Changes in cerebral perfusion hormone profile and cerebrospinal fluid flow across the third ventriculostomy after endoscopic third ventriculostomy in patients with aqueductal stenosis: a prospective study

Clinical article

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Object. The object of the present study was 3-fold: 1) to study regional cerebral perfusion before and after endoscopic third ventriculostomy (ETV) in patients with obstructive hydrocephalus by using ⁹⁹ᵐTc ethyl cysteinate dimer SPECT; 2) to study any correlation between clinically successful third ventriculostomy and CSF flow across the third ventriculostomy; and 3) to determine any changes in hormone profile following ETV.

Methods. The authors prospectively studied 15 patients with aqueductal stenosis who underwent ETV during the last 2 years. All the patients underwent pre- and postoperative MR imaging, brain ⁹⁹ᵐTc ethyl cysteinate dimer SPECT, and hormone profile studies.

Results. Eight patients were infants. The mean follow-up duration was 17.6 months. Thirteen patients (86.7%) exhibited clinical improvement after surgery. In all patients with clinical improvement the studies documented CSF flow through the ventriculostomy site. Clinical progress could be correlated with SPECT changes in 14 cases (93.3%). In the 13 clinically successful cases, 12 were substantiated by improvement on SPECT scans, whereas in the 2 failed cases, SPECT images revealed no improvement of perfusion defects. Hormone analysis conducted in 14 patients revealed hyperprolactinemia in 8, low triiodothyronine values in 2 patients, and hypocortisolemia in 1, which was reversed after ETV.

Conclusions. Clinical improvement is not well correlated with a decrease in ventricular size following ETV. Brain SPECT is a valuable tool for the follow-up of patients with hydrocephalus after ETV, particularly in cases in which MR imaging findings are not clear. There are subtle hormonal changes in patients with hydrocephalus that may improve following ETV. (DOI: 10.3171/2008.10.PEDS08148)

Key Words • cerebrospinal fluid • endoscopy • hydrocephalus • magnetic resonance imaging • outcome • third ventriculostomy • ventriculoperitoneal shunt

Hydrocephalus is defined as imbalance of CSF formation and absorption, which produces a net accumulation of fluid within the cerebral ventricles that usually leads to elevation of ICP. Hydrocephalus is not a disease but results from various conditions affecting the CSF pathways, leading to imbalance in CSF flow dynamics. Continuous ventricular enlargement can have a deleterious effect on the developing brain and can lead to thinning of the cortical mantle, atrophy of white matter, decreased cerebral perfusion, spongy edema of the brain, and stretching and denuding of the ependyma.²³,²⁷,²⁸

There are few conditions treated by neurosurgeons that are at once so gratifying and as frustrating as hydrocephalus. Treatment of hydrocephalus has seen more advances during the last century than any neurosurgical condition. Advancements in endoscopic techniques have led to a revival of third ventriculostomy in the management of hydrocephalus. Initially reported to work best in patients

Abbreviations used in this paper: ECD = ethyl cysteinate dimer; ETV = endoscopic third ventriculostomy; ICP = intracranial pressure; VP = ventriculoperitoneal.
with later-onset aqueductal stenosis, ETV is now used in many centers for a wider variety of indications with varying success rates, depending on the origin of the hydrocephalus and the patient’s age.3–7,11,12,15–17 Endoscopic third ventriculostomy has a well-established role in the treatment of obstructive hydrocephalus. The patients were followed up with repeated neurological examination, brain MR imaging, and hormone profile studies. At 2 months after surgery, all patients except for one had a decrease in the size of the ventricles may not be present in all patients despite the presence of clinical improvement. Recent studies evaluating the ICP changes and CSF flow dynamics following ETV have shown that ICP reduces following ETV even if there is no significant change in ventricular size.26

The use of 99mTc ECD SPECT has been shown to be a valuable tool for objective assessment of cerebral perfusion in patients with minor head injury, subarachnoid hemorrhage, normal-pressure hydrocephalus, and hydrocephalus secondary to various causes following VP shunt insertion.1,13,14,19,26,31,32 To the best of our knowledge, ours is the first study in the literature to use brain SPECT as an adjunctive tool for the follow-up of patients with hydrocephalus who have undergone ETV. Additionally, we hypothesize that in cases involving obstructive hydrocephalus, there is hypothalamic dysfunction due to ballooning of the third ventricle, which can lead to hormonal disturbances due to hypothalamic-pituitary axis dysfunction that may be reversible following relief of intraventricular pressure.

Methods

This prospective study was conducted in the neurosurgery department at our institute between October 2005 and September 2006. To maintain the uniformity of the surgical technique, a single surgeon (A.S.) performed the surgeries in all patients. A detailed history and physical examination were done in all cases. Each patient underwent preoperative MR imaging, brain 99mTc ECD SPECT, and hormone profile studies. At 2 months after surgery, all patients were followed with repeated neurological evaluation, postoperative MR imaging with CSF flow studies, SPECT, and hormone profile studies. Change in ventricular size was assessed using the Evan index by comparing pre- and postoperative imaging studies. Also CSF flow was analyzed across the third ventricular floor using cine MR imaging. The SPECT studies were conducted as previously described. The change in cerebral perfusion in the affected region was evaluated using the computer software SISCOS with SPM analysis (Statistical Parametric Maps) in which pre-ETV images were subtracted from post-ETV images. The SPECT images were interpreted by 2 nuclear medicine physicians (S.A.S. and C.S.B.) who were blinded to the subjects and results of MR imaging and CSF flow studies. Panels for hormone investigation included serum growth hormone, prolactin, cortisol, triiodothyronine, thyroxine, and thyroid-stimulating hormone.

Operative Technique

The ETV was performed in all cases through a right frontal precoronal bur hole. Following dural incision, a rigid sheathed endoscope was advanced into the right lateral ventricle and then through the foramen of Monro, into the third ventricle. After studying the anatomy of third ventricle and structures visible across the third ventricle, a stoma was made in the third ventricular floor in between the mammillary bodies and infundibular recess. The stoma was enlarged by inflating the balloon of the Fogarty catheter.

Scan Acquisition and Image Processing

We performed 99mTc ECD SPECT of the brain to determine the regional/global cerebral blood flow. Image acquisition began almost 20 minutes after the injection of radiotracer. All scans were acquired using the same dual-head gamma camera (GE Medical Systems), fitted with a low-energy, high-resolution, general-purpose collimator. Data were acquired in a 128 × 128–pixel matrix at each of 120 projections at 25 seconds per projection over a 360° rotation around the individual’s head. Tomographic reconstruction was performed on an Integra workstation using a method of filtered back projection. Transaxial, coronal, and sagittal slices were reconstructed using a Butterworth filter, Nyquist frequency (cycles/cm) of 1.404, and cutoff frequency of 0.56; a Chang attenuation correction of 0.11 cm was applied. Images were transferred to a workstation for processing using SPM-based image analysis software.

Statistical Analysis

Statistical parametric maps of regional blood flow were erected using SPM 2 software run on a workstation loaded with MATLAB 6.1 (Matrix Laboratory version 6.1). The SPM software was used to detect any significant difference in the cerebral blood flow before ETV and 2 months after ETV. We set the significance threshold at p < 0.05 (uncorrected height threshold) where height is in the voxel intensity, and then subtraction of the pre-ETV SPECT images from the post-ETV SPECT images was performed.

Steps in SPM Analysis

The proceeding steps were followed in the SPM analysis: 1) conversion of the transverse oblique slices of the brain SPECT images from the interfile format to the DICOM format; 2) conversion of the DICOM format images to the analyze format; 3) coregistration of the 2 images with the post-ETV images as the target image and pre-ETV image as the source image; 4) realignment of the coregistered images; 5) subtraction of the pre-ETV image from the post-ETV image following normalization; and 6) overlaying of the subtracted image on the mean SPECT image hence obtained.

Results

Between September 2005 and October 2006, a total of 15 consecutive patients with newly diagnosed aqueductal stenosis were admitted and surgically treated at our institute. All patients underwent ETV performed by a single surgeon (A.S.). All the patients were prospectively followed with repeated neurological examination, brain MR imaging with CSF flow studies, brain SPECT, and hormone profile analysis.

There were 10 male patients and 5 female patients...
whose age ranged from 2 months to 18 years—8 were infants and 4 were up to 2 years of age. The most common presenting signs/symptoms were progressive increase in head size (12 cases), delayed milestones (9 cases), headache associated with vomiting (2 cases), seizures (2 cases), and eye deviation (2 cases). The duration of symptoms ranged from 2 months to 12 years. There was no case of surgery-related death. Operative complications included a CSF leak in 1 patient (managed with suturing of the wound) and meningitis in another patient (managed with intravenous antibiotic agents). The mean follow-up duration was 17.6 months (range 9–26 months). Of the 15 patients, 13 patients improved clinically (success rate 86.7%), and of 8 infants, ETV was successful in 7 (success rate 87.5%). Hence, the success rates were comparable in both infants and older children. Of 13 clinically successful cases, follow-up MR imaging and no flow across the third ventricular floor. The initial preoperative SPECT scan revealed perfusion defects in all cases. The decrease in perfusion was most marked in the region of the frontal, parietal, and temporal lobes. Of 13 successful cases, 12 (92.3%) noted improvement in perfusion defects whereas in the 2 failed cases, 1 had early failure within 2 months of surgery and the other patient had initial improvement followed by delayed failure 1.5 year following surgery (Fig. 3).

In the cases of clinical failure, each patient exhibited clinical symptoms of raised ICP at the time of failure, and we observed an increase in the Evan index and absent CSF flow across the third ventricular floor on postoperative MR images compared with preoperative images. In the patient with early failure there was no improvement in perfusion defects on follow-up brain SPECT, whereas in the patient with delayed failure we initially observed improvement in perfusion defects followed by late progression of perfusion defects at the time of delayed failure. Hence, changes in cerebral perfusion could be cor-

Fig. 1. Various imaging studies obtained in a 6 month-old child with gross hydrocephalus and a thin cortical mantle. A and B: Axial T2-weighted MR images obtained before (A) and 2 months after (B) ETV with no significant change in the size of the ventricles but improved visualization of sulci and gyri, along with clinical improvement in patient. C: Sagittal cine MR image acquired after ETV revealing good flow across the ventriculostomy site. D and E: Serial SPECT images showing marked improvement in cerebral perfusion in the bilateral frontal, parietal, and occipital lobes (E) compared with preoperative SPECT images (D).
related with clinical outcome in 14 cases (93.3%). Only 1 patient with improvement following surgery and cine MR imaging–documented CSF flow did not have improvement in perfusion defects. In both cases of clinical failure, patients underwent VP shunt insertion. Changes in the Evan index, clinical condition, cerebral perfusion, and CSF flow are shown in Table 1.

Of the 15 cases, hormone profile studies could be conducted in 14 cases. In 8 cases we observed an increased prolactin level that normalized following ETV. In 2 cases we documented a decrease in triiodothyronine values, and in 1 patient we noted a low serum cortisol level that improved after ETV. All the hormonal derangements were present in clinically successful group and these parameters improved following surgery. In the failure group, there was no hormonal derangement. Detailed pre- and postoperative hormone profile data are shown in Table 2.

Discussion

While the benefits of neuroendoscopy to resolve intraventricular obstruction in many patients with hydrocephalus are clear to some neurosurgeons, to others a great deal of uncertainty surrounds this indication. Many patients with obstructive hydrocephalus worldwide undergo shunt placement due to an ongoing skeptical attitude toward ETV, its complications, and long-term efficacy. Nevertheless, despite some skepticism and controversy over the benefits of ETV in general, many neurosurgeons believe that in patients with obstructive hydrocephalus, including infants, ETV should be offered. At the very least, patients and families should be offered a choice of ETV or shunt therapy, when applicable.

The success rates of ETV in patients with obstructive hydrocephalus has varied from 30 to 100%, depending on
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the cause of hydrocephalus, age of the patients, criteria for the selection of the patients, and the definition of success. Although initial reports indicated lower success rates in patients younger than 1 year of age, a few recent studies have shown higher success rates in this patient group also. In this study, our success rate was 87.5% in infants with aqueductal stenosis–related hydrocephalus, which further underscores the importance of age and origin of hydrocephalus when considering ETV as treatment of choice in this age group.

In 1998 Brockmeyer and associates studied the role of ETV in 97 patients from different age groups; there were 5 patients with aqueductal stenosis < 1.5 years, and the authors reported an overall success rate of 49 and 60% in patients with aqueductal stenosis < 1.5 years. Schwartz et al. performed ETV in 16 patients from different age groups; follow-up included clinical examination, imaging, ICP assessment, and CSF flow studies, and the success rate of ETV was 87.5%. Buxton and colleagues reported an efficacy rate of 30% in 27 infants treated with ETV. Mo-

![Fig. 3. A–C: Serial brain SPECT images obtained in a patient with congenital hydrocephalus who initially improved following ETV and who experienced late deterioration 1.5 year after ETV.](image-url)
hanty et al.\textsuperscript{24} performed ETV in 72 patients from different age groups and reported a success rate of 82%. Murshid\textsuperscript{25} performed ETV in 27 patients (16 patients < 1 year of age) and reported an overall success rate of 81% (22 of 27) in the overall group with no shunt insertion needed. Singh\textsuperscript{26} and reported an overall success rate of 81% (22 of 27) in patients older than 2 years of age and 100% improvement following ETV in the overall group with no shunt insertion needed. Costa Val\textsuperscript{27} performed ETV in 66 children younger than 2 years of age and reported a 70% clinical improvement following ETV in patients younger than 2 years of age and 100% improvement in patients older than 2 years of age. Costa Val\textsuperscript{28} performed ETV in 53 children less than 2 years of age and reported an overall success rate of 62.2%; the success rate in aquaductal stenosis group was 85.7% and in infants less than 1 month of age it was 90%. Costa Val concluded that the success rate of ETV is more dependent on the etiology of the hydrocephalus rather than the age of the patients. Beems and Grotenhuis\textsuperscript{29} performed ETV in 66 children younger 2 years of age, including 54 children younger than 1 year of age, and reported a 53% success rate in the entire group and an 87% success rate in the group of patients with obstructive hydrocephalus. There are now studies proving the fact that clinical improvement following ETV can be independent of ventricular size.\textsuperscript{5}

In addition to the problems of inconsistent standards and small patient numbers, another drawback to most studies to date has been the extremely minimalist definition of success and failure. The only criterion for success used in most studies has been some variation on the single point of freedom from shunt dependency. (Even that single point has not been applied consistently, with some studies insisting on total shunt freedom after a single ETV attempt, some including as successes shunt freedom after a repeat ETV as well, and short-term follow-up times that do not define or address the risks of delayed failure.) Relying on a single criterion of shunt freedom completely ignores the related, and equally significant, aspects of patient success and failure, such as neurodevelopmental impact, long-term morbidity, or cost comparison, both human and financial, including hospitalization time, number of surgeries, and number of sick days.

In cases of failed ETV, cine MR imaging is useful for determining whether repeat ETV should be undertaken. In cases in which there is no CSF flow across the third ventricular floor, repeat ETV may be considered. In patients in whom ETV has failed clinically but in whom there is CSF flow across the third ventricular floor, VP shunt insertion may be another treatment of choice.

Although alteration in cerebral perfusion has been documented in many brain pathological entities in children, few investigators have studied the changes in cerebral perfusion in children with hydrocephalus.\textsuperscript{14,18,26,31,32,38} It has been hypothesized that early shunt implantation may lead to a better outcome in patients with hydrocephalus and that a delay in CSF diversion may lead to irreversible brain damage.\textsuperscript{31} Nayak et al.\textsuperscript{26} have shown that, following CSF diversion, there is improvement in cerebral perfusion that leads to improved clinical symptoms, particularly in the pediatric population. Additionally, patients with an increased ventricular size and no signs of raised ICP may benefit from early SPECT scanning.\textsuperscript{20} Patients who have perfusion defects may benefit from early CSF diversion. Our study clearly shows that SPECT is a useful follow-up tool in such patients. Although many patients may not have a significant decrease in the size of ventricles following ETV, but such patients have improvement in perfusion defects with a high degree of clinical correlation compared with MR imaging or CT scanning. Hence, changes in ventricular size should never be taken

**TABLE 1: Changes in Evan index, clinical condition, cerebral perfusion, and CSF flow across the stoma in patients with aquaductal stenosis who underwent ETV**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (mos), Sex</th>
<th>Duration of Symptoms (mos)</th>
<th>Evan Index</th>
<th>Preop</th>
<th>Postop</th>
<th>Clinical Condition</th>
<th>Changes in SPECT</th>
<th>CSF Flow Across ETV</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2, M</td>
<td>2</td>
<td>0.46</td>
<td>0.44</td>
<td>improvement</td>
<td>improvement</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8, M</td>
<td>8</td>
<td>0.52</td>
<td>0.44</td>
<td>improvement</td>
<td>deterioration</td>
<td>present</td>
<td></td>
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<tr>
<td>3</td>
<td>6, M</td>
<td>6</td>
<td>0.63</td>
<td>0.58</td>
<td>improvement</td>
<td>improvement</td>
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<td>4</td>
<td>18, M</td>
<td>18</td>
<td>0.72</td>
<td>0.59</td>
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<td>improvement</td>
<td>present</td>
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<tr>
<td>5</td>
<td>22, M</td>
<td>20</td>
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<td>0.49</td>
<td>improvement</td>
<td>improvement</td>
<td>present</td>
<td></td>
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<tr>
<td>6</td>
<td>10, M</td>
<td>8</td>
<td>0.68</td>
<td>0.62</td>
<td>improvement</td>
<td>improvement</td>
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<td></td>
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<tr>
<td>7</td>
<td>3, F</td>
<td>3</td>
<td>0.58</td>
<td>0.43</td>
<td>improvement</td>
<td>improvement</td>
<td>present</td>
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</tr>
<tr>
<td>8</td>
<td>18, M</td>
<td>16</td>
<td>0.77</td>
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<td>improvement</td>
<td>present</td>
<td></td>
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<tr>
<td>9</td>
<td>18, F</td>
<td>18</td>
<td>0.44</td>
<td>0.42</td>
<td>improvement</td>
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<tr>
<td>10</td>
<td>2, M</td>
<td>2</td>
<td>0.64</td>
<td>0.59</td>
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<td>improvement</td>
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<td>216, M</td>
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<td>12</td>
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<td>60</td>
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<td>0.76</td>
<td>deterioration</td>
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* This patient initially improved and then experienced late deterioration 1.5 years after surgery.
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**TABLE 2: Summary of data in 14 patients in whom hormone studies were obtained**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>T3 (70–170 ng/dl)</th>
<th>T4 (4.5–12.5 µg/dl)</th>
<th>TSH (0.4–4.0 µU/ml)</th>
<th>Cortisol (5–25 µg/dl)</th>
<th>GH (0.2–2.0 ng/ml)</th>
<th>Prolactin (1.9–17 ng/ml)</th>
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<tr>
<td></td>
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* Values in parentheses indicate reference ranges, and all values in the table are presented in the units in parentheses. Abbreviations: GH = growth hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.

as criterion for deciding the outcome after ETV in patients with hydrocephalus. There are isolated case reports showing hormonal dysfunction in patients with hydrocephalus preoperatively as well as after ETV.

In 2007, Fritsch and associates reported changes in hormonal function after ETV and concluded that hormonal dysfunction—hypoprolactinemia and decreased levels of gonadotropins—may occur after ETV in patients with hydrocephalus. Ours is the first study to evaluate changes in hormone profile in patients with hydrocephalus preoperatively and following ETV. Our hypothesis that in patients with aqueductal stenosis there is third ventricular dilation leading further to dysfunction of hypothalamic-pituitary axis and this was supported by the hypoprolactinemia seen in 8 (57.1%) of 14 evaluated patients. Dysfunction of other hormones was seen in a significant number of patients (3 [21.4%] of 14 patients). Whether hormonal replacement in these patients can lead to improvement in prognosis will require further study.

**Conclusions**

Endoscopic third ventriculostomy should be considered the treatment of choice in patients with obstructive hydrocephalus. The origin of hydrocephalus rather than a patient's age should be considered the sole criterion for determining whether to undertake ETV in infants. Our study shows that brain SPECT is a useful, objective, follow-up tool for patients with hydrocephalus because it can demonstrate improvement in cerebral perfusion. Ventricular size alone should never be the sole criterion in determining the success of ETV in patients with hydrocephalus, particularly pediatric patients. In cases of failed ETV, cine MR imaging is useful for predicting which group of patients will benefit from repeat ETV. There are subtle hormonal changes in patients with obstructive hydrocephalus that may improve following CSF diversionary procedures. Further study will be required to assess whether hormonal replacement will benefit this group of patients.

**Disclaimer**

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

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