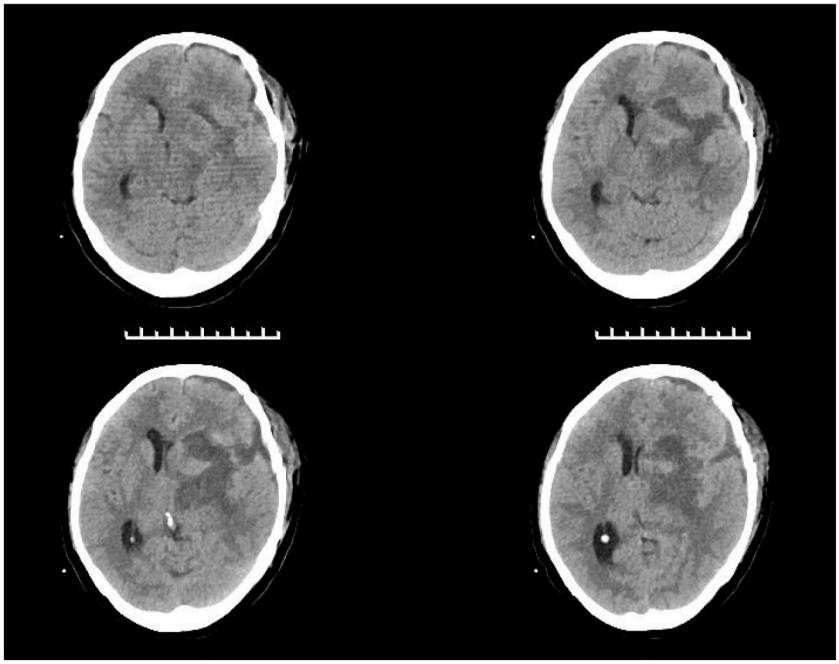

Fig. 5. CT head examination was performed on the 19th day after operation.

pathological signs positive. CT examination showed a small amount of bleeding in the right basal ganglia (Fig. 7). Later, the patient was transferred to the rehabilitation department for further treatment.

2. Discussion

After the surgical treatment of intracerebral hemorrhage, the brain tissue is difficult to reexpand due to long-term hematoma compression, and there is a gap between the brain and the dura, which may lead to the occurrence of subdural effusion or hematoma.

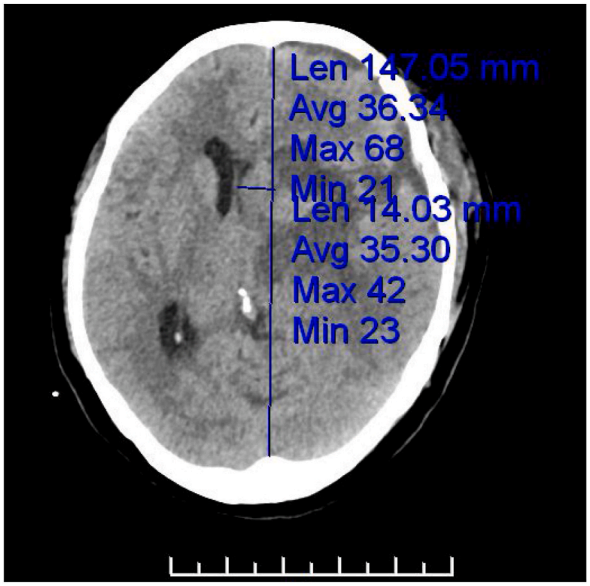

Fig. 6. The midline structure was shifted 14.03 mm to the right.

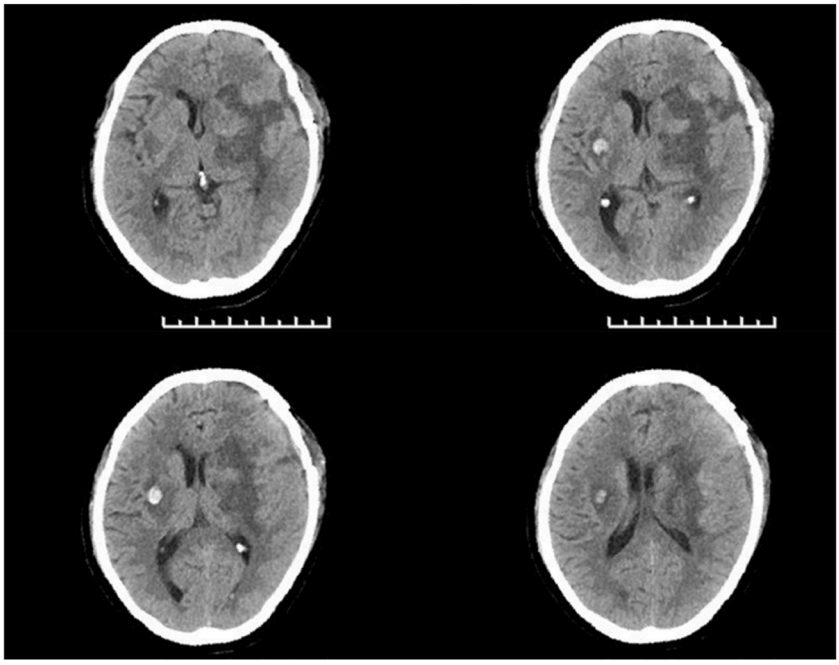

Fig. 7. On the 28th day after operation, CT head examination showed that cerebral edema was reduced, midline structure was generally normal, ventricular compression was improved, and subdural effusion/hematoma was absorbed on the left frontal and parietal.

This will not only produce local compression symptoms affecting neurological function, but may also lead to inflammatory cascades, creating a vicious cycle. In addition, blood may re-flow into the cleared cavity. Abnormal inflammation and neovascularization instability in the hematoma cavity are the main causes of neovascularization dysfunction, increased permeability, promoted blood leakage and gradually expanded hematoma, and accelerated the progression of delayed cerebral edema. In this case report, we learned from the experience of predecessors in the treatment of chronic subdural hematoma. For delayed cerebral edema after intracerebral hemorrhage surgery, we adopted routine medication plus dexamethasone, which saved the patient's life and avoided the second operation.

Dexamethasone is a glucocorticoid hormone that stabilizes cell membrane and lysosome activity, reduces endothelial cell damage,

reduces blood-brain barrier permeability, and reduces cerebral edema. At the same time, it can inhibit the lipid peroxidation of nerve cell membrane, reduce the inflammatory reaction after injury and protect the brain tissue.

Meanwhile, by studying the mechanism, we hypothesized that KLF2 plays an important role in the treatment of delayed cerebral edema after intracerebral hemorrhage. KLF2 is a Krüppel-like factor. Krüppel-like factors (KLFs) generally act as transcription factors in animals and have unique structures. The C-terminus of KLFs is a DNA-binding domain composed of three highly conserved C_2H_2 zinc finger structures, and adjacent zinc fingers are linked by the conserved sequence TGEKP(Y/F) X [7]. The N-terminal of KLF2 has an acidic protein motifs, which not only functions as a transcriptional activator, but also interacts with transcriptional repressors to exert transcriptional repression under certain circumstances [8]. KLF2 is highly expressed in endothelial cells and is an important inhibitory vascular protective factor, which can inhibit angiogenesis mediated by vascular endothelial growth factor and maintain hemodynamic stability through a variety of ways. Some studies have shown that the low expression of KLF2 is closely related to vascular permeability. In vitro studies found that after dexamethasone treatment, mouse endothelial cells showed different levels of high expression of ZO-1 and KLF2, suggesting that dexamethasone can protect the stability of the BBB and reduce exudation [9]. The NF-κB family consists of five different DNA-binding proteins, which are key regulators of innate and acquired immune responses and play important roles in cell proliferation, inhibition of apoptosis, stimulation of angiogenesis and metastasis. NF-κB can be activated rapidly in response to oxidative stress, proinflammatory cytokines and other stimuli. KLF2 and NF-κB are mutual antagonists. KLF2 can inhibit the induction of NF-κB-dependent genes, specifically, KLF2-mediated inhibition of NF-κB signaling leads to the suppression of cellular responses to proinflammatory cytokines and the attenuation of inflammatory processes [10]. These mechanisms suggest that dexamethasone can directly increase the expression of ZO-1 and inhibit NF-κB-mediated inflammatory response by upregulating the expression of KLF2, which are beneficial to weaken the initial factors of delayed brain edema and alleviate the secondary blow caused by the mass effect.

In addition, KLF2, a key regulator of brain endothelial function and cerebrovascular homeostasis, has been shown to function in vitro by regulating the key BBB tight junction factor occludin. It is gratifying that KLF2 can mediate neuronal protection from ischemia and hypoxia injury through multiple pathways. The experimental results suggest that KLF2 overexpression can inhibit neuronal apoptosis in vitro and in vivo by binding to interferon regulatory factor 4 (IRF4) promoter. Thus, IRF4 binding in histone deacetylase 7 (HDAC7) promoter is promoted to enhance its expression, thereby inhibiting neuronal cell apoptosis and brain injury [11]. Similarly, KLF2 reversed all effects of OGD exposure. KLF2 was found to significantly increase the levels of BDNF and TrkB in oxygen-glucose deprived cells, but these effects were blocked by the BDNF/TrkB inhibitor K252a. K252a also decreased cell viability and increased apoptosis, inflammatory cytokines, ROS production, and TLR2/TLR4 expression in oxygen-glucose deprived BV2 cells treated with KLF2, implying that K252a could reverse the effects of KLF2 on these cells. Our results suggest that KLF2 may protect BV2 microglia from OGD injury by activating the BDNF/TrkB pathway [12].

Although we have used this regimen in several patients with similar imaging findings or clinical symptoms, and achieved good results. However, there is the possibility of deviation due to the small sample data and short observation time, so it is still necessary to accumulate clinical data. More importantly, the presence of a hyperdense hemorrhage in the contralateral basal ganglia on postoperative day 28, as shown on imaging in this case (the patient was asymptomatic), remains to be determined whether this is associated with the use of dexamethasone, although similar findings have not been seen in other clinical cases.

3. Conclusion

By referring to the treatment strategy of chronic subdural hematoma, we used dexamethasone in the treatment of delayed cerebral edema after intracerebral hemorrhage, and the effect was remarkable. Dexamethasone can stabilize cell membrane and lysosome activity and reduce blood-brain barrier permeability. In addition, it can also directly promote the high expression of ZO-1 to maintain the stability of blood-brain barrier and increase the expression of KLF2. KLF2 plays a role by affecting BBB tight junction factor occludin, and reduces the impact of ischemia and hypoxia on nerve cells through BDNF/TrkB and IRF4/HDAC7 pathways. Although dexamethasone treatment has achieved certain effects, sample accumulation and continuous monitoring of immune function are still needed to reduce adverse effects.

Statement

We have complied with all relevant ethical regulations for work with human participants, and that informed consent was obtained. Guardian of this patient provided written informed consent. The human study was approved by the Ethics Committee of the Affiliated Suqian First Hospital of Nanjing Medical University [No. 2021-KYSB-0076].

Fundings

This work was financially supported by the Medical Research Project of Jiangsu Provincial Health Commission (M2020081), the Suqian Sci & Tech Program (Grant No. K202104), and the Science and Technology Development Fund of Nanjing Medical University (NMU20210294).

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Only imaging data is included in the manuscript and is available.

Declaration of competing interest

The authors have no conflict of interests.

Abbreviations

ZO-1	Zonula occludens-1
KLF2	Krüppel-like factors 2
ICH	Intracerebral hemorrhage
CTA	Computed tomography angiography
EVM	Eye opening/Verbal response/Motor response (Glasgow Scale for details)
BBB	Blood brain barrier
OGD	Oxygen and glucose deprivation

References

[1] S. Michinaga, Y. Koyama, Pathogenesis of brain edema and investigation into anti-edema drugs, Int. J. Mol. Sci. 16 (2015) 9949–9975, https://doi.org/10.3390/ijms16059949.
[2] A.M. Cook, et al., Guidelines for the acute treatment of cerebral edema in neurocritical care patients, Neurocrit Care 32 (2020) 647–666, https://doi.org/10.1007/s12028-020-00959-7.
[3] Y.Y. Deng, et al., Progress in drug treatment of cerebral edema, Mini Rev. Med. Chem. 16 (2016) 917–925, https://doi.org/10.2174/1389557516666160304151233.
[4] R.M. Jha, et al., Emerging therapeutic targets for cerebral edema, Expert Opin. Ther. Targets 25 (2021) 917–938, https://doi.org/10.1080/14728222.2021.2010045.
[5] J.A. Stokum, V. Gerzanich, K.N. Sheth, W.T. Kimberly, J.M. Simard, Emerging pharmacological treatments for cerebral edema: evidence from clinical studies, Annu. Rev. Pharmacol. Toxicol. 60 (2020) 291–309, https://doi.org/10.1146/annurev-pharmtox-010919-023429.
[6] P.J. Hutchinson, et al., Trial of dexamethasone for chronic subdural hematoma, N. Engl. J. Med. 383 (2020) 2616–2627, https://doi.org/10.1056/NEJMoa2020473.
[7] J.S. Presnell, C.E. Schnitzler, W.E. Browne, KLF/SP transcription factor family evolution: expansion, diversification, and innovation in eukaryotes, Genome Biol Evol 7 (2015) 2289–2309, https://doi.org/10.1093/gbe/evv141.
[8] N.M. Pollak, M. Hoffman, I.J. Goldberg, K. Drosatos, Kruppel-like factors: crippling and un-crippling metabolic pathways, JACC Basic Transl Sci 3 (2018) 132–156, https://doi.org/10.1016/j.jacbts.2017.09.001.
[9] D. Wang, et al., Atorvastatin combined with dexamethasone promote hematoma absorption in an optimized rat model of chronic subdural hematoma, Aging (Albany NY) 13 (2021) 24815–24828, https://doi.org/10.18632/aging.203717.
[10] K.T. Turpaev, Transcription factor KLF2 and its role in the regulation of inflammatory processes, Biochemistry (Mosc.) 85 (2020) 54–67, https://doi.org/10.1134/S0006297920010058.
[11] F. Wu, C. Li, KLF2 up-regulates IRF4/HDAC7 to protect neonatal rats from hypoxic-ischemic brain damage, Cell Death Discov 8 (2022) 41, https://doi.org/10.1038/s41420-022-00813-z.
[12] J. Zhou, M. Wang, D. Deng, KLF2 protects BV2 microglial cells against oxygen and glucose deprivation injury by modulating BDNF/TrkB pathway, Gene 735 (2020), 144277, https://doi.org/10.1016/j.gene.2019.144277.