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Original Article

A multi-center study of neuro-endoscopic treatment for ventricular infection

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Abstract: Treatment of ventricular infection is challenging. Parenteral antibiotic therapy has limited efficacy owing to the blood brain barrier. Other treatment options like intraventricular irrigation and intrathecal injection of antibiotics have a limited role owing to complications. In this study we investigate a novel minimally invasive neuroendoscopic approach for treatment of infection of ventricular system. A total of fourteen patients (9 male and 5 female) with ventricular infection were enrolled in the study. All patients were assessed and treated via neuroendoscope. The infection severity was evaluated, followed by removal of the intraventricular sediment and mural pus. Through the help of reserved bilateral drainage tubes, postoperative irrigation with antibiotic saline was carried out for a period of two to four weeks. Additionally, in patients with hydrocephalus, ventriculoperitoneal (VP) shunt operation or endoscopic third ventriculostomy (ETV) was also performed. One patient died of respiratory failure, and the remaining thirteen patients were cured with a mean Glasgow outcome scale (GOS) grade of 2.8±0.9. Among the nine patients with hydrocephalus, five underwent VP shunt, three received ETV, and one underwent VP shunt after a failed attempt at ETV treatment. The duration of follow-up period ranged from 5 to 22 months (median 12.5 months), and no recurrence of ventricular infection was reported. Our results suggest the potential of neuroendoscope as a valuable tool for assessment and treatment of ventricular infection. Postoperative continuous irrigation with antibiotic saline appears to have a key role in achieving favorable outcomes using this method.

Keywords: Antibiotic irrigation, hydrocephalus, neuroendoscope, ventricular abscess, ventricular system infection

Introduction

Intractable ventricular infection is a serious complication associated with a high attendant disability and mortality. Diagnosis and treatment of ventricular infection is inherently challenging. The key challenges include, lack of effective antibiotic drugs that can traverse the blood-brain barrier (BBB) to achieve optimal therapeutic concentration in the target lesions. The efficacy of simple intraventricular irrigation or intrathecal injection is limited by complications like subarachnoid adhesion, inflammatory septum, intraventricular abscess, mural pus, and deposits [1-3]. In this study, we present our experience with the use of a novel surgical approach using neuroendoscope for managing fourteen patients with ventricular infection. The treatment outcomes and sequelae have been analyzed.

Materials and methods

The study was approved by the Institutional Review Board and Ethics Committee of multi-center institutions. The cohort included 14 patients (9 male and 5 female) with ventricular infection in Beijing Shijitan Hospital, Peking Union Medical College Hospital, Peking University Third Hospital, Beijing Tongren Hospital and the Second Affiliated Hospital of Nanjing Medical University, from March, 2010 to March, 2013.

Clinical presentation

The average age of participants at the time of surgery was 35.4 years (range 26-46 years). All

Table 1. Clinical characteristics of the fourteen patients with ventricular infection

Parameters	Value
Male/Female (n)	9/5
Age at time of surgery (mean ± SD, years)	31.4 ± 7.4
Age at onset (mean ± SD, years)	28.2 ± 5.9
Duration [median (range), years]	0.6 (0.1–1.5)
Blood pressure	
Systolic pressure (mean ± SD, mmHg)	126.3 ± 7.55
Diastolic pressure (mean ± SD, mmHg)	76.4 ± 6.54
Symptoms and signs (n)	
Fever	14
Intracranial hypertension	10
Spasm	3
Consciousness disorders	2
Meningeal irritation	8
Ventricular dilation	9
CSF leukocyte count (mean ± SD, $\times 10^9$)	4.460 ± 1.140
Peripheral blood indexes	
Leukocyte count (mean ± SD, $\times 10^9$)	1.357 ± 0.640
Neutrophile granulocyte (mean ± SD, %)	73.7 ± 10.23

patients had received systemic antibiotics for a period of one to six months before the neuroendoscopic intervention which failed to control the ventricular infection. The infection-related interventions included endoscopic third ventriculostomy (ETV) in three cases, ventriculoperitoneal (VP) shunt in nine cases, VP shunt along with ommoya capsule implantation in one case, and pituitary adenoma resection via transsphenoidal approach in one case.

The major clinical manifestations included fever (14 cases with a temperature ranging from 37° to 42°C), symptoms of intracranial hypertension including headache and vomiting (10 cases), seizures (three cases), altered sensorium (two cases), and signs of meningeal irritation such as neck stiffness (eight cases). The clinical profiles are summarized in **Table 1**. Computed tomography (CT) and magnetic resonance imaging (MRI) showed ventricular dilatation in nine patients, linear enhancement of ventricular wall in eight patients, intraventricular fibrous septum in eight patients and intraventricular abscess in three patients.

Laboratory investigation

The peripheral blood leukocyte count was elevated in 13 patients (range, 13×10^9 to 31×10^9/L), and serum C-reactive protein (CRP) was elevated in all patients (15.5 to 89.6 mg/L). The cerebrospinal fluid (CSF) showed turbid appearance in 12 patients; Pandy's test was positive in all patients; CSF leukocyte count was increased in all the patients (100 to 9600×10^6/L); CSF total protein level was increased in 11 patients (512 to 2400 mg/L); the glucose level was reduced in 12 patients (15 to 21 mmol/L), and the chloride level was reduced in 11 patients (76 to 115 mmol/L). Bacterial culture was positive in all patients, including six cases of *Staphylococcus epidermidis*, three cases of *Staphylococcus aureus*, three cases of *Enterococcus faecium*, five cases of *Pseudomonas aeruginosa*, four cases of *Klebsiella pneumonia*, two cases of *Aerobacter cloacae*, and five cases of mixed bacterial infection.

Surgical approach

A four-channel ventriculoscope (Aesculap Inc. Germany) with the external diameter of 6 mm and working length of 15 cm was used. The internal diameter of endoscope channel, instrument channel, flush and the drainage channel was 2.8 mm, 2.2 mm, 1.4 mm, and 1.4 mm respectively. The viewing angle of endoscope was 30°.

Perioperative intraventricular irrigation was performed with antibiotic saline. The antibiotic therapy was guided by bacterial sensitivity testing and the ability to penetrate blood-brain barrier (BBB). The intrathecal concentration obtained was maintained between $1/10^{th}$ and $1/20^{th}$ of that achieved with systematic administration. Under general anesthesia, the intraventricular structures were explored with neuroendoscope through a frontal horn approach. The intraventricular sediment, mural pus and inflammatory funicular fiber were cleared; the inflammatory septum was recanalized; the wrapped drainage tube was dissociated from choroid plexus or purulent fibrous bundles; intraventricular abscess was either removed by complete en bloc resection or drained by fenestration. An external drainage tube was reserved for postoperative antibiotic-saline irrigation. Perioperative irrigation of ventricle with antibiotic saline was maintained throughout the procedure. Patients with co-existing hydrocepha-

Table 2. Radiological findings and outcomes

Characteristics	Numbers
Radiological appearance (n)	
Ventricular size normal	4
Ventricular size reduced	2
Ventricular size unchanged	3
The ventricular wall linear enhancement disappeared	5
The ventricular wall linear enhancement alleviated	3
Intraventricular abscess disappeared	2
Intraventricular abscess linear enhancement	1
Complications (n)	
Subcutaneous effusion	3
Subdural effusion	3
Intracranial pneumatosis	5
Incision infection	0
CSF leakage	0

lus underwent a further CSF bypass surgery (ETV or VP shunt).

Follow up and prognosis

Follow-up data of patients were obtained during individual office visits or through telephonic interviews. Immediate postoperative MRI was followed up by repeat MRI scans at discharge, and semi-annually or annually thereafter. The Glasgow outcome scale (GOS) was used for the objective assessment of the patient's recovery in five categories. The clinical symptoms and neurological functions were assessed independently by three neurosurgeons, and reviewed by another evaluator.

Results

Clinical and radiological data

The intracranial hypertension was resolved in the nine cases. Altered sensorium was significantly alleviated in two cases, and signs of meningeal irritation resolved in eight cases. Among the nine patients with secondary hydrocephalus, five underwent VP shunt, three received ETV and one underwent VP shunt, after failure of ETV treatment. Among the nine patients with ventricular dilation, repeat CT brain and MRI showed normalization of the ventricle size in four patients; reduced ventricular size in two patients and lack of any change in three patients. The linear enhancement of ventricular wall disappeared in five cases, and alleviated in three cases. Out of the three patients with intraventricular abscess, abscess was completely resolved in two patients following complete resection, while one patient showed linear enhancement following fenestration drainage (**Table 2**).

Laboratory findings in the postoperative period

The blood leukocyte counts and CRP values returned to normal in all the study participants. The CSF was rendered colorless and transparent in ten patients, while in four patients, a yellowish hue was retained. The Pandy's test returned negative in all the patients. The CSF leukocyte counts were 0 to 10×10^6/L, total protein counts were 0 to 40 mg/L, the glucose level was 22 to 40 mmol/L, and the chloride level was 120 to 135 mmol/L. No abnormal bacterial growth was detected from CSF culture.

Postoperative complications

Three patients in this cohort developed a subcutaneous effusion while three patients developed subdural effusion and five patients developed intracranial pneumatosis. No instance of skull wound infection, CSF leakage or other ETV-related severe complication was reported. Further, no blockage, infection or rejection reaction was reported in any of the patients (**Table 2**).

Follow-up data

The follow-up period ranged from 5 to 22 months, and no recurrence of ventricular infection was reported. The trapped fourth ventricle, detected in one patient following VP shunt, was treated by ETV with aqueduct plasty. Apart from this exception, favorable treatment outcomes were achieved in all patients. One patient died of respiratory failure, while the remaining thirteen patients were cured with a mean GOS grade of 2.8±0.9.

Discussion

The ventricular system infection is a serious complication affecting neurosurgical patients with a reported incidence rate of 0.2 to 1%, and in a large proportion of cases, the causality of

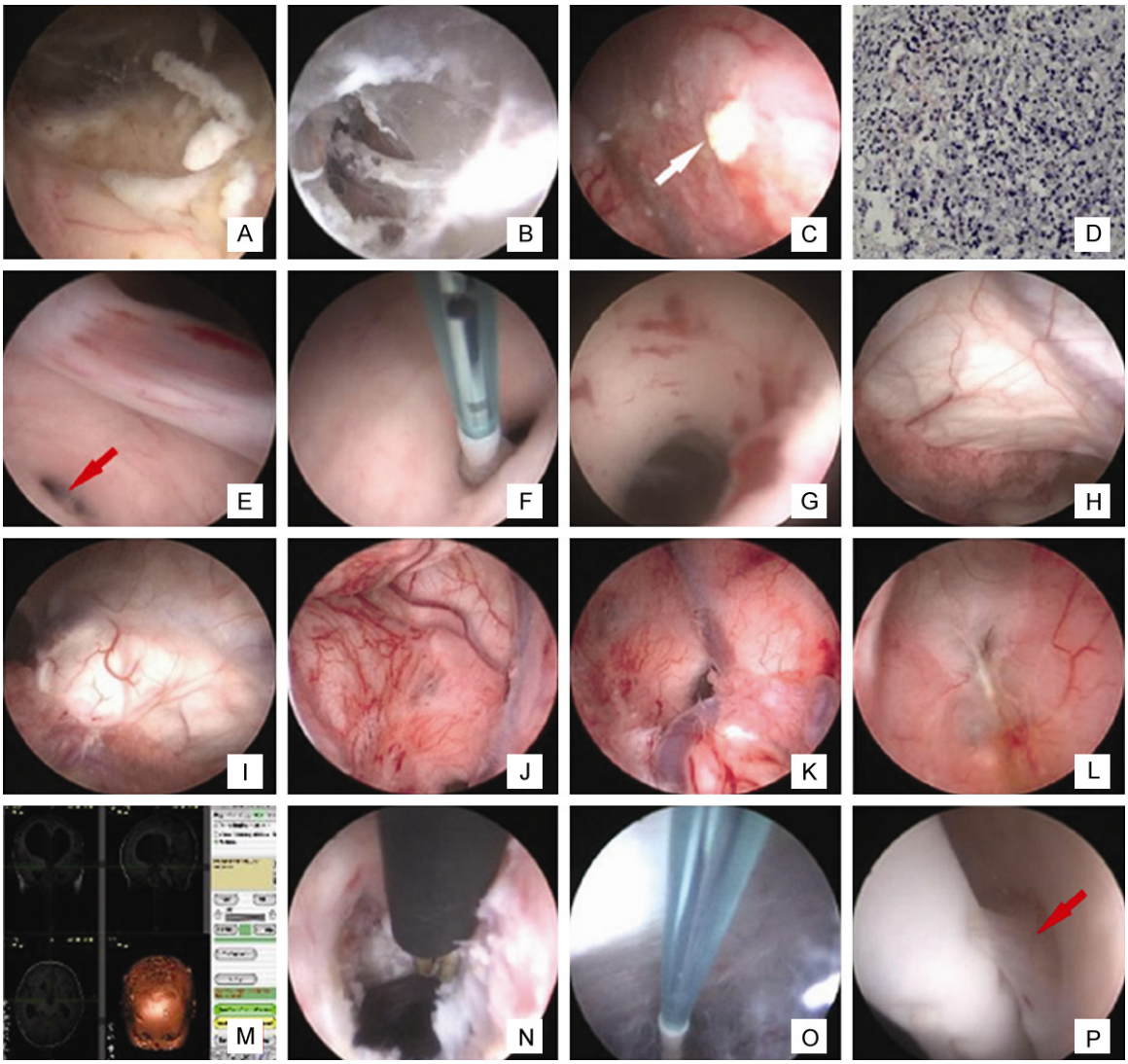

Figure 1. A, B: Neuroendoscope showing intraventricular sediments and funicular fibers. C: Particulate ependymitis in the internal wall of the ventricle (white arrow). D: Pathological examination of ventricular sediments and fibrous trabs showing inflammatory cell infiltrations and few astrocytes. E: An atresia of mid-brain aqueduct (red arrow) F, G: The recanalization of the atretic mid-brain aqueduct and aqueduct plasty was performed. H, I: Internal wall of the ventricle before lavage with antibiotic saline. J, K: Angiectasis and apparente hyperemia in the internal wall of ventricle following 2-week lavage. L: Illegible anatomic landmarks at the bottom of the third ventricle induced by ventricular infections. M: Intraoperative neuronavigation guaranteed the safety and efficacy. N: Following successful fistulization, stomal plasty was performed on patients with incrassated third ventricle. O: Neuroendoscopy in basal cistern via fistula, and traversing it thoroughly to rebuild the cerebrospinal fluid (CSF) circulation. P: Adhesion between the ventricular terminal of the tube and the ventricular wall (red arrow).

ventricular infection has an iatrogenic component [1, 4, 5]. The traditional therapeutic approach to the treatment of ventricular infection has relied on intrathecal and systemic use of antibiotics and lumbar cistern drainage with a poor prognostic outlook. Treatment of ventricular infection is challenging owing to several peculiar factors. These include the selective permeability of blood brain barrier (BBB), the inflammatory septum and development of deposits in ventricles. Concomitant hydrocephalus, if present, aggravates the clinical condition.

Endoscopic neurosurgery

Minimally invasive interventions have a special relevance in neurosurgery, with endoscopic

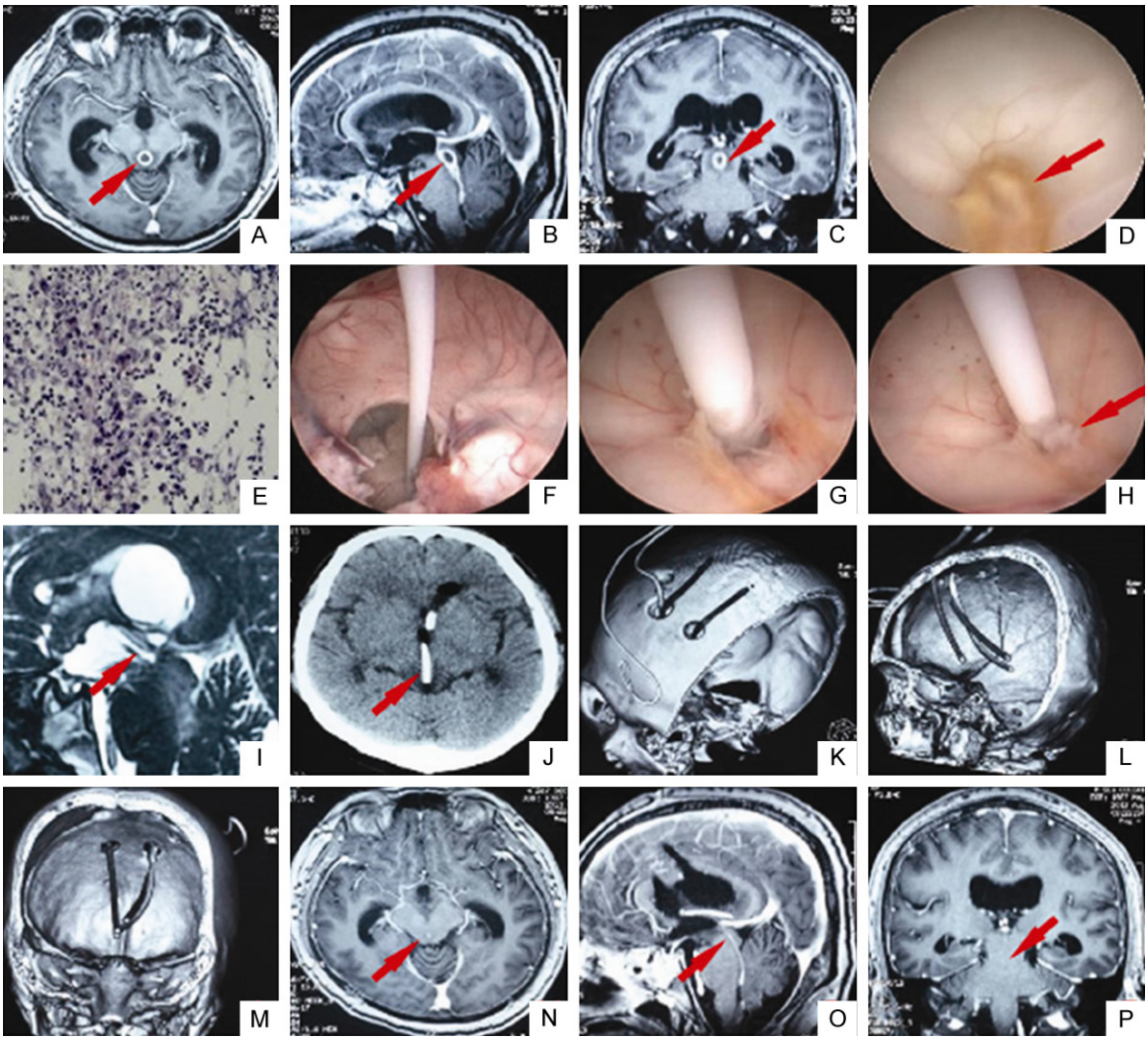

Figure 2. A-C: Enhanced magnetic resonance (MR) images showing abscesses in the midbrain aqueduct and the fourth ventricle, presenting as annular contrast enhancement in the midbrain aqueduct (red arrow), and narrowing fourth ventricle with linear contrast enhancement. D: Yellow tissue sediments observed in the ingress of midbrain aqueduct (red arrow). E: Pathological examination showing inflammatory cell infiltration. F: Implantation of drainage tube into third ventricle through the right foramina of Monro. G: Implantation of drainage tube into the abscess. H: Overflowing pus from the aqueduct following the infusion of antibiotic saline through drainage tube (red arrow). I, J: Magnetic resonance T2 weighted images and CT scan showing implantation of drainage tube into the abscess through the ingress of midbrain aqueduct (red arrow). K-M: Brain three-dimensional (3D) reconstruction CT showing the drainage tubes. N-P: Enhanced MR images showing the disappearance of the annular contrast enhancement in aqueduct and the residual linear enhancement in aqueduct and the fourth ventricle (red arrow).

neurosurgery being especially suited for ventricular interventions owing to the distinct advantage of superior exposure. The advantages of using endoscope for the diagnosis and treatment of ventricular infections are manifold: 1) It allows for a better visual evaluation of the severity of infection (**Figure 1A-D**); 2) The intraventricular mural pus and funicular fiber can be efficiently removed through the endoscope; 3) With the aid of postural maneuvering and use of gravity, the endoscope allows for efficient removal of ventricular sediment, tissue dross as well as sludged blood from hard-to-approach areas like third ventricle and temporal and occipital horns of lateral ventricle; 4) It allows for manual recanalization of both inflammatory septum and the atresia of interventricular foramen or midbrain aqueduct, thus improving the CSF circulation and facilitating better irrigation of antibiotic saline (**Figure**

1E-G); and 5) The intraventricular abscess can be effectively drained under endoscope, including complete *en bloc* resection and the fenestration drainage. The complete abscess resection procedure was used for abscesses located around the drainage tube or those in functionally unimportant regions; fenestration drainage is suitable for the patients in which abscess adheres tightly to the important structures such as brain stem. In the present study, two cases with peritubal abscess underwent complete resection, while another case in which abscesses were located in midbrain aqueduct and the fourth ventricle, received fenestration drainage, the postoperative MRI showing continuous linear enhancement (**Figure 2**). The neuroendoscopic treatment of ventricular infections usually require multi-stage surgical approach. The clinical outcome in the present cohort is significantly better than that treated with systemic and intraventricular antibiotics reported in the literature [6, 7].

Perioperative ventricular irrigation with antibiotic saline

Antibiotic therapy for ventricular infection requires several considerations [8, 9]. 1) Systemic administration of antibiotics may not be able to achieve optimal concentrations in CSF owing to the BBB. Besides, antibiotic resistant is a common challenge and particularly in long standing cases. The hepatic and renal function may be affected due to the long-term use of antibiotics. 2) Intrathecal injection of antibiotics via lumbar puncture is an invasive procedure with a high risk of complications. The strict restriction of dosage of drugs administered through this route is another limitation that could hinder achievement of optimal concentration. Moreover, subarachnoid adhesion obstructs the diffusion of pharmaceutical ingredients. 3) Continuous ventricular lavage and local administration of antibiotics bypassing the blood-cerebral barrier helps achieve optimal antibiotic concentration in the target lesions. This allows for reduced dosage of antibiotics and can potentially reduce the duration of treatment. Furthermore, the antibiotic saline could clear the blood components, sediments, tissue dross, and inflammatory mediators in the CSF. The preoperative administration of antibiotics helps to control the systemic inflammation and improves patient's resilience to surgical and anesthetic stress. Antibiotic saline should be prepared and repeated according to the half-life of specific drugs, concentration being 1/10 to 1/20 of that in systematic administration [10]. During the second surgical exploration via neuroendoscopy after intraventricual irrigation, the angiectasis and apparent hyperemia could be noted in the internal wall of ventricle after irrigation (**Figure 1H-K**), which was absent in the previous operation. Thus, reasonable selection of appropriate concentration and perfusion time should be emphasized to avoid complications like intracranial hemorrhage and epilepsy.

The precautionary measures to be considered are: 1) Continuous monitoring of the pulsatility of liquid level in drainage bags. 2) Keeping a vertical distance of 12-16 cm between the liquid level and the frontal angle of lateral ventricle, to ensure the adequacy of lavage and drainage. 3) Maintaining the temperature of the antibiotic saline at body temperature to avoid chills. 4) Hourly monitoring of the lavage and drainage flow making sure that the lavage flow is lower than or equal to the drainage flow. 5) Observing the appearances and characteristics of drainage fluid. 6) Prophylactic use of antiepileptic drugs. 7) Being vigilant for chemical ependymitis or fungal infection.

Treatment for concomitant hydrocephalus

The endoscopic third ventriculostomy can be carried out in case of obstructive hydrocephalus with an identified cause. Three key points should be emphasized. 1) Intraoperative localization should be attempted with intraoperative ultrasound or neuro-navigation to ensure the safety and efficacy, given the possibility of structural changes and poor visualization of anatomic landmarks as a sequel to ventricular infection (especially at the bottom of the third ventricle). The VP shunt should be a standby option in case of difficulty encountered during ventriculostomy or if its efficacy is uncertain. 2) After successful fistulization, stomal plasty should be performed on the patients with incrassated third ventricle (ventriculus tertius), to decrease the risk of fistula closure. In cases with subarachnoid adhesions, neuroendoscopy has the advantage of allowing for access to basal cistern via fistula, or even traversing it thoroughly for restoration of CSF circulation

(**Figure 1N**, **1O**). If the adhesion obscures the visual field and prevents recognition of the surrounding structures, VP shunt would be the preferred treatment. 3) The ventricular infection usually leads to the adhesion between the tube's ventricular terminal and ventricular wall or choroid plexus, which should be separated meticulously to prevent intracranial hemorrhage.

In patients with communicating hydrocephalus, VP shunt operation is the better treatment option. Despite the reported 50% success rate of Although the ETV treatment for communicating hydrocephalus has a reported success rate of 50% [11-13], VP shunt operation should be more reliable since ventricular infection may aggravate hydrocephalus by influencing the absorption of CSF.

The following two factors should be considered in determining the optimal timing for intervention: 1) The body temperature and CSF laboratory indexes should have returned to normal for at least 7 days after pausing the intraventricular irrigation; 2) The peripheral blood indexes should have returned to normal for more than 3 days. For patients with normal body temperature and peripheral blood findings, and CSF laboratory indexes being close to normal, VP shunt should be considered in order to avoid risk of drainage-related superinfection. In the present study, two patients with communicating hydrocephalus underwent continuous intraventricular irrigation for four weeks. Once the body temperature and laboratory indexes of peripheral blood and CSF turned normal, a VP shunt was performed, followed by the systemic antibiotic therapy for 1-2 weeks, postoperatively.

Complications

The common complications include the following: 1) wound infection at site of incision, CSF leakage and subcutaneous hydrops; 2) Complications related to ETV treatment; 3) The blockage, infection and rejection reaction to the drainage tube [10, 13-15].

Meticulously planned preoperative design of incision is key to avoid complications. Aseptic details and nursing care of drainage tube is essential for preventing superinfection. The tube should be replaced after 2 weeks of continuous intraventricular irrigation.

Neuroendoscopy is a novel minimally invasive therapeutic modality for efficient assessment and treatment of ventricular infection. The approach allows for adequate drainage of ventricular sediment and mural pus, recanalization of ventricular septation, and resection or fenestration drainage of abscess, which are some of the key advantages of this approach. The continuous perioperative irrigation with antibiotic saline also plays a significant role in the success of the treatment. Additionally, nutritional therapy and systemic administration of antibiotics are important adjuncts for achieving favorable treatment outcomes.

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Disclosure of conflict of interest

None.

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References

[1] Hellwig D, Kuhn TJ, Bauer BL and List-Hellwig E. Endoscopic treatment of septated chronic subdural hematoma. Surg Neurol 1996; 45: 272-277.

[2] Jho HD and Alfieri A. Endoscopic endonasal pituitary surgery: evolution of surgical technique and equipment in 150 operations. Minim Invasive Neurosurg 2001; 44: 1-12.

[3] Rodziewicz GS, Smith MV and Hodge CJ Jr. Endoscopic colloid cyst surgery. Neurosurgery 2000; 46: 655-660; discussion 660-652.

[4] Au-Yong A and Coats T. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. C Reactive Protein and the diagnosis of intracranial infection. Emerg Med J 2007; 24: 218-219.

[5] Mollman HD and Haines SJ. Risk factors for postoperative neurosurgical wound infection.

A case-control study. J Neurosurg 1986; 64: 902-906.
[6] Remes F, Tomas R, Jindrak V, Vanis V and Setlik M. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. J Neurosurg 2013; 119: 1596-1602.
[7] Deye G, Lewis J, Patterson J and Jorgensen J. A case of Leuconostoc ventriculitis with resistance to carbapenem antibiotics. Clin Infect Dis 2003; 37: 869-870.
[8] Reichert MC, Medeiros EA and Ferraz FA. Hospital-acquired meningitis in patients undergoing craniotomy: incidence, evolution, and risk factors. Am J Infect Control 2002; 30: 158-164.
[9] Healthcare Infection Control Practices Advisory Committee and Hand-Hygiene Task Force; Society for Healthcare Epidemiology of America; Association for Professionals in Infection Control and Epidemiology; Infection Diseases Society of America. Guideline for hand hygiene in healthcare settings. J Am Coll Surg 2004; 198: 121-127.
[10] Buxton N, Turner B, Ramli N and Vloeberghs M. Changes in third ventricular size with neuroendoscopic third ventriculostomy: a blinded study. J Neurol Neurosurg Psychiatry 2002; 72: 385-387.
[11] Fukuhara T, Vorster SJ and Luciano MG. Risk factors for failure of endoscopic third ventriculostomy for obstructive hydrocephalus. Neurosurgery 2000; 46: 1100-1109; discussion 1109-1111.
[12] Kamikawa S, Inui A, Tamaki N, Kobayashi N and Yamadori T. Application of flexible neuroendoscopes to intracerebroventricular arachnoid cysts in children: use of videoscopes. Minim Invasive Neurosurg 2001; 44: 186-189.
[13] Gangemi M, Mascari C, Maiuri F, Godano U, Donati P and Longatti PL. Long-term outcome of endoscopic third ventriculostomy in obstructive hydrocephalus. Minim Invasive Neurosurg 2007; 50: 265-269.
[14] McLaughlin MR, Wahlig JB, Kaufmann AM and Albright AL. Traumatic basilar aneurysm after endoscopic third ventriculostomy: case report. Neurosurgery 1997; 41: 1400-1403; discussion 1403-1404.
[15] Karachi C, Le Guerinel C, Brugieres P, Melon E and Decq P. Hydrocephalus due to idiopathic stenosis of the foramina of Magendie and Luschka. Report of three cases. J Neurosurg 2003; 98: 897-902.