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Endoscopic Third Ventriculostomy in Obstructive Infantile Hydrocephalus: Remarks about the So-Called 'Unsuccessful Cases'

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Key Words
Endoscopic third ventriculostomy · Infancy · Obstructive hydrocephalus · Prognostic factors · Outcome shunt malfunction

Abstract
Background: The failure rate following endoscopic third ventriculostomy (ETV) in infants younger than 2 years of age has been reported to be higher compared with that of older children, and it is unclear whether ETV might be superior to shunt placement in this age group. ***Methods:*** Between 2003 and 2009, 23 patients younger than 6 months and without a previous history of shunting underwent ETV in our institution. A review of the literature was performed on the basis of publications presenting detailed data on age and etiology in every single patient. ***Results:*** In our own patients, total success rate was 39.1%. In the successful cases, median age was 140 days, whereas in the unsuccessful cases it was 47 days. The difference between the two groups was statistically significant (p = 0.01). The median ages of both successful and unsuccessful groups corresponded to data gained from an analysis of the literature (p = 0.04). At a median follow-up of 47 months, 2 out of 14 patients shunted after a failed ETV were revised for ventriculoperitoneal shunt malfunction. ***Conclusion:*** The impact of age on ETV failure in infants is clear and becomes crucial during the first 2 months of life, even when excluding etiological factors. Nevertheless, age cannot be considered the only parameter of the decision-making process, especially in these very young patients. Probably, the definition of 'unsuccessful ETV' should be re-evaluated in light of decreased risk of shunt malfunction observed after a failed ETV.

Introduction

Endoscopic third ventriculostomy (ETV) is a well-established procedure for the treatment of obstructive hydrocephalus although outcome is reported to be worse in small children and especially in infants. Conflicting reports on which patients are most likely to benefit from the procedure are animating the neurosurgical literature. The debate mainly focuses on the influence of age [1–6], etiology [7–15], or both [16–20], and on the success rates of ETV.

Publications in favor of an influence of age on ETV success highlight the highest failure rates in children below a defined age cutoff ranging from 6 months to 2 years; however, the worst outcome and controversies concern the population of premature newborns and infants less

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Table 1. Summary of patient characteristics and outcomes

Patient/sex	Age days	Diagnosis	Preoperative signs/ symptoms	Procedure	Re-ETV	Complications	Outcome[1]	Follow-up months	VPS revisions n
1 AA/F	142	IAS	tense AF and IHC	ETV	–	–	VPS (8)	49	–
2 BK/F	55	PFC	vomiting and setting-sun sign	ETV	–	–	VPS (20)	12	–
3 BM/F	139	IAS	tense AF and IHC	ETV	after 26 days	–	VPS (40)	64	–
4 BA/M	65	DWM	tense AF and IHC	ETV + ECC	–	–	VPS (42)	19	–
5 BL/F	1	PHH	antenatal diagnosis	ETV	–	–	VPS (13)	84	1 (after 17 months)
6 CT/F	36	DWM	tense AF, IHC and drowsiness	ETV + ECC	–	–	VPS (22)	19	–
7 CJ/M	83	AH	antenatal diagnosis	ETV	–	–	VPS (29)	67	–
8 DJ/F	6	IAS	antenatal diagnosis	ETV	–	–	VPS (132)	45	–
9 DA/F	31	PHH	antenatal diagnosis	ETV	–	–	VPS (11)	75	2 (after 11 and 41 months)
10 DS/M	150	OEH	setting-sun sign	ETV	–	–	shunt-free	6	–
11 FA/M	170	CM	tense AF and IHC	ETV	–	–	shunt-free	81	–
12 FF/F	18	QC	antenatal diagnosis	ETV + ECC	–	seizures	VPS (105)	6	–
13 FA/F	15	IAS	antenatal diagnosis	ETV	–	–	shunt-free	50	–
14 FC/F	169	IAS	tense AF and IHC	ETV	–	–	shunt-free	58	–
15 GM/M	140	IAS	tense AF and IHC	ETV	–	–	shunt-free	49	–
16 KT/M	95	PFC	IHC	ETV	–	–	shunt-free	73	–
17 LE/M	157	IAS	tense AF and IHC	ETV	–	–	shunt-free	72	–
18 MS/M	80	PHH	tense AF and IHC	ETV	–	–	VPS (66)	84	–
19 MG/M	39	IAS	IHC	ETV	–	–	VPS (15)	12	–
20 ML/F	138	IAS	IHC and large head	ETV	–	–	shunt-free	84	–
21 RL/M	34	PHH	antenatal diagnosis	ETV	–	–	VPS (14)	84	–
22 SD/F	70	PFC	tense AF, IHC, vomiting	ETV	–	–	VPS (7)	26	–
23 WL/M	45	IAS	IHC	ETV	–	forniceal injury	shunt-free	15	–

[1] The interval between ETV and shunt insertion is given in parentheses (days).

PFC = Posterior fossa cyst; DWM = Dandy-Walker malformation; OEH = occipital encephalocele-associated hydrocephalus; CM = Chiari I malformation; QC = quadrigeminal cyst; AF = anterior fontanel; IHC = increased head circumference; ECC = endoscopic cystocisternostomy.

than 6 months of age with several studies showing success rate of ETV ranging from 0 to 67% [2, 10, 12, 15, 18, 21–26].

We retrospectively analyzed the data of 23 infants younger than 6 months with obstructive hydrocephalus admitted to our Pediatric Neurosurgical Unit in Bron (Lyon) who underwent ETV, as a first choice of treatment, with the intent to assess its effectiveness and discuss the reasons of its failure. We also performed a review of the literature looking for a possible dependence of ETV failure on age or etiology of hydrocephalus.

Material and Methods

Between January 2003 and September 2009, 183 pediatric ETVs (population younger than 18 years) were performed, including 23 infants less than 6 months of age with diagnosed obstructive hydrocephalus and without a previous history of shunting. In the 23 patients considered in our study, age ranged from 1 to 170 days with a median age of 70 days, and male:female ratio was 11:12. Diagnosis of hydrocephalus was made on the basis of clinical manifestation and on the basis of magnetic resonance imaging (MRI) in the majority of cases or indirectly inferred from triventricular dilatation in CT scan or ultrasound examination. Idiopathic aqueductal stenosis (IAS) was the etiology of hydrocephalus in 10 infants. The other etiologies were posthemorrhagic hydrocephalus (PHH) in 4 patients, posterior fossa cysts in 3 patients, Dandy-Walker malformation in 2 patients, Chiari I malformation in 1 patient, quadrigeminal cyst in 1 patient, hydrocephalus associated with occipital encephalocele in 1 patient and triventricular hydrocephalus in 1 patient with achondroplasia. No children had a shunt device before ETV. Patients with Dandy-Walker malformation and the patient with quadrigeminal cyst also underwent endoscopic cystocisternostomy during the same surgery. The patient with occipital encephalocele developed hydrocephalus 4 months after the excision of the encephalocele sac with repair of the defect had been conducted. A summary of patient characteristics and outcome is listed in table 1.

ETV procedures were performed with a rigid endoscope (Hopkins 30°, Karl Storz, Tuttlingen, Germany) at the lateral edge of the open anterior fontanel or a right frontal burr hole placed slightly anterior to the coronal suture and medial to the midpupillary line. The same procedure was followed in all cases: the third ventricular floor was fenestrated between the mamillary bodies

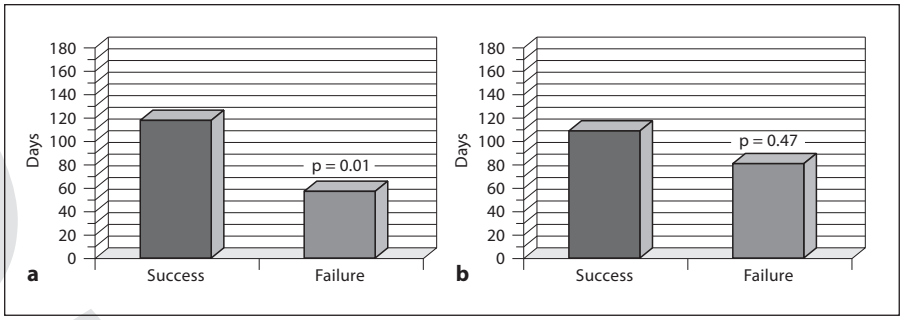

Fig. 1. Bar graph showing age distribution in both outcome groups (our own series). **a** For all patients. **b** For patients with IAS.

and the infundibular recess by applying brief pulses of bipolar coagulation on the surface followed by blunt penetration through the floor; a Fogarty microballoon catheter was used to dilate the opening. The endoscope was passed through the opening in the floor and, when necessary, additional intracisternal blunt dissection was performed until the direct visualization of the structures of the interpeduncular and prepontine cistern was obtained. Sparse ventricular bleeding was easily controlled by gentle irrigation with normal saline solution at body temperature. No patient in this series had substantial intraventricular hemorrhage during surgery requiring extraventricular drainage postoperatively.

Complications of the endoscopic procedure included early postoperative seizures in 1 patient and an intraoperative forniceal injury in another patient. No postoperative infection, hemorrhage or cerebrospinal fluid (CSF) leak was observed in this series of patients.

During the follow-up period, all children underwent postoperative clinical evaluation and neurodiagnostic imaging (MRI or CT scan). Ventriculoperitoneal shunt (VPS) was recommended for infants who did not experience improvement in clinical signs of hydrocephalus or who relapsed. In children who improved after ETV, MRI was done at 3 months or later; serial clinical evaluations were performed at 2 and 6 months and then yearly. ETV was judged to be successful when shunting could be avoided.

Statistical Analysis

Statistical analysis was performed on Graph Pad Prism 4.0 using the Mann-Whitney U nonparametric test to analyze the differences between groups. Values of $p < 0.05$ were considered statistically significant.

Results

Overall, at a median follow-up period of 50 months (range 6–84) ETV was successful in 9 of the 23 patients (39.1%). In infants with a successful ETV the median follow-up period was 58 months (range 6–84). In the remaining 14 patients (60.9%) with unsuccessful ETV, VPS was performed. The interval between ETV and shunt insertion ranged from 7 to 132 days with an average of 37.4 days. In 1 patient, repeat ETV was performed 26 days after the first ETV; however, he ended up in ventriculoperitoneal shunt insertion because of recurrence of clinical and radiological signs of hydrocephalus 2 weeks later. In the 9 successful cases, etiology was IAS in 6 patients, Chiari I malformation in 1 patient, posterior fossa cyst in 1 patient and occipital encephalocele in 1 patient; the median age of this group was 140 days and the mean age 119 days (range 15–170). In the ETV failure group the median age was 47 days and the mean age 57 days (range 1–142). The differences between the two groups were statistically significant ($p = 0.01$) and the age distribution showed a strong tendency for failure to occur more frequently in the first 2 months of life. When analyzing infants only with IAS (only 10 patients), similar distributions, but not significant ($p = 0.47$), were found (fig. 1).

In patients younger than 2 months (n = 10), success rate was 20% while in patients from 2 to 6 months of age (n = 13), success rate was 53.8%. The highest success rate was obtained in the primary aqueductal stenosis group with a successful ETV in 6 out of 10 patients. In infants with IAS younger than 2 months (n = 4) the success rate was 50%, whereas in patients from 2 to 6 months (n = 6) it was 66.6%. In patients with etiology other than IAS (n = 13) success rate of ETV was 23% and all successful procedures were performed in infants older than 2 months of age.

At a median follow-up of 47 months, 2 out of 14 infants (14.2%) shunted after a failed ETV have been surgically revised for VPS malfunction. Both were 1 month old and underwent ETV for PHH. The first had one episode of VPS malfunction after 17 months from the implant, whereas the other had two episodes after 11 and 41 months, respectively.

Analysis of Literature Data

Careful analysis of the literature, looking for a possible dependency of ETV failure on age or etiology of hydrocephalus, was performed on the basis of publications presenting sufficiently detailed data of every single patient

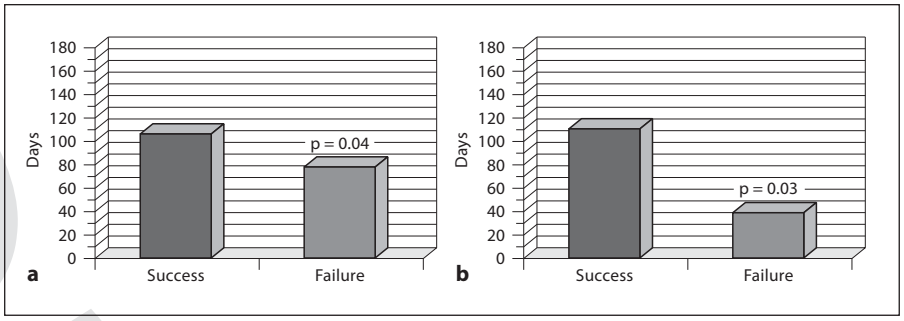

Fig. 2. Bar graph showing age distribution in both outcome groups (data from the literature). **a** For all patients. **b** For patients with IAS.

(e.g. in the form of tables presenting raw data) to allow an exact analysis of both patient age and etiology of the hydrocephalus. Only infants younger than 6 months of age, who underwent ETV as a first choice of treatment and with follow-up times of at least 6 months, if not shunted, were included in the meta-analysis.

The publications selected for meta-analysis [2, 4, 21, 22, 24, 27–30] give detailed data on ETV outcome in 53 infants (median age 86 days).

Overall, ETV was successful in 21 patients (39.6%) and eventually failed in 32 patients. In infants with a successful ETV median age was 120 days and mean age 107 days (range 0–183), whereas in nonsuccessful cases median age was 60 days and mean age 78 days (range 8–188). The differences were statistically significant ($p = 0.04$). In patients younger than 2 months of age ($n = 22$), success rate was 22.7% while in patients from 2 to 6 months of age ($n = 31$), success rate was 51.6%.

In the IAS group ($n = 20$), ETV was successful in 50% of cases. Median and mean ages were 135 and 112 days, respectively, in successful cases and 33 and 40 days in unsuccessful cases. The differences were statistically significant ($p = 0.03$) with a success rate in infants less and older than 2 months of age of 25 and 87.5%, respectively (fig. 2). The success rate of ETV in patients with etiology other than IAS ($n = 33$) was 33%.

Discussion

The analysis of the literature, confirming our data, shows that overall success rate of ETV, as a first choice of treatment, for children younger than 6 months is about 40%. This finding is also supported by the recent publication by Kulkarni et al. [3] that assessed ETV outcome in a large cohort of children (618 patients younger than 19 years) collected from a collaborative international network and developed a simplified scoring system to predict a successful ETV. This is one of the largest sample sizes currently in the literature validated with a rigorous statistical technique. In their study, age was the strongest predictor of success with infants, especially those younger than 6 months (99 patients), having the lowest predicted ETV success (44.4%) with progressively higher success seen as a child ages; the effect of etiology and presence of a previous CSF shunt appeared to be significant but much less in magnitude than age.

Warf et al. [31] reported an impressive single-center prospective series of children treated with ETV; the success rate of the procedure in infants younger than 6 months was 34%. However, two remarkable peculiarities of this study must be pointed out: the dominant etiologies of postinfectious and myelomeningocele-associated hydrocephalus and the unilateral/bilateral choroid plexus cauterization performed during the endoscopic procedure.

The finding of a probability of ETV success gradually increasing over time during the first year of life is confirmed also by a retrospective German multicenter study [32] and by the large series reported from Jones et al. [33].

When we analyzed the age distribution of ETV outcome in our population study and in the analysis of the literature, we found a tendency for failures to occur more frequently in the first 2 months. The existence of a cutoff age for the success rate of ETV during the first 6 months was reported by other studies [22, 25, 34], also in the series of Ogiwara et al. [26] only based on infants younger than 6 months.

We are convinced that something happens over the course of time that changes the pathophysiology of CSF flow and increases the success rate of ETV over time. Another factor influencing the lower reported success rate in younger infants is, probably, the definition of 'unsuccessful ETV'. Considering a longer time of adaptation, in comparison with adults, as the reason of persistence of higher ICP despite a good stoma [35], we think that some

patients (even in our group) are evaluated as unsuccessful and shunted too early.

Regarding the etiology of hydrocephalus, our study, supported by the analysis of the literature, confirms the highest previously reported ETV success rate worldwide in infants with triventricular hydrocephalus caused by isolated primary aqueductal stenosis and a very low success rate in patients with PHH.

Patients with PHH, in our series, were all younger than 3 months of age and ETV eventually failed in all cases. The median interval between ETV and shunt insertion was 13.5 days. Our failure in PHH is in line with many reports in the literature and reflects our inability, to date, to determine the contribution of hyporesorption in patients with PHH or postinfectious hydrocephalus.

In case of PHH, a promising approach is to determine the proportion of hyporesorption by examining the transforming growth factor-β_1 level in CSF, as recently reported by Lipina et al. [36]. In our opinion, their study opens up a new scenario for decision making in PHH and goes in the right direction: improving patient selection by use of biological markers waiting for a progress in imaging tools. Nevertheless, to date, taking an accurate medical history from the parents (any suggestion of postnatal or prenatal bleeding, fetal infection or postnatal meningitis must not be overlooked) remains the first step towards identifying possible risk factors for an underlying problem associated with, or leading to, impaired absorption of CSF [37].

An interesting finding in our series is that patients shunted after a failed ETV showed a decreased risk of shunt malfunction compared with our own previous experience and with the known risk of shunt malfunction in shunted hydrocephalic patients reported in the literature [38, 39].

We revised only 2 patients out of 14 (14.2%) during a median follow-up time of 47 months. This phenomenon, that a failed ETV may have some advantages over time in terms of lower revision rate, was also observed by Beem and Grotenhuis [40].

Shim et al. [41] compared the outcome of 31 infants treated with implantation of VPS and ETV and of 45 infants treated only with VPS. They found a higher success rate in the VPS plus ETV group (success was defined as no need for any subsequent surgical procedure of CSF diversion) with remarkable results in PHH and postmeningitic hydrocephalus. They did not try to provide evidence for the continuing patency of any of the ETVs or VPSs and suggested that the functioning procedure in the VPS plus ETV group could replace the malfunctioning one [41]. We do not speculate about this phenomenon but we think that it deserves further investigation.

Despite the increasing popularity of ETV, there is no consensus on which is the treatment of choice for infantile hydrocephalus. Controversy continues over which are appropriate candidates for the endoscopic procedure essentially because of our incomplete understanding of hydrocephalus and, above all, of the embryogenesis and the morphological/functional development of CSF dynamics. Despite a variety of classification systems for hydrocephalus have been suggested [17, 42–47], the conventional 'bulk flow' model [48] – even if it fails to explain other forms of hydrocephalus than that caused by obstruction of the intraventricular CSF pathways or ventricular outflow – remains the most attractive for neurosurgeons probably because, beyond the descriptive and simplified aspect of hydrocephalus, it implies alternatives of treatments.

However, in the last years, the concept of communicating versus obstructive hydrocephalus has been challenged; it was suggested that variable sites for obstruction to flow may be important for treatment, and that there could be a number of parallel flow routes that are genetically determined and age-dependent [49, 50].

The hydrodynamic hypothesis suggested by Greitz et al. [51] and Greitz [52] considers, in addition to a pure bulk flow problem, the dynamic pulsatile nature of the CSF movement in concert with the venous and arterial pulsatility and the pulsatile movement of the brain itself. The hydrodynamic viewpoint could explain how, apart from the intraventricular interruption of CSF bulk flow, an obstruction of the intraventricular and extraventricular CSF spaces changes local and global compliance and in consequence, pulsatility patterns, which leads to a hydrocephalic condition [51, 52]. Future therapy of pediatric hydrocephalus could be improved when more detailed knowledge of the CSF flow routes and cerebral hydrodynamics is forthcoming.

Conclusion

Based on our data, on the review of the literature and above-mentioned citations we can doubtless affirm that the pathophysiology of hydrocephalus remains the very Achilles' heel of any treatment paradigms of infantile hydrocephalus.

The major limit of all case series in the literature, even in our study, is the unavoidable subjectivity in defining etiology – secondary versus primary aqueductal steno-

sis – and 'unsuccessful ETV' which follows the decision to shunt, which is, sometimes, too hasty considering the longer time of adaptation in infants. At the current state of knowledge, looking forward to the results of the ongoing International Infant Hydrocephalus Study trial, the endeavor to improve success rate by selection of patients should not be exaggerated because the risk is to exclude some patients who might benefit from the procedure. In infants with etiology other than primary aqueductal stenosis we probably have to reevaluate the definition of 'unsuccess', considering also the finding that patients shunted after a failed ETV could present a decreased risk of shunt malfunction.

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