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The role of endoscopic third ventriculostomy in the treatment of hydrocephalus

Clinical article

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Object. Hydrocephalus remains a major public health problem. Conventional treatment has relied on extracranial shunting of CSF to another systemic site, but this approach is associated with a high rate of complications. Endoscopic third ventriculostomy (ETV) is a novel treatment for select forms of hydrocephalus that can eliminate the need for implantation of a lifelong ventricular shunt system. However, the indications for ETV are contested and its long-term effectiveness is not well established.

Methods. The authors selected 100 consecutive patients who underwent ETV for hydrocephalus beginning in 1994. Patients were enrolled and treated at a single institution by a single surgeon. The primary outcome was success of ETV, with success defined as no need for subsequent surgery for hydrocephalus.

Results. Ninety-five patients satisfied the inclusion criteria. The mean follow-up period was 5.1 years (median 4.7 years) with follow-up data available for as long as 17 years. Patients commonly presented with headache (85%), ataxia (34%), emesis (29%), and changes in vision (27%). The success rate for ETV was 75%. Twenty-one patients (22%) in the series had malfunctioning shunts preoperatively and 13 (62%) were successfully treated with ETV. Preoperative inferior bowing of the third ventricle floor on MRI was significantly associated with ETV success ($p < 0.05$).

Conclusions. Endoscopic third ventriculostomy is an effective and durable treatment for select patients with hydrocephalus. When successful, the procedure eliminates the lifelong complications associated with implanted ventricular shunts.
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Key Words • **endoscopy** • **hydrocephalus** • **minimally invasive surgery** • **neuroendoscopy** • **endoscopic third ventriculostomy**

Hydrocephalus, the pathological accumulation of CSF in the brain affecting children and adults, was known to Hippocrates in the fifth century BC and remains a major public health problem today.[24,29,31,32] There is no effective medical cure for hydrocephalus. Since the 1950s,[10,11,17] the conventional treatment has been extracranial CSF shunting to another body cavity, most commonly the peritoneum, cardiac atrium, or pleura. Despite continued refinement of shunt systems, they remain troublesome devices with high rates of failure related to malfunction or infection and significant morbidity and mortality.[15,25] The annual cost of treating hydrocephalus in the US is nearly $2 billion,[22] with affected patients often requiring multiple shunt revisions over the course of their lifetime.[1,7,23]

Symptomatic hydrocephalus is almost always related to obstruction of the circulation of CSF. When the obstruction occurs outside the ventricles, the condition is called communicating hydrocephalus.[18] If the obstruction

Abbreviations used in this paper: ETV = endoscopic third ventriculostomy; ETVSS = ETV Success Score; IVH = intraventricular hemorrhage.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

occurs within the ventricular system (such as stenosis of the sylvian aqueduct), thereby preventing communication between the ventricles and subarachnoid space, the hydrocephalus is called noncommunicating. Nearly a century ago, William Jason Mixter, working at Massachusetts General Hospital, developed a minimally invasive procedure named ETV to treat noncommunicating hydrocephalus and performed it successfully in a 9-month-old infant. The procedure, published in the *Boston Medical and Surgical Journal*,[14] the forerunner of the *New England Journal of Medicine*, involved making a small puncture in the floor of the third ventricle to enable CSF to enter into the subarachnoid space and bypass a ventricular obstruction farther downstream. Mixter's ETV operation became the favored treatment of hydrocephalus, but the procedure gradually fell out of favor because of high morbidity and mortality rates associated, in part, with the primitive nature of the surgical instruments.

With advances in optics and miniaturization, there has been renewed interest in ETV as a means of treating select forms of hydrocephalus without the need for lifelong implantation of an extracranial CSF shunt and its attendant problems.[28] Despite recent widespread enthusiasm for ETV, several questions remain unanswered. The selection criteria for patients who will benefit from ETV continue to be contested, and the long-term benefits remain unclear.[8,21] Surgeon experience and institutional differences in treatment strategies have obscured the optimal role of ETV in the treatment of hydrocephalus.[13,20] In this report, we studied 100 consecutive patients who underwent ETV for hydrocephalus by a single surgeon to evaluate the selection criteria and long-term results for this procedure.

Methods

Study Design

This was a retrospective, single-surgeon, single-institution study to evaluate the effectiveness of ETV. Our primary hypothesis was that ETV could be used to manage hydrocephalus in patients with noncommunicating hydrocephalus. Secondary aims included determining if patients with ventricular shunts could potentially be rendered independent of these systems, determining if surgeon experience played a role in long-term outcome, and evaluating ETV selection criteria. The institutional review board at the participating site approved the study.

Study Population

Patients eligible for inclusion in this study had undergone ETV at Rainbow Babies and Children's Hospital in Cleveland, Ohio, and were under the primary care of the senior author (A.R.C.). One hundred consecutive ETV cases were selected between November 1994 and February 2008. Of the 100 patients, only those with clinical follow-up evaluations longer than 30 days postoperatively were included for analysis.

Data Collection and Processing

Initial Evaluation. Initial evaluation included a medical history, neurological and ophthalmological examination, and MRI studies. The nature and duration of the patient's symptoms were recorded, along with neuroradiological findings. Data from the patient's evaluation were collected for analysis with a scoring scale, the ETVSS (Table 1).[10,12,16]

Endoscopic Third Ventriculostomy. Endoscopic third ventriculostomy was performed in a standardized fashion.[2] The patient was placed under general anesthesia and positioned supine, brow up. Frameless stereotactic localization was used to optimize an entry site, and a bur hole was placed just medial to the midpupillary line and immediately in front of the coronal suture. The lateral ventricle—usually on the right side—was cannulated with a rigid endoscope sheath, and CSF was collected for routine laboratory studies and, when applicable, for additional cytology and tumor markers. Under visual guidance, the endoscope was advanced through the foramen of Monro into the third ventricle. Fenestration of the third ventricle floor was made in front of the mammillary bodies as anteriorly as possible, most commonly using a 4-F Fogarty balloon catheter that was repeatedly inflated and deflated to create an opening of approximately 5 mm in diameter (Fig. 1).

Hospital Course and Follow-Up. Clinical information was recorded from the immediate 1–2 days postoperatively until time of discharge. External ventricular drains were not used routinely. Patients returned for evaluation and were contacted at least 30 days after surgical intervention. For long-term patient outcomes, patients were either evaluated or contacted on the telephone (date last accessed for patients was November 11, 2011), which provided a 17-year period for evaluation. Patients were surveyed concerning symptoms (persistence or improvement) and whether further surgery was required for hydrocephalus.

Major Outcomes and Definitions

The primary outcome of the study was the success rate of ETV as indicated by the absence of additional surgery for hydrocephalus. The secondary outcome of determining shunt independence was also analyzed, and patients were determined to be shunt independent if they had their system removed or ligated and remained without a shunt during the follow-up period. Complications

TABLE 1: Calculation of the ETVSS

Score*	Patient Age	Origin of Hydrocephalus	Previous Shunt
0	<1 mo	postinfectious	previous shunt
10	1 to <6 mos		no previous shunt
20		IVH, myelomeningocele, nontectal brain tumor	
30	6 mos to <1 yr	tectal tumor, aqueductal stenosis, other cause	
40	1 yr to <10 yrs		
50	≥10 yrs		

* The ETVSS is calculated as patient age score + origin of hydrocephalus score + previous shunt score.

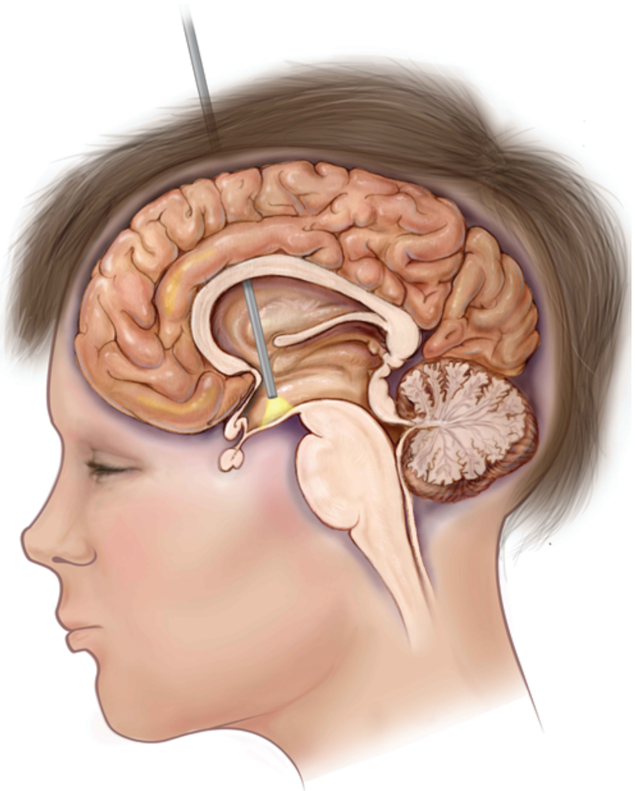

Fig. 1. Operative approach for ETV. This illustration reveals the relevant anatomy in relation to the floor of the third ventricle prior to its fenestration. The lighted endoscope is shown.

were recorded. The secondary outcome of determining if surgeon experience with ETV influenced patient outcomes was analyzed using a comparison between the first and last 33 ETV cases. Patients were considered at high risk of ETV failure if they had a history of CNS infection, previously underwent a myelomeningocele repair, or had a history of IVH resulting from premature birth.

Finally, secondary outcome analysis was conducted for ETV selection criteria using the ETVSS, a scoring system used by various groups treating hydrocephalus[10,12,16] (Table 1). The ETVSS is derived from a combination of 3 factors: patient age at surgery, origin of hydrocephalus, and presence of a previous shunt system. Points are awarded based on the criteria and summed among the 3 conditions, and the score roughly approximates the percentage of ETV success at 6 months postoperatively.[12] The highest possible score of 90 approximates a 90% chance of ETV success and the lowest score of 0 represents 0% success rate. Groups of patients can be stratified based on their ETV score with a high (≥ 80), moderate (50–70), and low (≤ 40) ETVSS.[16] For example, a 9-year-old patient with a tectal tumor and no previous shunt would receive an ETVSS of 80 (40 + 30 + 10), or 80% likelihood that ETV would be successful 6 months after the ETV. For all patients, the predicted ETV success (based on the ETVSS) was compared with actual ETV success. The ETVSS correctly predicted ETV success if ETV was successful and the ETVSS was ≥ 50, or if the ETVSS was ≤ 40 and accurately predicted ETV failure.

Statistical Analysis

Statistical computations were performed using JMP (version 10.0, SAS institute, Inc.) and Microsoft Excel 2011. Statistical significance was chosen at a p value < 0.05 for the Fisher exact test and Z-test with 2-tailed p values and unpaired Student t-tests.

Results

Study Population

We selected 100 consecutive patients who underwent ETV between November 1994 and February 2008 by the senior author. Five patients were excluded from data analysis because they did not meet the inclusion criteria of at least a 30-day follow-up period. Four of these patients were lost to follow-up and 1 patient died of a malignant pineal tumor; the death was unrelated to the ETV. The final analysis was performed on 95 patients. Baseline data were recorded for each patient in relation to presenting signs and symptoms (Table 2). The mean age of the patients was 19.7 years (median 17 years). Five (5%) of the 95 patients were under 1 year of age, 51 (54%) were children and adolescents (≤ 18 years of age), while the remaining 39 (41%) were adults.

Patients presented with a variety of neurological symptoms and signs (Table 2) consistent with elevated intracranial pressure, including headache (81/95, 85%) and vision complaints, with 32 patients (34%) having papilledema on examination and 26 (27%) noting a change in their vision or loss of a portion of their visual fields. Three patients (3%) had a sixth cranial nerve palsy. Twenty-two patients (23%) presented with macrocephaly and 21 (22%) had altered mental status, presenting with periods of delayed or absent responses or coma. Neurocognitive effects were noted in 10 patients (11%) with altered executive functioning and other psychiatric manifestations, such as visual and auditory hallucinations.

While a majority of the patients had not undergone previous treatment for any CNS disorder, 30 patients (32%) had previous shunts placed for the treatment of hydrocephalus. Twenty-one (70%) of these 30 patients with previously placed shunts presented with a failure in their shunt system.

Causes of Hydrocephalus and Neuroradiological Findings

Patients presented with a variety of hydrocephalus causes necessitating ETV, most commonly aqueductal stenosis (35 patients, 37%) that resulted in noncommunicating hydrocephalus. Twenty-three patients (24%) had a nontectal brain tumor, while 16 (17%) had a midbrain tectal tumor and 6 (6%) had intracranial cysts. Nine patients (10%) had a history of a repaired myelomeningocele and 3 (3%) had been treated for recent (< 1 month) CNS infections (Table 2). Overall, 20 patients (21%) had prior CNS infections or a history of IVH (7 patients, 7%) as a result of premature birth.

Each preoperative MR image was coupled with the clinical information to generate an ETVSS metric for each patient. A majority of patients (n = 65, 68%) presented with an ETVSS ≥ 80, and 90 patients (95%) of pa-

TABLE 2: Baseline characteristics of study patients and neurological presentations

Characteristic	Value (%)
mean age at ETV surgery ± SEM (yrs)	19.7 ± 1.5
range	5 mos to 77 yrs
≤1 yr old	5 (5)
13 mos to 18 yrs	51 (54)
>18 yrs	39 (41)
sex	
male	46 (48)
female	49 (52)
neurological signs & symptoms at presentation	
mean duration ± SEM (days)	163 ± 34
range	1 day to 5 yrs
headaches	81 (85)
papilledema	32 (34)
ataxia / imbalance	32 (34)
vomiting episodes	28 (29)
changes in visual acuity / visual fields	26 (27)
macrocephaly	22 (23)
altered mental status	21 (22)
nausea	19 (20)
psychiatric	10 (11)
weakness	9 (9)
seizures	4 (4)
cranial nerve deficit	3 (3)
bladder incontinence	2 (2)
preop shunt	30 (32)
preop shunt failure	21 (22)
origin of hydrocephalus	
aqueductal stenosis	35 (37)
nontectal brain tumor	23 (24)
tectal tumor	16 (17)
myelomeningocele	9 (9)
intracranial cyst	6 (6)
CNS infection	3 (3)
Chiari malformation Type I	3 (3)
neuroradiological findings	
ETVSS	
≥80	64 (67)
50–70	26 (27)
<40	5 (5)
third ventricle bowing	76 (80)

tients had an ETVSS ≥ 50. In addition, preoperative MRI identified inferior bowing of the third ventricular floor in 76 patients (80%; Table 2).

Other Procedures

Endoscopic third ventriculostomy was combined with several concurrent endoscopic procedures including biopsy of an intraventricular lesion in 20 (21%) of 95 cases (Table 3). In these 20 patients, 9 biopsies (45%) were aborted for the following reasons: vascularity of the tumor, a large massa intermedia obstructing view of the lesion, a small third ventricle, hemorrhage impairing the view, and periforaminal veins obstructing access to tumor.

Cyst fenestrations (n = 3, 3%) and opening of the septum pellucidum to connect isolated lateral ventricles (n = 2, 2%) were also performed along with an ETV. A 4-F Fogarty balloon catheter technique for perforation of the floor of the third ventricle (n = 77, 81%) was the preferred technique for manual control of ETV dilation. Laser-assisted ETV was performed early in the series and abandoned because of concern about the risk of thermal damage to adjacent vascular structures.[2] External ventricular drainage was used in 12 cases (13%) early in the series. When ETV was performed in conjunction with biopsy of a posterior third ventricle tumor, the bur hole was placed more anteriorly, using frameless stereotactic image guidance.

Patient Outcome

Patients were followed up for a mean of 5.1 years (range 6 weeks to 17 years, median 4.7 years), with the longest follow-up data available up to 17 years postoperatively (Table 3). Endoscopic third ventriculostomy was successful in 71 cases (75%), with the greatest success achieved in children 13 months of age and older (71%) and in adults (77%). Success rates of ETV were also calculated based on the presenting origin of hydrocephalus, with 71% success (25/35) for aqueductal stenosis, 74% (17/23) for nontectal tumors, 81% (13/16) for tectal tumors, 67% (4/6) for intracranial cysts, and 100% (3/3) for Chiari Type I malformations. The ETV success rates for high-risk patients included in this study were 66% (2/3) for patients with a recent CNS infection and 55% (11/20) in patients with any history of a CNS infection. Endoscopic third ventriculostomy was successful in 56% (5/9) of patients with a myelomeningocele and in 29% (2/7) of patients with any history of IVH.

The effectiveness of the ETVSS for patient selection was evaluated and found to significantly predict ETV outcome ($p < 0.0001$, 2-tailed Fisher exact test). Endoscopic third ventriculostomy was effective in 83% (54/65) of patients with an ETVSS ≥ 80 and in 60% (15/25) of patients with an intermediate ETVSS (50–70). In 73 cases (77%), the ETVSS accurately predicted the success of the procedure. Eleven (50%) of the unsuccessful predictions occurred in the ≥ 80 score range. Preoperative MRI identified inferior bowing of the third ventricle floor and this finding was significantly ($p < 0.05$, Fisher exact test) associated with ETV success in 79% (60/76) of the affected patients (Table 3).

A Kaplan-Meier survival curve for cumulative ETV success was calculated for the patient cohort (Fig. 2). There was an increased risk of early ETV failure during the first month, after which the success rate of ETV gradually plateaued. Endoscopic third ventriculostomy failures were noted as late as 16 years after the first ETV. Twenty-one patients (22%) in the series had malfunctioning shunts and 13 (62%) were successfully treated with ETV. Nine patients who had not previously had a shunt

TABLE 3: Characteristics of ETV and outcome in 95 patients*

Characteristic	Value (%)
ETV procedure	95 (100)
right	85 (89)
left	10 (11)
ETV & biopsy	20 (21)
unable to perform biopsy	9/20 (45)
ETV & cyst fenestration	3 (3)
ETV & septostomy	2 (2)
perforation technique	
Fogarty balloon catheter	95 (100)
size 4	77 (81)
size 3	18 (19)
YAG laser	2 (2)
bipolar cautery	2 (2)
outcome	
mean follow-up ± SD (yrs)	5.1 ± 0.47
range	1.1 mos to 17.0 yrs
successful ETV	71 (75)
failed ETV	26 (27)
ETV success by age	
≤1yr	3/5 (60)
13 mos to 18 yrs	36/51 (71)
>18 yrs	30/39 (77)
success by origin of hydrocephalus	
aqueductal stenosis	25/35 (71)
nontectal brain tumor	17/23 (74)
tectal tumor	13/16 (81)
myelomeningocele	5/9 (56)
intracranial cyst	4/6 (67)
recent CNS infection	2/3 (67)
Chiari malformation Type I	3/3 (100)
success by ETVSS	
≥80	54/65 (83)
50–70	15/25 (60)
<40	2/5 (40)
success by third ventricle bowing*	60/76 (79)
shunts	
postop shunt removed	13/29 (45)
need for new shunt following ETV	9/66 (14)
mean time until shunt placed ± SD (days)	221 ± 114
median (days)	21
complications	
CSF leak	2 (2)
bacterial meningitis	1 (1)
subdural hematoma	1 (1)
diabetes insipidus	1 (1)
infection at site	1 (1)
aborted procedure	1 (1)
postop seizure	1 (1)
death	0 (0)

* $p < 0.05$, Fisher exact test. Abbreviation: YAG = neodymium-doped yttrium-aluminum-garnet laser.

system required placement at a mean of 7.4 months following initial ETV (median 21 days). Ten (35%) of 26 patients with initial ETV failures underwent a second ETV during their clinical follow-up evaluations. Four of these patients had successful treatment with a second ETV, and the remaining 6 patients needed placement of a shunt. At the time of endoscopic reexploration, the previous site of the ETV was frequently noted to have scarred over or have tumor invasion.

To determine if single surgeon experience is a factor in ETV success, we performed a subgroup analysis on the first and last 33 cases from the 95 patients (Table 4). The characteristics of the 2 patient populations did not differ significantly in age, ETVSS, or risk factors such as prior CNS infections, prior IVH, or presence of a shunt. The ETV success rate was significantly different ($p < 0.05$, 2-tailed Z-test) between the 2 groups, with 19 (58%) of 33 patients in the first group experiencing successful ETV compared with 27 patients (82%) in the later group. A significant difference in the length of follow-up in the postoperative period ($p < 0.005$, 2-tailed unpaired Student t-test) was also found, with the first 33 patients having a mean follow-up of 7.6 years and the last 33 patients having a mean follow-up of 3.5 years.

Complications

There was 1 intraoperative hemorrhagic event that required aborting the biopsy procedure, necessitating placement of an external ventricular drain following irrigation to drain residual blood. There were no procedures

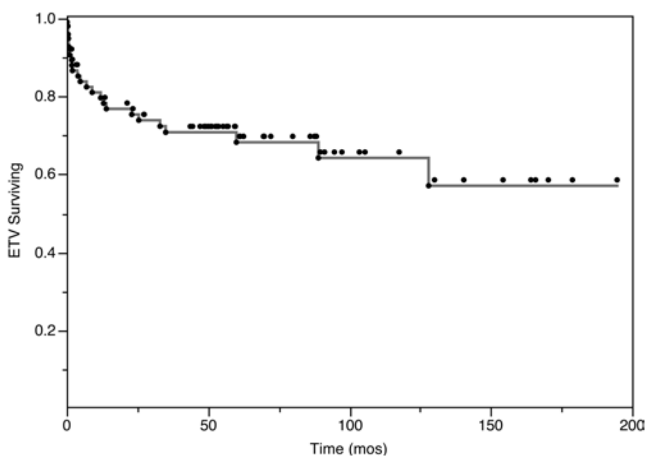

Fig. 2. Kaplan-Meier cumulative survival curve for the 95 patients undergoing ETV. The number of censored events are shown as dark circles along the graph. The survival results reflect the risk of early ETV failure.

TABLE 4: Comparison of first and last 33 cases and outcomes

Variable	First 33 Cases	Last 33 Cases
mean age at ETV surgery (yrs)	20.3 ± 3.4	15.7 ± 2.4
≤1 yr	2 (6)	2 (6)
13 mos to 18 yrs	16 (48)	20 (61)
>18 yrs	15 (45)	11 (33)
ETVSS		
≥80	20 (61)	22 (67)
50–70	11 (33)	8 (24)
<40	2 (6)	3 (9)
successful ETV*	19 (58)	27 (82)
risk factors		
prior CNS infection	8 (24)	7 (21)
prior myelomeningocele	5 (15)	2 (6)
prior IVH	4 (12)	3 (9)
preoperative shunt	13 (39)	11 (33)
outcome		
success by ETVSS		
≥80	13/20 (65)	20/22 (91)
50–70	6/11 (55)	5/8 (63)
<40	0/2 (0)	2/3 (67)
mean follow-up ± SEM† (yrs)	7.6 ± 1.2	3.5 ± 0.4

* $p < 0.05$ with 2-tailed Z-test.
† $p < 0.005$ with unpaired Student t-test.

that required additional surgical intervention or interventional neuroradiology evaluation or treatment for hemorrhage. A CSF leak occurred in 2 cases, along with 2 cases of infection (1 case of bacterial meningitis was confirmed by CSF sampling and another case was a local skin infection). One patient has a seizure postoperatively, 1 patient developed diabetes insipidus, and 1 patient had a small subdural hematoma that was observed without operative intervention. The overall infection rate was 2% and there were no reported deaths in this series (Table 3).

Discussion

The conventional treatment for symptomatic hydrocephalus—extracranial CSF shunting—has made this once fatal neurological disorder now survivable. However, shunts are associated with a high complication rate and often require repeated revisions during a patient's lifetime. Following recent technological advances, there has been a resurgence of interest in ETV for the treatment of noncommunicating hydrocephalus.

While ETV appears to be an effective treatment for hydrocephalus, questions remain pertaining to optimal patient selection criteria and long-term results.[9] We have sought to control interinstitutional biases and varying patient selection schemes[34] by reviewing a series of 100 consecutive patients who underwent ETV by a single surgeon at a single institution. From our series, we have elucidated 3 factors influencing patient selection.

The first finding is that the ETVSS significantly correlated with ETV success. The ETVSS is a recently developed tool to aid in patient selection.[12] Our findings support other reports[12,20,30] suggesting that the ideal candidate for ETV has noncommunicating hydrocephalus with no history of CNS infection or IVH. Older patients (≥ 10 years of age) with aqueductal stenosis and without the presence of a shunt have a high likelihood for ETV success. The large proportion of patients in our series with an ETVSS ≥ 80 suggests a bias toward patient selection for optimization of the 3 criteria: older age, aqueductal stenosis or tectal tumor as causes of hydrocephalus, and absence of a previous shunt. The ETVSS was initially developed to predict short-term postoperative outcomes and there have only been isolated reports[5] on the long-term effectiveness of the ETVSS in predicting ETV results up to 3 years. Our findings suggest that the relevance of the ETVSS in patient selection may extend to adults and children over many years of follow-up. Endoscopic third ventriculostomy selection criteria have continued to expand to include patients with infection,[23] neural tube defects,[26,33] and other forms of hydrocephalus,[19] patients who were conventionally believed to be at higher risk of ETV failure. With long-term follow-up data on these high-risk patients, ideal patient selection criteria will be further elucidated.

The second observation from our findings is that preoperative MRI of the third ventricle floor may aid in patient selection. An inferiorly bowed third ventricle floor is defined by convex displacement below the plane through the optic chiasm and mammillary bodies or the plane containing the optic chiasm and anterior commissure,[4,6] and this was predictive of ETV success in our patient cohort. Third ventricle floor deformation resulting from increased intracranial pressure suggests that a pressure gradient exists and may aid in maintaining ETV patency.[3] There have been some reports describing third ventricle morphology as a predictor of ETV success,[4] but these studies have been limited by cohort size, age,[6] and length of follow-up data. Our findings in adults and children confirm that preoperative neuroradiological imaging can be helpful in optimizing ETV success and should factor into patient selection.

We have also identified that surgeon experience with ETV may correlate with success rates for this procedure. Improved outcomes observed in the final third of our cases, when compared with the first third, may result from improved surgeon familiarity with the technique. Similarly, these findings may reflect a changing surgeon bias toward selecting patients with higher ETVSS or the continued improvement in endoscopic equipment that has evolved over the past 2 decades. The improvement in ETV outcome is most likely multifactorial. The reported morbidity and mortality outcomes for ETV are generally low,[27,35] although life-threatening complications can occur. Patients undergoing ETV should be followed long term by neurosurgeons; we treated several patients for ETV failures as late as 16 years following their initial surgery. We identified only minor complications resulting from ETV, with an overall infection rate of 2%. Finally, although we calculated success rates for ETV associated with ≤ 1 year of age and for various causes, including myelomeningocele, intracranial cysts, recent CNS infection, and Chiari Type I malformations, the sample sizes in these groups are small and do not allow for definitive recommendations on their management with ETV.

Conclusions

Improved patient selection criteria along with low complication rates makes ETV amenable to more widespread use for the treatment of hydrocephalus. International efforts have used ETV to reduce the economic burden of ventricular shunts in developing countries, where financial resources and access to medical care are limited. Endoscopic third ventriculostomy appears to be an effective method for treating selected patients with hydrocephalus and freeing them from the long-term complications of implanted ventricular shunts.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Cohen, Vogel, Robinson. Acquisition of data: Vogel, Bahuleyan, Robinson. Analysis and interpretation of data: all authors. Drafting the article: Cohen, Vogel. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Vogel. Administrative/technical/material support: Cohen, Robinson. Study supervision: Cohen, Robinson.

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