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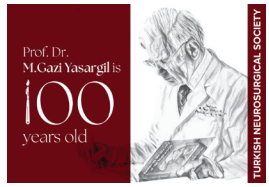

A Two-Step Therapeutic Strategy in the Management of Critical Neonatal Hydrocephalus

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ABSTRACT

AIM: To identify novel therapeutic strategies to improve the outcomes of neonatal hydrocephalus.

MATERIAL and METHODS: The treatment strategies for cases of neonatal hydrocephalus in our hospital between February 1, 2015, and February 1, 2024 reviewed and analyzed, with the aim of identifying valuable factors to assist in treating future patients with critical neonatal hydrocephalus. We further conducted literature searches and summarized the relevant treatment strategies.

RESULTS: A total of 64 neonates were included. The causes of hydrocephalus by case number were as follows: 59.1% due to cerebral hemorrhage, 24.0% due to intracranial infection, and 16.9% due to other causes. Additionally, 32.8% of patients had ultra-low birth weight (ULBW), 14.1% had very low birth weight (VLBW), and 53.1% had low birth weight (LBW). Preterm babies comprised 84.3% of all patients, whereas term babies comprised only 15.7%. Additionally, all treatments for patients involved surgery, with 3.06% undergoing endoscopic third ventriculostomy (ETV), 29.59% undergoing ventriculoperitoneal shunt (VPS), 32.65% undergoing extra-ventricular drainage (EVD), 1.53% undergoing ventriculoatrial shunt (VAS), and 20.41% undergoing Ommaya reservoir. Based on the collected information, we propose a novel two-step surgical treatment process for intensive neonatal hydrocephalus. In the first step, the patient's physical status (weight and corrected gestational age) is improved and intracranial infection or bleeding are controlled. In the second step, a permanent shunt is placed once the patient meets the surgical criteria.

CONCLUSION: Based on our experience, we proposed a two-step treatment strategy for the surgical management of critical neonatal hydrocephalus. Moreover, we clarified the detailed criteria for each step of the treatment plan to promote a higher success rate in saving children's lives. The prognosis of critical neonatal hydrocephalus can be favorable if appropriately treated.

KEYWORDS: Two-step therapeutic strategy, Critical neonatal hydrocephalus, Surgical management, Prognosis

ABBREVIATIONS: CPC: Choroid plexus cauterization, **CPE:** Choroid plexus epithelial, **CSF:** Cerebrospinal fluid, **ETV:** Endoscopic third ventriculostomy, **EpCs:** Dysfunctional ventricular cells, **ETVSS:** ETV Success Score, **EVD:** Extra ventricular drainage, **iNPH:** normal pressure hydrocephalus, **IVH:** Intraventricular hemorrhage, **LBW:** Low birth weight, **NEL:** Neuroendoscopic lavage, **NTDs:** Neural tube defects, **ULBW:** Ultra-low birth weigh, **VAD:** Ventricular access device, **VAS:** Ventriculoatrial shunt, **VL:** Ventricular lavage, **VLBW:** Very low birth weight, **VP:** Ventriculoperitoneal, **VPS:** Ventriculoperitoneal shunt, **VPS35:** Vesicular protein sorting-associated protein 35, **VSGS:** Ventriculo-subgaleal shunt

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INTRODUCTION

Hydrocephalus is a common disease, characterized by abnormal cerebrospinal function, which commonly leads to abnormal ventricular expansion (37). The clinical manifestations of this condition vary with age (37), although signs of enlarged fetal ventricles can be detected using prenatal ultrasonography after 18 weeks of gestation (24). Hydrocephalus in infants represents a major public health problem. The estimated incidence of congenital and acquired infant hydrocephalus ranges between 80 and 125 cases per 100,000 births, varying by region (56). The epidemiological complexity of hydrocephalus in infants varies globally, with different causes in different regions, primarily linked to the income level of the population. High birth rates in low-income regions can lead to a higher incidence of hydrocephalus in infants. However, advanced healthcare resources help to reduce this burden in other regions (24). Infants with hydrocephalus commonly present with abnormal enlargement of the head circumference, irritability, vomiting, bulging of the fontanel, or separation of the cranial sutures (68). After infancy, hydrocephalus generally presents as headaches, vomiting, and developmental delays. Hydrocephalus significantly affects neurocognitive and motor development in children (49), and neuroimaging plays a central role in the early diagnosis and evaluation of hydrocephalus (3).

Neonatal hydrocephalus is caused by various factors. Intracranial hemorrhage, infections, benign and neoplastic lesions, genetic predisposition, neural tube defects (NTDs), anatomic structure abnormalities, and cerebrospinal fluid circulation disorders can all result in neonatal hydrocephalus (27,42,44, 54,63,65).

Newborns, particularly premature infants, have low body weight and immature body functions. In this patient group, hydrocephalus is often extremely critical. Although some patients with hydrocephalus and a known cause may have favorable outcomes, patients with complex and critical hydrocephalus often face more significant treatment difficulties. However, timely and effective treatment can help to ensure a good prognosis. Patients with untreated hydrocephalus exhibit high morbidity and mortality rates (5).

Guidelines published in the *Journal of Neurosurgery* in the updated 2020 version based on the existing literature regarding hydrocephalus treatment state that the criteria for surgical intervention for patients with hydrocephalus vary based on the individual characteristics of each patient, including weight, physical condition, and clinical presentation (8,22). Permanent surgical treatments, transient surgical interventions, and transient non-surgical interventions are all considered treatment options. Permanent surgical interventions for hydrocephalus include overcoming an obstruction using neuroendoscopy (e.g., endoscopic third ventriculostomy) or shunt placement to affect cerebrospinal fluid (CSF) diversion from production within the ventricle to absorption in the body cavity, most commonly in the peritoneum, atrium, or pleural cavity. However, permanent CSF diversion is associated with a high risk of failure and often necessitates reintervention (29). Transient surgical interventions for hydrocephalus include continuous and intermittent CSF drainage. Continuous CSF drainage can be achieved by placement of an external ventricular drain (EVD) or creation of a ventriculosubgaleal shunt (VSGS), whereas intermittent CSF drainage can be induced by serial lumbar punctures, serial transfontanelle aspiration, or placement of a transcutaneous tappable reservoir (29). The removal intraventricular bleeding debris by neuroendoscopic lavage (NEL) has also been prospectively studied in the international multicenter "TROPHY" study (59). Temporary non-surgical medical interventions include medications such as acetazolamide and hyperventilation (29).

This article summarizes the cases of neonatal hydrocephalus treated at our hospital from February 1, 2015, to February 1, 2024. We further outline our two-step treatment strategy for such patients, analyze the indications, efficacy, and surgical complications of critical neonatal hydrocephalus, and evaluate the treatment outcomes. The aim of this study was to offer new insights into the appropriate timing of surgery in intensive care newborns with hydrocephalus.

MATERIAL and METHODS

Patient Selection

In this article, we reviewed the diagnostic and therapeutic data of neonatal hydrocephalus patients admitted to our hospital between February 1, 2015, and February 1, 2024. A total of 64 cases of neonatal hydrocephalus were screened as the study subjects. All patients were treated at our hospital and met the following inclusion criteria: diagnosed with hydrocephalus within 28 days after birth, in a critical condition, and required surgical treatment. As this study comprised only a retrospective analysis of anonymized data, there was no risk of breaching patient confidentiality or causing medical harm. As such, this study was approved by the Ethics Committee of the University of Affiliated Hospital, and the requirement for informed consent was waived. The ethical review number is 202403680421.

Data Collection

Comprehensive patient information was retrieved from the hospital medical record management system. These data included information related to the patients' medical history, sex, weight, gestational age, history of prematurity, Apgar score, type of surgery, and prognosis. Key data included gestational age, weight, surgical modality, and final treatment outcomes. The outcome indicators included symptomatic improvement and improved imaging performance.

Therapeutic Strategies

This article summarizes the appropriate treatment strategies for patients with critical neonatal hydrocephalus. The treatment plan for each patients was individualized according to the patient's condition, gestational age, corrected gestational age, weight, and other factors. Neonatal hydrocephalus is commonly associated with complications and requires comprehensive treatment. The detailed treatment process of our patients is illustrated in Figure 1. In the initial phase of treatment, we provided symptomatic supportive therapy to help

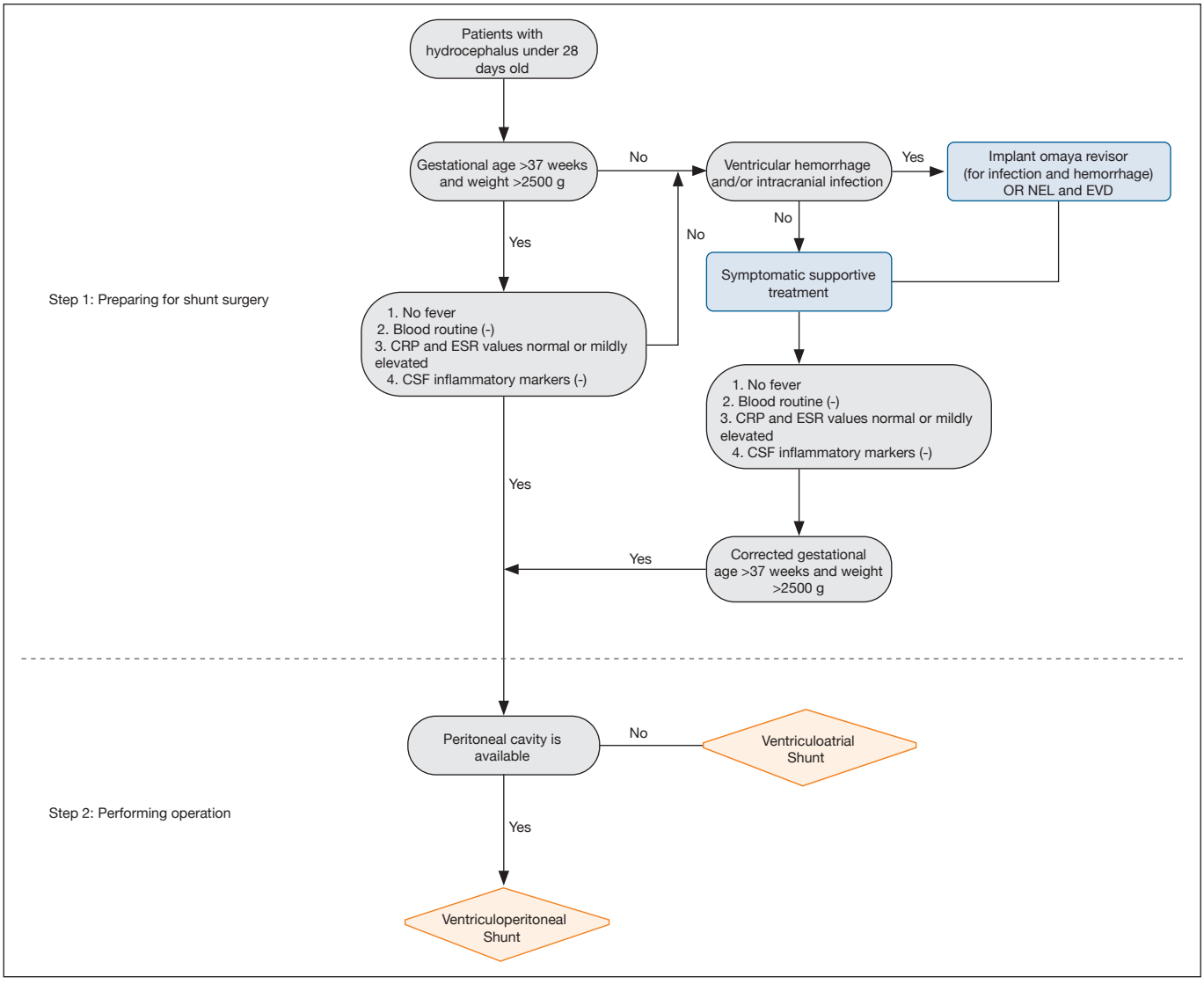

Figure 1: Surgical flow chart of the two-step treatment strategy for critical neonatal hydrocephalus. The ovals indicate the current condition of the child, the rectangles indicate the different treatments, and the contents of the diamonds indicate the different surgical procedures. **CRP:** C-reaction protein, **ESR:** Erythrocyte sedimentation rate, **CSF:** Cerebrospinal fluid, **NEL:** Neuroendoscopic lavage, **EVD:** Extra ventricular drainage, **VPS:** Ventriculoperitoneal shunt, and **VAS:** Ventriculoatrial shunt.

patients meet the necessary conditions for physical well-being (gestational age or corrected gestational age > 37 weeks and weight > 2,500 g). If the patient experienced a concurrent intracranial infection or ventricular hemorrhage during this stage, the Ommaya revision could be implanted, or neuroendoscopic lavage and external ventricular drain could be implemented to improve that condition. Once the patient's physical condition advanced to the second stage, ventriculoperitoneal shunt surgery was performed.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics version 25. Means and standard deviations were used to represent continuous variables, and frequencies and percentages were used to represent categorical variables. Statistical significance was set at $p<0.05$.

RESULTS

Demographics and Etiologies of 64 Patients

After careful screening, 64 patients with critical neonatal hydrocephalus were included in this study, of whom 38 were male and 26 were female. Among them, 21 were ultralow-weight neonates, 9 were very-low-weight neonates, and 34 were low-weight neonates. The gestational age at birth was < 37 weeks in 54 patients and > 37 weeks in 10. Detailed demographic information is provided in Table I. Of these neonates, 42 had hydrocephalus due to intracranial hemorrhage, 17 had intracranial infection, and 12 had cerebral hemorrhage of unknown origin. Some patients had both intracranial hemorrhage and infection, while double counting of the etiologies of hemorrhage and infection was performed.

Table I: Demographics and Etiologies of 64 Patients

Sex	No. (%)	Weight	No. (%), Mean ± SD	GA	No. (%), Mean ± SD	Apgar Scores	No. (%)	Etiology	No[1]. (%)
M	38 (59.4)	<=1000g	21 (32.8), 895.2 ± 120.7319	<37W	54 (84.3), 29.466 ± 3.6027	0-3	0 (0)	hemorrhage	42 (59.1)
F	26 (40.6)	<=1500g	9 (14.1), 1176.6 ± 137.0219	>=37W	10 (15.7), 37.993 ± 0.8649	4-7	10 (15.6)	infection	17 (24)
		<=2500g	34 (53.1), 2448 ± 615.1062			8-10	54 (84.4)	others	12 (16.9)
Total	64 (100)		64 (100)		64 (100)		64 (100)		71 (100)

M: *Male,* ***F:*** *female,* ***g:*** *gram,* ***GA:*** *Gestational age,* ***W:*** *week.*
1: Since some patients had both intracranial hemorrhage and infection, there was double counting of the etiology of the hemorrhage and infection.
In fact, the total number of patients with hydrocephalus of different etiologies remained at 64. However, the proportion of different etiologies was calculated according to the total count (including those with repeated counts, i.e. the value of the total count was 71).

Surgical Management of 64 Patients

Following implementation of our two-step treatment strategy, 61 children had a good prognosis, including three who did not receive further systematic treatment because their guardians abandoned them, with an overall improvement rate of 95.3%. Forty patients underwent external ventricular drainage (EVD) with the Ommaya Reservoir, 61 underwent EVD alone, 58 underwent ventriculoperitoneal shunt (VPS), 3 underwent ventriculoatrial shunt (VAS), 6 underwent endoscopic third ventriculostomy (ETV), 15 underwent NEL, and 10 underwent choroid plexus cauterization (CPC). Ultimately, 61 patients experienced relief and improvement of symptoms, while three patients voluntarily discontinued treatment and were requested to be discharged. Detailed information is presented in Table II.

Table II: Surgical Type and Surgical Numbers for 64 Patients

Surgical Type	No[1]. (%)
NEL	15 (7.65)
ETV	6 (3.06)
CPC	10 (5.10)
EVD	64 (32.65)
Ommaya reservoir	40 (20.41)
VPS	58 (29.60)
VAS	3 (1.53)
Total	196 (100.00)

NEL: *Neuro endoscopic lavage,* ***ETV:*** *Endoscopic third ventriculostomy,* ***CPC:*** *Choroid plexus cauterization,* ***EVD:*** *Extra ventricular drainage,* ***VPS:*** *Ventriculoperitoneal shunt,* ***VAS:*** *Ventriculoatrial shunt.*
1: *Duplicate counts exist for some procedures as some patients underwent multiple surgical treatments. As a practical matter, the total number of patients with hydrocephalus remains 64. However, some patients may have had multiple surgeries. the total number of surgeries for all patients was 196. The proportion of different types of surgeries was calculated using the formula: (count of a specific kind of surgery/196) x 100%.*

Procedure of Surgical Management

After searching and analyzing the treatment process of patients with critical neonatal hydrocephalus and performing a review of the literature, we summarized our two-step strategic process for treating critical neonatal hydrocephalus.

In this two-step strategy (shown in Figure 1), treatment goals were defined at each step to improve patient prognosis. For such patients, specific management strategies should be adopted, while reasonable timing of surgery is important. We selected one typical cases to validate the proposed surgical treatment procedure, as outlined below.

Illustrative Case

The patient's perioperative head circumference and imaging manifestations are illustrated in Figure 2. The exemplar case was that of a child born on November 30, 2022, at an outside hospital after 26 weeks of gestation, with a birth weight of 1000 g. Five days later, the patient was diagnosed with cerebral hemorrhage and hydrocephalus (Figure 2A,F). The patient was admitted to our hospital on December 23, 2022. The corrected gestational age was 30 weeks. The patient received supportive treatment after admission, and her condition gradually stabilized. On January 10, 2023, at 32 weeks' corrected gestational age, the patient's health indicators improved, and she underwent an Ommaya revision implantation to drain the intracerebroventricular blood (Figure 2B). Subsequently, the patient received intensive care and supportive treatment until March 9, when a corrected gestational age of 40 weeks was reached. Ventriculoperitoneal shunt surgery was performed under general anesthesia (Figure 2C), and the patient's general condition was stable postoperatively. On June 28, the patient's clinical symptoms and imaging manifestations had significantly improved (Figure 2D,G). Approximately one year later, the patient returned to the hospital to undergo a fol-

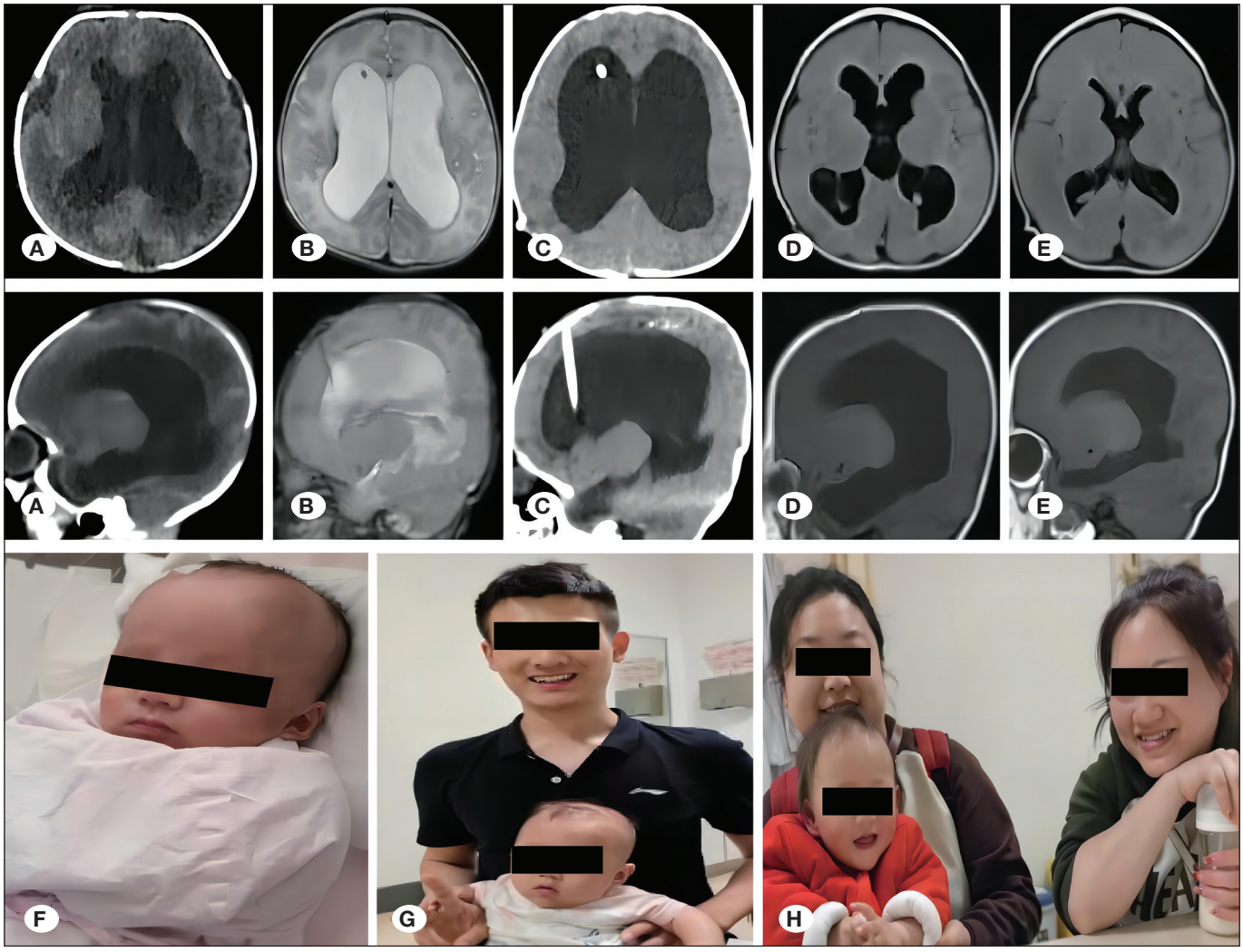

Figure 2: Radiographic and superficial presentation of typical cases at different time points during the perioperative process. **A&F:** Two sections of the patient before operation I showing the enlargement of ventricle expanded head circumference performance. **B)** Two section of patient after ommaya revisor implantation. **C)** Two section of patient after Ventriculoperitoneal shunt(VPS). **D&G)** 4 months after VPS indicating the normal ventricles and the performance of the child's reduced head circumference. Information of patient were erased to avoid leaking information. Patient information was erased to avoid leaking information. **E&H)** 1 year after VPS indicating the normal ventricles and the satisfaction of parents. Patient information was erased to avoid leaking information.

low-up examination. Her cognitive status had improved in the intervening period, and her morphology and size were normal (Figure 2E). The parents expressed their satisfaction with the treatment (Figure 2H).

DISCUSSION

Neonatal hydrocephalus is a chronic pathological condition that significantly affects the cognitive function and motor development in children, consequently inflicting significant burdens on the entire family. As such, it is crucial to address overall family support and functionality in early interventions (2,67). In this context, one study surveyed the families of several patients who had undergone shunt surgery, identifying various perinatal and clinical factors which significantly affected patients' quality of life (33). Treatment for hydrocephalus generally requires CSF shunt surgery. Most newborns with hydrocephalus generally require surgical intervention as treatment (10,29). Current surgical treatments include VSGS, NEL, EVD, Ommaya reservoir implantation, ETV, VAD (ventricular access device), and any combination of these approaches (29). In clinical practice, prevention and management of infection are essential to ensure successful treatment. As such, optimization of the appropriate timing of therapeutic interventions and disease management is necessary (18). Of these treatment strategies, VSGS and NEL are the two effective modalities for hydrocephalus following brain hemorrhage. NEL is a promising surgical technique for treating hydrocephalus (25). Sometimes combining these two treatment options reduces the risk of infection and multiatrial hydrocephalus (23,30). Early neuroendoscopic ventricular irrigation has been shown to be a fea-

sible and safe therapeutic option that effectively reduces the incidence of complications (e.g., intracranial infections and polycystic hydrocephalus) in neonatal hydrocephalus patients (20). Indeed, one meta-analysis showed that patients treated with ventricular lavage (VL) showed significantly reduced incidences of shunt dependence and risk of infection (48). Multiventricular hydrocephalus is more common in premature infants with meningitis and intraventricular hemorrhage (IVH). To date, the pathophysiological mechanism underlying intraventricular membrane formation remains unclear, although some studies have suggested that it may be related to an inflammatory response or chronic shunting (4). In addition, various complications, such as hydrocephalus, commonly accompany myelomeningoceles. Patients with myelomeningoceles have a higher risk of infection than those with other diseases requiring shunt surgery. Early shunt surgery as well as the use of small valves may further reduce the incidence of complications (35). Placement of a ventriculoperitoneal (VP) shunt is the primary method for diverting CSF in patients with access to neurosurgical care. However, if the peritoneal cavity is not suitable, other distal sites for CSF drainage include the pleural cavity and right cardiac atrium (36). Moreover, intracranial glymphatic system studies have shown that shunt surgery may improve glymphatic system disorders among patients with idiopathic normal pressure hydrocephalus (iNPH) (57).

In addition to surgical treatment, certain medications can prevent acute crises in specific cases. Acetazolamide was the most commonly used drug, and has been hypothesized to reduce CSF formation by modulating AQP-4 in the choroid plexus (62). Additionally, osmotic diuretics can be used during the acute phase (6).

Animal models of hydrocephalus can replicate human hydrocephalus to some extent, aiding in the investigation of its pathophysiology and the development of potential non-surgical treatments (6,43). In animal models, dilatation of the ventricles is associated with the loss of epithelial cells, proliferation of astrocytes, and scarcity of the peripheral white matter (12). Studies have also shown that iron-mediated free radical production is involved in hydrocephalus following IVH, suggesting that iron metabolism is a key pathway involved in the alterations of CSF circulation (11,16,26,40,51,70). One prior review provides a comprehensive overview of the role of choroid plexus epithelial (CPE) cells in the development of hydrocephalus; among these, multiple transporter proteins located in the parietal and luminal membranes have been extensively investigated and may be novel therapeutic targets (69).

Regardless of the etiology, neonatal hydrocephalus has a universally significant negative effect on perinatal myelination in animal models and patients (7). The pro-inflammatory reactions associated with microglia may also affect oligodendrocyte function and mediate the hypomyelination phenotype in neonatal hydrocephalus (1,19). Hydrocephalus following germinal matrix hemorrhage is also common. Gliosis after hemorrhage disturbs normal cerebrospinal fluid dynamics, while the redistribution of vascular pulsation may be an essential factor in the development of hydrocephalus (38). Dysfunctional ventricular cells (EpCs) are believed to promote hydrocephalus. Indeed, Wu et al. suggested that vesicular protein sorting-associated protein 35 (VPS35) could prevent neonatal hydrocephalus by promoting the differentiation and survival of EpCs, while inhibiting microglial activation (66). Indeed, patients with surgically treated neonatal hydrocephalus develop varying degrees of neuroinflammation and long-term neurological deficits, and therefore require additional pharmacological therapy (34). Bindarit inhibits the nuclear factor (NF)-kB pathway in response to various inflammatory stimuli. Improvement in neuroinflammation is critical to ensure white matter and neuronal maturation in neonatal hydrocephalus. Studies on the use of bindarit in combination with surgical treatment with CSF shunts have indicated that this strategy may provide long-term benefits for neuronal improvement in neonatal hydrocephalus (34).

At present, there are currently no complete set of standards for the surgical treatment of neonatal hydrocephalus, with significant differences observed in clinical practice (13). For example, Cohen and Flibotte discussed the different intervention timings and methods applied, calling for more randomized controlled trials to further clarify the benefits of early intervention and explore new treatment methods to improve the prognosis of premature infants (14). However, extensive research has shown that the timing of shunt surgery and choice of weight threshold for patients with hydrocephalus should be evaluated individually on a case-by-case basis (53,55,58,64). Indeed, one study suggested that one of the indications for shunt surgery is a weight between 1800 and 2000 g (58). Some studies have outlined more stringent indications for surgery in neonates with lower birth weights and gestational age (46,47), with others showing that neonates with birth weights less than 1500 grams commonly experience multiple perinatal complications (52). Unfortunately, the literature on the role of neonatal weight thresholds in maintaining shunt function is limited.

Neonates with critical neonatal hydrocephalus usually have very low birth weight and poor health status. Extremely and very preterm babies included newborns born at 32 weeks of gestation (28). Babies who are not born at full term miss a critical part of their neurodevelopment, as weeks 24–40 of gestation represent a critical period for brain development (31). In addition, preterm infants are prone to cerebral hemorrhagic complications, which can lead to hydrocephalus (41). Because hydrocephalus following intracerebral hemorrhage is often highly critical and complex, multidisciplinary cooperation is essential for course management (15).

Treatment of hydrocephalus has several obstacles. First, critically ill neonatal patients tolerate surgery poorly. Secondly, even when surgery is attempted, the prognosis is often poor, making the management of neonatal hydrocephalus even more challenging. Based on our therapeutic experience, we take a two-stage approach for the management of critical neonatal hydrocephalus. The first step was to proactively create conditions for future surgery. At this stage, our treatment goals were to control the infection, increase weight, advance the gestational age, clear the cerebrospinal fluid, and enhance the body's ability to tolerate surgery. During this period, infants continue to develop a relatively stable environment that

is critical for their health and well-being. Once babies are older than 37 weeks and weigh more than 2500 g, their overall health improves, and they become more resistance to surgery. The second step of our treatment strategy involved relieving hydrocephalus and performing a final shunt surgery.

The final treatment for hydrocephalus is limited to a VPS and ETV (61); however, their application must be individualized (37). Current research has indicated a high rate of ETV failure in newborns and infants (45,60), which may be related to anatomy (60). VPS is thus the primary treatment for hydrocephalus. However, age and weight remain crucial factors influencing shunting success, particularly in neonates (17). As arachnoid granulations are not yet fully mature, ETV surgery is not recommended for children younger than 6 months (45). Studies have suggested that the ETV Success Score (ETVSS) could be used to meaningfully select good candidates for ETV (39). The ETVSS is a means of predicting ETV success based on the calculation of scores ranging from 0 (extremely low opportunity for ETV success) to 90 (extremely high opportunity for ETV success). With the increasing use of ETV in clinical practice, the ETVSS has been further utilized to measure the prognostic impact of factors, such as age and etiology, enabling a more accurate prediction of ETV success. Therefore, this study was performed based on a review of previous studies and our clinical experience. In patients with intensive neonatal hydrocephalus, high-risk factors such as low body weight, hemorrhage, and infection make them unsuitable for surgical treatment with ETV. In summary, VP shunts are commonly used to treat pediatric hydrocephalus (32). VP shunt surgery is effective at improving neurological outcomes in patients with hydrocephalus (9,50,71). Among the various risk factors associated with shunt failure, patient age, etiology of hydrocephalus, type of hydrocephalus, and timing of surgery may all play a role (22). Therefore, in this study, we proposed a two-step strategy for the treatment of neonatal patients with critical hydrocephalus, aiming to achieve optimal surgical indications for the patient, resulting in a favorable prognosis.

CONCLUSION

Neonatal hydrocephalus is a common complication of neurosurgery for which early diagnosis is crucial to ensure patients receive timely treatment. By analyzing and summarizing our experience with the treatment of neonatal hydrocephalus, we found that timely and reasonable treatment commonly results in a good prognosis for patients with critical neonatal hydrocephalus. We hope that our two-stage surgical treatment procedure will provide new insights into the treatment of neonatal hydrocephalus.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: GX
Data collection: QO, JW
Analysis and interpretation of results: YY, KW, YxY
Draft manuscript preparation: QO
Critical revision of the article: GX, MH, ZZ
All authors (QO, JW, YY, KW, YxY, MH, ZZ, GX) reviewed the results and approved the final version of the manuscript.

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