Intraoperative assessment of cerebral aqueduct patency and cisternal scarring: impact on success of endoscopic third ventriculostomy in 403 African children

Clinical article

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Object. In the setting of a developing country where preoperative imaging may be limited, the authors wished to determine whether cisternal scarring or aqueduct patency at the time of surgery was sufficiently predictive of the failure of endoscopic third ventriculostomy (ETV) to justify shunt placement at the time of the initial operation.

Methods. The status of the prepontine cistern and aqueduct at the time of ventriculoscopy was prospectively recorded in 403 children in whom an ETV had been completed. Kaplan-Meier methods were used to construct survival curves. A Cox proportional hazards model was used to provide estimates of HRs for the time to ETV failure. Several independent variables were tested in a single multivariable model, including those previously shown to be associated with ETV survival, that is, age, hydrocephalus etiology, and extent of choroid plexus cauterization (CPC). In addition, intraoperative variables of particular interest were included in the analysis: status of the aqueduct at surgery (closed vs open) and status of the prepontine cistern at surgery (scarred vs clean/uncarried). Multicollinearity was not a concern since the variance inflation factors for all variables were < 2. The examination of stratified survival curves confirmed the appropriateness of the proportional hazards assumption for each variable.

Results. Overall actuarial 3-year success was 57%. Consistent with previous results, age, hydrocephalus etiology, and extent of CPC were significantly associated with ETV success. A closed aqueduct and an unscarred cistern were each independently associated with significantly better ETV success (HRs of 0.66 and 0.44, respectively). The presence of cisternal scarring more than doubled the risk of ETV failure, and an open aqueduct increased the risk of failure by 50%.

Conclusions. Intraoperative observations of the aqueduct and prepontine cistern are independent predictors of the risk of ETV failure and can be used to further refine outcome predictions based on age, hydrocephalus etiology, and extent of CPC. Further studies will test validity in several African centers and determine what threshold of failure risk should prompt shunt placement at the initial operation. (DOI: 10.3171/2009.9.PEDS09304)

Key Words • endoscopic third ventriculostomy • hydrocephalus • choroid plexus cauterization • outcome prediction • developing countries

The value of being able to predict the likely success or failure of a given treatment option is magnified in an environment that hinders ready access to care in the event of failure. Such is the case in the treatment of pediatric hydrocephalus in developing countries, as in Uganda18-21 where the inability of most patients to easily obtain urgent treatment for shunt malfunction provided the impetus for us to explore ETV as an alternative to shunt dependence. The probability of shunt malfunction in the first year after placement and subsequently over time is universally recognized.15,16 If, however, the likelihood of failure for primary treatment with ETV in a particular child were known to exceed that expected for shunting, then a shunt may be the optimal choice.

Based on our large patient population in Uganda, we initially showed that an age younger than 1 year at time of treatment and the absence of visible evidence of flow across the ETV stoma at the time of surgery each significantly correlated with ETV failure.20 It was later shown that adding bilateral lateral ventricle CPC to the procedure increased the likelihood of success in those younger...
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than 1 year old.\textsuperscript{19} We subsequently demonstrated the value of age, hydrocephalus etiology, and extent of CPC as significant independent variables in predicting ETV success, developing a scoring system (CCHU ETV Success Score) that predicts success based on these 3 parameters.\textsuperscript{22}

Logic and the early experience with ETV in Uganda suggested scarring of the cisterns and an open aqueduct as independent predictors of ETV failure. Without access to MR imaging, these factors were difficult to determine prior to surgery, although we did find that aqueduct patency could be reliably predicted by the size of the fourth ventricle on preoperative cranial ultrasonography.\textsuperscript{20} Evaluation of the first 300 children demonstrated that aqueduct obstruction significantly correlated with ETV success in those younger than 1 year of age with PIH (PIH Type C) as compared with those with open aqueducts (PIH Type A). The differences were not significant for other etiologies.\textsuperscript{20}

Beginning in June 2001, we prospectively recorded ventriculoscopic observations at the time of ETV, including whether the prepontine cistern was scarred and whether the ostium of the aqueduct was open, closed, or narrowed. Our goal was to determine if factors discovered at the time of surgery would sufficiently predict ETV failure to justify proceeding to shunt placement at the time of the initial operation. We here report the results of our analysis.

Methods

The institutional review board of CCHU approved this study.

Patient Population

We prospectively collected data from all ETV procedures in patients 20 years of age and younger that were consecutively performed at CCHU in Mbale between June 2001 and May 2007. The majority of children were from Uganda, but others were from Kenya, Tanzania, Malawi, Somalia, Rwanda, Congo, and Mauritius. The cost of all treatment was subsidized. All patients had symptomatic, high-pressure hydrocephalus and underwent preoperative imaging via cranial ultrasonography or CT. Magnetic resonance imaging, a standard preoperative imaging modality in developed countries, was not available. Endoscopic third ventriculostomy was the primary treatment offered to all children presenting with hydrocephalus, regardless of age or disease etiology. Shunts were used only if ETV failed or could not be performed for technical reasons. A few children had undergone previous treatment with a CSF shunt and presented with a shunt malfunction for which ETV was performed. In cases of multiple ETV procedures in the same patient, only data from the first procedure was included in our analysis. Data from some of these patients have appeared in previous publications.\textsuperscript{19–22}

Surgical Procedure and Data Collection

The procedure performed in all patients and described in detail elsewhere was a standard ETV via a frontal trajectory, with a fenestration made in the floor of the third ventricle and/or the lamina terminalis using a flexible endoscope.\textsuperscript{20} Starting in January 2003, CPC was also performed whenever technically feasible.\textsuperscript{19}

Beginning in 2001, we began to prospectively record the status of the cerebral aqueduct and prepontine cistern as seen at surgery. The limited preoperative imaging modalities available in our setting made it virtually impossible to determine cisternal scarring before surgery. In a previous study, however, we had demonstrated the excellent correlation between the preoperative aqueduct status on cranial ultrasonography and the intraoperative endoscopic observations of the aqueduct ostium.\textsuperscript{20} Because our current analysis is limited to patients in whom we were able to make such intraoperative assessments, our sample represents only a subset of the larger population we treated. Importantly, all patients in the current report, by definition, at least had a successful ETV attempt; that is, no aborted ETV procedures are included in this analysis. The status of the aqueduct was recorded as either clearly closed, narrowed, or clearly open, as determined from direct inspection of the ostium without entering the aqueduct with an endoscope. (For statistical analysis, the status was categorized as either closed or not closed.) The prepontine cistern was assessed after fenestration of the third ventricle floor and was recorded as scarred or not scarred (clean). The determination of scarring was a qualitative rather than a quantitative assessment, but a consistent standard was applied in identifying a scarred cistern as one that contained anything more than typical strands of normal-appearing arachnoid. Once the Liliequist membrane had been fenestrated, thickened membranes that even partially obstructed free passage of the endoscope into the cistern were considered to consist of scarring.

The operating surgeon recorded these intraoperative features at the time of surgery, prior to the determination of a child’s outcome. Between June 2001 and June 2006, the senior author (B.C.W.) primarily determined the status of the cistern and aqueduct; in many of the later cases, however, such determinations were jointly agreed on by 2 surgeons and, in some cases, by the second surgeon independently.

Endoscopic third ventriculostomy failure was defined as the need for any subsequent surgical procedure for definitive CSF diversion or death related to hydrocephalus management. We used standard treatment success criteria, as described in detail elsewhere,\textsuperscript{19–21} to determine whether further surgery was required: a shift in head circumference growth to a normal or less-than-normal rate, as plotted on a standard growth chart; decompression of the anterior fontanel; relief from symptoms of elevated intracranial pressure (such as irritability and vomiting); resolution of abnormal eye findings (for example, sunsetting or cranial nerve VI palsy); and a decrease or arrest in ventriculomegaly as determined on ultrasonography or CT scanning by using the Evans index or frontooccipital horn ratio.\textsuperscript{11}

Statistical Analysis

Kaplan-Meier methods were used to construct survival curves. A Cox proportional hazards model was used to provide estimates of HRs for the time to ETV failure. We tested several independent variables in a single multi-
variable model, including variables that we had shown to be associated with ETV survival: age (< 6 months, 6 to < 12 months, ≥ 12 months), hydrocephalus etiology (postinfectious, myelomeningocele, or other), and CPC (none, partial/unilateral, or complete/bilateral). Moreover, we included the intraoperative variables that were of particular interest to us in this analysis: status of the aqueduct at surgery (closed vs open) and status of the prepontine cistern at surgery (scarred vs clean/uncarded). Multicollinearity was of no concern because the variance inflation factors for all variables were < 2. The examination of stratified survival curves confirmed the appropriateness of the proportional hazards assumption for each variable. All analyses were performed with SPSS Advanced Statistics 17.0 (SPSS Inc.).

Results

A summary of characteristics of the 403 patients is listed in Table 1. The long-term survival curve for ETV success is shown in Fig. 1. The actuarial 3-year success rate was 57% (95% CI 52–62%). Results of the Cox regression model are also shown in Table 1. Consistent with our previous results, age, hydrocephalus etiology (postinfectious, myelomeningocele, or other), and extent of CPC were significantly associated with ETV success. Both the presence of a closed aqueduct and a clean/uncarded prepontine cistern were independently associated with a significantly better chance of ETV success. The magnitude of their effect was quite substantial, with HRs of 0.66 and 0.44, respectively.

The proportion of patients with clean cisterns and closed aqueducts varied according to the etiology of hydrocephalus (both p < 0.001, chi-square test; Table 2). However, we found that the effects of a clean cistern and closed aqueduct on ETV success were similar across etiologies. Specifically, the addition of interaction terms between etiology and either variable to the Cox regression model were not significant (both p > 0.54), and the magnitude of the HRs was similar when the analysis was stratified by etiology—although these stratified analyses suffered from lower power because of a limited sample size.

The adjusted survival curves are shown in Figs. 2 and 3 and graphically demonstrate the importance of a closed aqueduct and a clean/uncarded prepontine cistern. These survival curves were created based on survival functions estimated at the mean value of all other covariates; that is, they are corrected for the effect of the other variables in the model.

Discussion

Based on the experience with combined ETV and CPC at CURE Children’s Hospital of Uganda, we developed a scoring system (CCHU ETV Success Score) that can be used to predict the likelihood of ETV success depending on patient age, etiology of hydrocephalus, and extent of CPC. In the present study we report 2 additional parameters—the ventriculoscopically determined

### TABLE 1: Summary of patient characteristics and Cox regression results

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>HR for ETV Failure (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age at ETV in mos</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>265 (65.8)</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>6 to &lt;12</td>
<td>81 (20.1)</td>
<td>0.74 (0.49–1.11)</td>
<td>0.14</td>
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<tr>
<td>≥12</td>
<td>57 (14.1)</td>
<td>0.52 (0.31–0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>etiology of hydrocephalus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postinfectious</td>
<td>232 (57.6)</td>
<td>0.66 (0.44–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>myelomeningocele</td>
<td>61 (15.1)</td>
<td>0.67 (0.40–1.14)</td>
<td>0.14</td>
</tr>
<tr>
<td>other</td>
<td>110 (27.3)</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td><strong>CPC performed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>132 (32.8)</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>partial/unilat</td>
<td>32 (7.9)</td>
<td>0.69 (0.40–1.20)</td>
<td>0.19</td>
</tr>
<tr>
<td>complete/bilat</td>
<td>239 (59.3)</td>
<td>0.44 (0.29–0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>status of aqueduct at op</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>closed</td>
<td>196 (48.6)</td>
<td>0.66 (0.45–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>open</td>
<td>207 (51.4)</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td><strong>status of prepontine cistern at op</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clean/uncarded</td>
<td>283 (70.2)</td>
<td>0.44 (0.32–0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>scarred</td>
<td>120 (29.8)</td>
<td>reference</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2: Proportions of clean cisterns and closed aqueducts according to hydrocephalus etiology

<table>
<thead>
<tr>
<th>Etiology of Hydrocephalus</th>
<th>No. of Cases</th>
<th>No. of Cases w/ Clean/Unscarred Cisterns (%)</th>
<th>No. of Cases w/ Closed Aqueducts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>postinfectious</td>
<td>232</td>
<td>134 (57.8)</td>
<td>148 (63.8)</td>
</tr>
<tr>
<td>myelomeningocele</td>
<td>61</td>
<td>49 (80.3)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>other</td>
<td>110</td>
<td>100 (90.9)</td>
<td>44 (40.0)</td>
</tr>
</tbody>
</table>
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Fig. 2. Adjusted survival curve showing the intraoperative aqueduct status.

Fig. 3. Adjusted survival curve revealing the intraoperative prepontine cistern status.

status of the aqueduct and the prepontine cistern—that promise to further refine a surgeon’s ability to determine whether the ETV procedure is likely to succeed.

It should be noted at the outset that the survival curves in Figs. 1–3 are consistent with our previous observation that the majority of ETV failures occur within the first 6 months after the procedure. This consideration is important in determining whether ETV or shunt placement should be the primary procedure in infants with hydrocephalus, especially in the developing world where access to care for treatment failure is likely to be delayed. The initial weeks and months following treatment are typically the time of closest clinical surveillance. Moreover, for infants, this window is the “safest” time for treatment failure, since the recurrence of rapid head growth and a full anterior fontanel virtually always precede any life-threatening effects of elevated intracranial pressure. The “flattening” of the ETV survival curve around 6 months contrasts with the pattern for shunt failure, which is one of continued failure over time. Although ETV failure does occur beyond 6 months, it appears to be uncommon. Thus, for a population of infants with parameters known to predict a chance of ETV failure that equals or even exceeds that for shunt failure, ETV may still be supported as the best initial treatment since virtually all failures will occur within this “safe window.”

It was initially assumed that the presence of arachnoid scarring in the interpeduncular and prepontine cisterns would diminish the chance of ETV success for 2 reasons: 1) proximate obstruction of CSF flow on the cisternal side of the ETV stoma; and 2) obstruction of CSF flow and absorption in the cortical subarachnoid spaces if observable scarring in the cisterns reflected the status of the other extraaxial CSF spaces. Once this assumption was supported by the observations reported here, we adopted the policy of proceeding to shunt placement in this particular population at CCHU as a “backup,” given what appeared to be an unacceptably high likelihood of failure requiring another operation as well as the possibility that the child's return to the hospital might be delayed or prevented. We had reported our 1-year shunt outcomes in the same institution among a similar patient population, with 84% of survivors (9.7% lost to follow-up and 15.9% 1-year mortality rate) free from shunt infection or failure.

Greenfield and coauthors have recently described a scoring system for predicting ETV outcome that was based on intraoperative observations in 102 patients and included cisternal scarring as a negative factor. We are the first to report the status of the prepontine cistern as a significant independent predictor of ETV success, and we demonstrate that when corrected for the affect of other variables known to influence outcome, the presence of scarring in the prepontine cistern more than doubles the risk of ETV failure.

That ETV was sometimes successful in treating hydrocephalus in patients with an open aqueduct seems counterintuitive and may be attributed to an obstruction of CSF flow distal to the aqueduct (such as fourth ventricle outlet obstruction or arachnoid scarring in the posterior fossa). However, ETV has also been reported to successfully treat idiopathic normal pressure hydrocephalus as well as communicating hydrocephalus due to trauma, hypertensive intracranial hemorrhage, tuberculous meningitis, and subarachnoid hemorrhage. An explanation for these findings may require the assumption of models for hydrocephalus outside the scope of this discussion.

This is the first study focused on the status of the aqueduct as an independent variable in ETV success. Although significantly and independently correlated with ETV failure (50% increased risk of ETV failure after correcting for other known variables), an open aqueduct is not as strongly predictive as the observation of cisternal scarring. This finding suggests that the presence of an open aqueduct should not automatically eliminate a patient as a candidate for ETV and that other factors should contrib-
ute to the consideration of treatment options. Specifically, in a prior study, when ETV was combined with CPC in patients with an open aqueduct (both postinfectious and non–postinfectious etiologies), 54 (64%) of 84 were successfully treated, and among patients older than 1 year, 14 (88%) of 16 were successfully treated. In the same study, among patients older than 1 year and with open aqueducts, treatment by ETV alone was successful in 10 (67%) of 15 patients. In infants with myelomeningocele—all younger than 1 year, and most with an open aqueduct ostium noted endoscopic treatment of hydrocephalus.

Practically speaking, the minimum threshold of likely success that should prompt shunt placement is not clear and may be contingent upon the treatment environment (that is, developing vs developed world). As noted above, since most ETV failures occur within 6 months, there may be circumstances that justify ETV/CPC as the initial treatment in infants, even if the short-term failure rate is not superior to that for shunting. Additional data will be required to provide a basis for any recommendation.

We acknowledge several limitations in our study. Our long-term follow-up of patients was limited, making it difficult to make any strong conclusions about ETV success several years after surgery. In our study we used the assessment of no more than 2 surgeons to determine aqueduct and cistern status; we must determine whether these assessments can be reliably performed by others and make the results more generalizable. Our future work at other African centers will help us assess the interobserver reliability of determining aqueduct and cistern status. The accumulation of more data will also allow us to formally integrate the intraoperative findings into our previously developed CCHU ETV Success scoring system. Although the results in our East African population may have broader relevance, given the great differences in population characteristics, any translation of the significance of our observations from the developing world to a developed world population must be done with caution. A major difference in our population of children, as compared with, for example, a North American population, is the predominance of PIH and the absence of posthemorrhagic hydrocephalus in prematurity. Although there may be pathophysiolo gical similarities between PIH and posthemorrhagic hydrocephalus in prematurity, the reported observations should not be extrapolated from the former disease to the latter. Additionally, MR imaging provides an obvious advantage in preoperative evaluation that was not available to any of the patients in our study. Nonetheless, we suggest that the absence of MR imaging availability should not argue against our results being valid for “developed-world” patients with the same etiology of hydrocephalus. Magnetic resonance imaging, especially with FIESTA (fast imaging employing steady state acquisition) or CISS (constructive interference in steady state) sequences, may indeed be an advantage in being able to predict cistern and aqueduct status preoperatively. Provided that preoperative MR imaging and intraoperative evaluation of the aqueduct and cistern are shown to correlate, data in the present study may help to support these MR imaging findings as preoperative predictors of the risk of failure.

Conclusions

Scarring in the prepontine cistern doubles the risk of ETV failure, and aqueduct patency increases this risk by 50%. These intraoperative observations can be used to further refine the risk of failure predicted according to a patient’s age, the etiology of hydrocephalus, and the extent of CPC. Unlike shunt failures, most ETV failures occur within 6 months of the operation. This fact must be considered when determining what threshold of predicted ETV failure should prompt one to proceed with shunt placement.

Disclosure

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

References

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