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Brain growth after surgical treatment for infant postinfectious hydrocephalus in Sub-Saharan Africa: 2-year results of a randomized trial

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Abstract

OBJECTIVE—Hydrocephalus in infants, particularly that with a postinfectious etiology, is a major public health burden in Sub-Saharan Africa. The authors of this study aimed to determine whether surgical treatment of infant postinfectious hydrocephalus in Uganda results in sustained, long-term brain growth and improved cognitive outcome.

METHODS—The authors performed a trial at a single center in Mbale, Uganda, involving infants (age < 180 days old) with postinfectious hydrocephalus randomized to endoscopic third ventriculostomy plus choroid plexus cauterization (ETV+CPC; n = 51) or ventriculoperitoneal

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Author Contributions

Conception and design: Warf, Schiff, Kulkarni. Acquisition of data: Mbabazi-Kabachelor, Mugamba, Ssenyonga. Analysis and interpretation of data: Warf, Schiff, Kulkarni, Mbabazi-Kabachelor, Donnelly, Levenbach, Monga, Peterson, Cherukuri. Drafting the article: Warf, Schiff, Kulkarni. Critically revising the article: Warf, Schiff, Kulkarni. Reviewed submitted version of manuscript: Warf, Schiff, Kulkarni, Mbabazi-Kabachelor, Mugamba, Ssenyonga, Levenbach, Monga, Peterson, Cherukuri. Approved the final version of the manuscript on behalf of all authors: Warf. Statistical analysis: Kulkarni. Administrative/technical/material support: all authors. Study supervision: Warf, Schiff, Kulkarni, Mbabazi-Kabachelor, Donnelly, Levenbach.

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Disclosures

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

Supplemental Information

Previous Presentations

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shunt (VPS; n = 49). After 2 years, they assessed developmental outcome with the Bayley Scales of Infant Development, Third Edition (BSID-III), and brain volume (raw and normalized for age and sex) with CT scans.

RESULTS—Eighty-nine infants were assessed for 2-year outcome. There were no significant differences between the two surgical treatment arms in terms of BSID-III cognitive score ($p = 0.17$) or brain volume ($p = 0.36$), so they were analyzed together. Raw brain volumes increased between baseline and 2 years ($p < 0.001$), but this increase occurred almost exclusively in the 1st year ($p < 0.001$). The fraction of patients with a normal brain volume increased from 15.2% at baseline to 50.0% at 1 year but then declined to 17.8% at 2 years. Substantial normalized brain volume loss was seen in 21.3% patients between baseline and year 2 and in 76.7% between years 1 and 2. The extent of brain growth in the 1st year was not associated with the extent of brain volume changes in the 2nd year. There were significant positive correlations between 2-year brain volume and all BSID-III scores and BSID-III changes from baseline.

CONCLUSIONS—In Sub-Saharan Africa, even after successful surgical treatment of infant postinfectious hydrocephalus, early posttreatment brain growth stagnates in the 2nd year. While the reasons for this finding are unclear, it further emphasizes the importance of primary infection prevention and mitigation strategies along with optimizing the child's environment to maximize brain growth potential.

Clinical trial registration no.: NCT01936272 (clinicaltrials.gov)

Keywords

brain growth; neurocognitive outcome; hydrocephalus; endoscopic third ventriculostomy; choroid plexus cauterization; ETV+CPC; ventriculoperitoneal shunt

Infant hydrocephalus is common worldwide and especially so in many low-income countries, with an estimated incidence of 180,000 infants per year in Sub-Saharan Africa alone.[1] A dominant contributor appears to be postinfectious hydrocephalus following neonatal sepsis.[2,3] Surgical treatment of hydrocephalus in this setting has proven to be safe[4] and with a favorable benefit-cost ratio.[5] A recent US National Institutes of Health–funded randomized trial in Uganda has shown that the two available treatment options—ventriculoperitoneal shunt (VPS) placement[6,7] and the newer endoscopic third ventriculostomy combined with choroid plexus cauterization (ETV+CPC)[8–13]—both relieve symptoms and allow the brain to grow at 1 year after treatment, often regaining a normal size.[14] These results also showed, for the first time, the importance of brain growth in infant hydrocephalus because of its positive correlation with cognitive outcome. This represents a paradigm shift in our thinking about hydrocephalus treatment, which has traditionally been aimed at reducing ventricle size and intracranial CSF volume; however, the randomized trial showed no such correlation between CSF volume and cognitive outcome.[14] Thus, these early results from the trial led to an important question: does successful surgical treatment in early infancy lead to sustained, long-term brain growth and improved cognitive outcome beyond the 1st year? That is, are these results just transient phenomena that later stabilize or even regress despite treatment? This question is especially relevant since the exact cause and mechanism of early brain growth after hydrocephalus treatment is not known, and it is not until 2 to 3 years of age that the human brain attains 80%–90% of its adult volume.[15]

The answers might have relevance not just to postinfectious hydrocephalus in Sub-Saharan Africa, but also to infant hydrocephalus from other causes worldwide. Therefore, we have continued to follow this cohort of randomized infants to determine long-term brain growth trajectories and correlations with developmental outcome 2 years after treatment, which we present herein.

Methods

Study Design and Participants

The present analysis describes the 2-year results of a randomized trial comparing ETV+CPC and VPS for postinfectious hydrocephalus, which was conducted at the CURE Children's Hospital of Uganda (CCHU), a freestanding pediatric neurosurgical hospital in Mbale, Uganda. Trial design and 1-year results have been published elsewhere.[14] In summary, eligible infants had an age < 180 days and met established criteria for postinfectious hydrocephalus,[3] excluding those with an active clinical CSF infection or CT evidence of congenital brain anomaly, severe anatomical brain distortion, or multiloculated hydrocephalus. Written consent was obtained from each mother in her home language. Randomization commenced on May 27, 2013, and continued until the desired 100 patients had been enrolled.

Interventions

The ETV+CPC arm underwent a standard unilateral frontal approach with flexible endoscopy.[8] If the floor of the third ventricle could not be opened or if there was intraoperative evidence of substantial prepontine cistern scarring (which correlates with a high rate of ETV+CPC failure),[13] a VPS was inserted instead.[16] These primary crossovers to VPS were analyzed as ETV+CPC in the intention-to-treat analysis. The VPS arm underwent placement of a Chhabra VPS as per the usual CCHU protocol.[6,7]

One hundred eligible patients were randomized on the basis of an a priori sample size calculation, which estimated that a clinically meaningful difference between treatment arms in the 12-month Bayley Scales of Infant Development, Third Edition (BSID-III), cognitive scaled score to affect decision-making would be 3 (roughly three-quarters of the expected standard deviation [SD]), assuming 20% mortality and a 5% loss to follow-up with alpha = 0.05 and power of 90%.

Follow-Up

Patients were seen for clinical assessment and head CT at approximately 24 months after surgery, and home visits were conducted for those who had failed to return for follow-up.

Outcomes

Developmental outcome was measured by trained evaluators, who, under the supervision of a neuropsychologist, used a culturally modified BSID-III to evaluate all children.[17] The children wore hooded jackets to blind the evaluators to their treatment allocation. The cognitive, gross motor, and fine motor scaled scores at 24 months after surgery were obtained. BSID-III scaled scores range from 1 to 19, with a general population mean of 10

and SD of 3. The language scale portion of the BSID-III was not administered, since at 24 months of age, the complexity of language and the cultural irrelevance of the test could become confounding factors and since we had no other validated instrument for language assessment at 24 months in any of the many local languages. Therefore, only the BSID-III cognitive and motor scales were administered. Baseline BSID-III was administered within 1 week before surgery to 1 day after surgery and included cognitive, motor, and language scales.

Other outcomes included all-cause mortality, infection, and time to treatment failure resulting in death or repeat surgery. Successful treatment was determined by previously described clinical and radiographic criteria.[3,6,8,18] In the case of treatment failure, the treating surgeon determined the type of repeat operation to perform (reopening of ETV, VPS placement, or VPS revision).[19]

Brain and CSF Volumes

We employed previously described[14] semi-automated image segmentation of each CT scan to calculate brain and CSF volume. Using normalized brain growth curves derived from 1067 healthy children's normal MRI scans in the North American National Institutes of Health Pediatric MRI Data Repository (https://nda.nih.gov/ndarpublicweb/Documents/Pediatric_MRI_Data.pdf), we quantified the normative growth percentile for the age and sex of each patient.[20] Normative data for Ugandan infants are not available. The individuals performing these volumetric assessments were blinded to the patients' BSID-III results.

Statistical Analysis

Comparison between treatment arms was performed as an intention-to-treat analysis of 24-month BSID-III cognitive scores using the Mann-Whitney U-test. An analysis of covariance was also performed, adjusting for age at randomization and baseline BSID-III cognitive score. Further analyses compared changes in BSID-III cognitive scores from baseline and compared the other BSID-III scores at 24 months. The Kaplan-Meier method was used to create time-to-treatment-failure curves that were compared with a log-rank test.

Brain volumes were converted to z-scores based on age- and sex-corrected volume distributions for North American infants.[20] Raw and normalized brain volumes and CSF volumes were compared between treatment arms using the Mann-Whitney U-test. We determined the proportion of patients who had substantial brain growth (an increase in brain volume z-score of 1 or more between baseline and 24 months), substantial brain volume loss (a decrease in brain volume z-score of 1 or more between baseline and 24 months), and normal brain volume (brain volume larger than 1 SD below the age- and sex-corrected mean). Differences between treatment arms were compared using Fisher's exact test. Paired data were compared with the Wilcoxon signed-rank test.

Analyses were performed to determine the relationship between brain volume and developmental outcome. Spearman correlation was assessed between all 24-month BSID-III scores and brain and CSF volumes separately. Two-year BSID-III scores and changes in BSID-III scores were compared between those who did and those who did not have

substantial brain growth and substantial brain volume loss by using the Mann-Whitney U-test.

We used the Hodges-Lehmann estimator to determine differences between medians with confidence intervals and the normal approximation to determine confidence intervals for differences between proportions.

The Appendix lists the trial structure and personnel. The study received ethics board approval at CCHU, Boston Children's Hospital, The Hospital for Sick Children, and The Pennsylvania State University. The independent Data Safety Monitoring Board provided oversight of the study conduct (see Appendix). The trial was registered at ClinicalTrials.gov (clinical trial registration no. NCT01936272).

Results

Between May 2013 and April 2015, 158 patients were screened (Fig. 1), 58 of whom were excluded, leaving 100 eligible randomized patients (51 randomized to ETV+CPC and 49 to VPS). We stopped recruitment after randomization of the predetermined number of eligible patients. Baseline data are shown in Table 1.

Treatment Complications

There were 15 deaths (9 at < 24 months): 1 attributed to treatment failure 8 months after ETV+CPC, 1 from infection at 5.5 months after initial ETV+CPC and then crossing over to VPS, 4 from acute gastroenteritis (at 7, 12, 24, and 29 months), 4 from malnutrition (at 12, 12, 21, and 30 months), 3 from febrile illness (at 32, 33, and 35 months), 1 from pneumonia (at 22 months), and 1 from measles (at 24 months). All-cause mortality and infection were similar between treatment arms (Table 2), and the former variable was comparable to rates in our prior retrospective study of survival after treatment for postinfectious hydrocephalus in this population, which found 2- and 5-year mortality rates of around 20% and 30%, respectively.[21]

There were 18 (35.3%) treatment failures for ETV+CPC and 15 (30.6%) for VPS (p = 0.67) (Table 2 and Fig. 2). Survival analysis showed no significant difference between the two arms (p = 0.32, log-rank test).

Developmental Outcome

Two-year developmental outcome was available for 89 patients (Fig. 1). There was no significant difference in BSID-III cognitive score between ETV+CPC and VPS groups (p = 0.17; Table 2), with similar results when adjusted for age at randomization and baseline BSID-III cognitive score (p = 0.15) and when using treatment received rather than intention to treat (p = 0.48). There was also no significant difference between groups in other BSID-III scores or in comparisons of their change from baseline (Table 2). When the two treatment groups were combined, only the BSID-III fine motor score showed significant improvement (p = 0.004) between baseline and 24 months, with no significant changes for cognitive or gross motor scores (p = 0.18 and p = 0.63, respectively).

Brain and CSF Volume Outcome

Baseline volume data were available for 99 patients (50 ETV+CPC, 49 VPS; Table 1) and 24-month volume data were available for 89 patients (44 ETV+CPC, 45 VPS; Fig. 3 and Table 2). The VPS arm demonstrated significantly lower CSF volume ($p < 0.001$) at 24 months than the ETV+CPC arm (data not shown). None of the brain volume data were significantly different between treatment arms in the intention-to-treat analysis (Table 2) or treatment-received analysis (data not shown), so analyses were performed with the two groups combined.

Raw brain volumes increased between baseline and 24 months ($p < 0.001$), but almost all of this increase was seen in the 1st year ($p < 0.001$), with very little change between 12 and 24 months ($p = 0.66$; Fig. 3A and B). Twenty-three patients (25.8%) demonstrated substantial normalized brain growth between baseline and 24 months, but these were almost all infants who had demonstrated that substantial growth in the first 12 months alone. Only 2 infants (2.2%) demonstrated substantial growth between 12 and 24 months. Normal brain volume was observed in 15.2% at baseline, 50.0% at 12 months, and only 17.8% at 24 months (Fig. 3C). A minority of patients (21.3%) suffered substantial normalized brain volume loss at 24 months compared to baseline, but 76.7% of all patients had substantial z-score decline between 12 and 24 months (Fig. 3C). There was no significant difference in the change in normalized brain volume in the 2nd year between those who experienced substantial normalized brain growth in the 1st year ($n = 24$, mean z-score change −1.53) and those who did not ($n = 65$, mean z-score change −1.35; $p = 0.3$).

Comparison of Volume and Developmental Outcomes

At 24 months, those with normal brain volume had higher median scores in all BSID-III domains and in all BSID-III changes from baseline (data not shown). Moderate (Spearman rho > 0.4) and statistically significant correlations were seen between 24-month brain volume (raw and normalized) and all BSID-III scores and BSID-III changes from baseline (Table 3). However, only low correlations (Spearman rho < 0.4) were seen with CSF volume and all developmental outcomes.

Discussion

Our longitudinal prospective results have revealed, for the first time, a particular temporal pattern in brain growth following treatment of infant postinfectious hydrocephalus in Sub-Saharan Africa. Specifically, we found that important gains are made in normalized brain volume in the 1st year after surgical treatment,[14] but they are largely lost by 2 years, as brain growth stagnates in the second 12 months. As a result, on average, these infants (15.2% of whom had normal brain volume at baseline) lost virtually all the brain volume gains they had made in the 1st year (50.0% of whom had normal brain volume) by the end of the 2nd year (only 17.8% of whom had normal brain volume). The raw brain volume results indicate that the decline in normalized brain volumes between 12 and 24 months did not reflect a true absolute loss of volume. Rather, brain volumes stagnated between 12 and 24 months rather than increasing, as would normally be expected for infants of that age. The important clinical implication of this finding is emphasized by the consistent positive correlation

we observed between brain volume and developmental outcome. Our findings raise key questions that could have relevance for the treatment and outcome of infant hydrocephalus, especially in regard to this and other causes of postinflammatory hydrocephalus (such as posthemorrhagic hydrocephalus of prematurity).[22,23]

First, what is the mechanism of brain growth early after treatment of infant hydrocephalus? Hydrocephalus causes cortical mantle compression, decreased cerebral blood flow, demyelination, and axonal degeneration.[24,25] Postnatal human brain growth normally results more from synaptogenesis and myelination than from neuronal cellular proliferation.[26] The majority of neurogenesis is complete at term, whereas gliogenesis peaks toward the end of gestation and continues through the 1st year of life. It is likely, but not proven, that an early increase in brain volume following hydrocephalus treatment in the 1st year reflects tissue decompression and reexpansion of cortical mantle, along with increased cerebral blood flow and blood volume. Our study was only able to assess brain volume by CT imaging, an unavoidable limitation in most Sub-Saharan Africa settings, which limited our ability to examine brain structural content in more detail. MRI would, for instance, enable us to segment and quantify white from gray matter growth (for which we are developing normative curves) and quantify myelination during the critical 2nd year of life. Regardless of the underlying cellular compartments responsible, however, the correlation of such increases in total brain volume with developmental outcome emphasizes the importance of this growth.

Second, why did brain growth stagnate in the 2nd year after treatment? By 2 to 3 years of age, the human brain is expected to have 80%–90% of its adult volume,[15] which adds particular importance to our assessment of brain volume at 2 years after treatment. In our cohort of infants, beyond the 1st year following surgery, the potential for brain growth appeared to have declined. The initial brain injury from infection and the inflammatory response in the early weeks of life could impact brain development differently at different stages because of temporal variations in the dominant mechanisms of brain growth. The effects of early brain injury could be projected over time with differential effects on future phases of brain development. The fact that there was no difference in these outcomes between treatment groups, that raw brain volume initially increased and then stabilized (rather than declined), and that the loss of normalized brain volume in the 2nd year was the same regardless of the extent of brain growth in the 1st year all suggest that brain growth and development might have been impacted more by the initial insult than by hydrocephalus or its mode of treatment. That is, it was the brain’s intrinsic growth potential that may have determined outcome at 2 years.

There are, however, other potential explanations as well. In the specific case of postinfectious hydrocephalus in Uganda, it is also possible that ongoing, and heretofore unrecognized, indolent brain infection could further hinder growth. Whether children with postinfectious hydrocephalus and apparently culture-negative ventricular CSF may harbor an occult, indolent bacterial or viral (e.g., cytomegalovirus) infection at the time of initial hydrocephalus treatment is a current area of investigation.[27] Certainly, the prevalence of unrelated diseases known to impact childhood survival in our patient population, such as malaria and malnutrition, may also hinder brain growth and development, especially

when gauged against norms for infants in high-income countries. The future availability of normative brain growth curves reflective of Ugandan children would improve the comparison against existing norms.

Third, should hydrocephalus treatment target brain volume growth rather than CSF reduction? This would represent a paradigm shift in our thinking about hydrocephalus, but our data suggest that it is larger brain volume—independent of CSF volume—that is the major determinant of outcome. Despite having persistently enlarged ventricles, the group treated with ETV+CPC had similar brain volume and developmental outcomes as the VPS group. Also, regardless of treatment, we continued to see significant positive correlations between brain volume and cognitive outcome that was not seen with CSF volume. For the time being, it remains technically challenging to obtain accurate brain volume measurements in a rapid enough fashion to guide clinical treatment decisions in most sub-Saharan African settings. We anticipate, however, that with the emergence of available inexpensive low-field MRI technologies[28,29] and continuing development of more automated machine learning segmentation protocols,[30] brain volume could become part of standard hydrocephalus assessment and follow-up in the way that ventricle size is currently.

Limitations of the Study

This study only addressed postinfectious hydrocephalus, which represents an etiology of infant hydrocephalus associated with some of the most severe primary brain injury, with very low brain volumes and poor developmental performance at baseline. Although postinfectious hydrocephalus is the most common cause of infant hydrocephalus in Sub-Saharan Africa—and likely globally as well—we cannot comment on the developmental and brain growth outcomes for other types of infant hydrocephalus. It is possible that in patients with greater structural brain integrity at baseline, the temporal pattern of posttreatment brain growth may be different. Also, concerns about malnutrition and other concomitant illnesses in this population further limit the ability to extrapolate our results to other populations. The study was conducted at a high-volume center with a great deal of experience in treating infant hydrocephalus; these results may not apply to low-volume or less experienced centers. Our assessment of developmental outcome was limited to a portion of the BSID-III and further limited by the generally poor function of this group of infants. More robust testing at an older age could provide different results; indeed, we intend to follow this cohort longer term to establish 5-year outcome results. Finally, it should be noted that all analyses were exploratory and should be considered hypothesis generating. As such, these results will, of course, need to be replicated in other infant cohorts to see if similar findings are obtained. The National Institutes of Health has, in fact, funded another large randomized trial that will address these issues in infants with hydrocephalus in North America (NCT04177914) using detailed MRI and developmental outcomes.

Conclusions

Even after successful surgical treatment of infant postinfectious hydrocephalus in Sub-Saharan Africa, early posttreatment brain growth stagnates in the 2nd year. Our findings underscore the importance of primary infection prevention and mitigation strategies along

with optimizing the child's environment to maximize brain growth potential and minimize the long-term effects of the initial brain insult.

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Appendix

Steering Committee

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ABBREVIATIONS

BSID-III	Bayley Scales of Infant Development, Third Edition
CCHU	CURE Children's Hospital of Uganda
ETV+CPC	endoscopic third ventriculostomy plus choroid plexus cauterization
VPS	ventriculoperitoneal shunt

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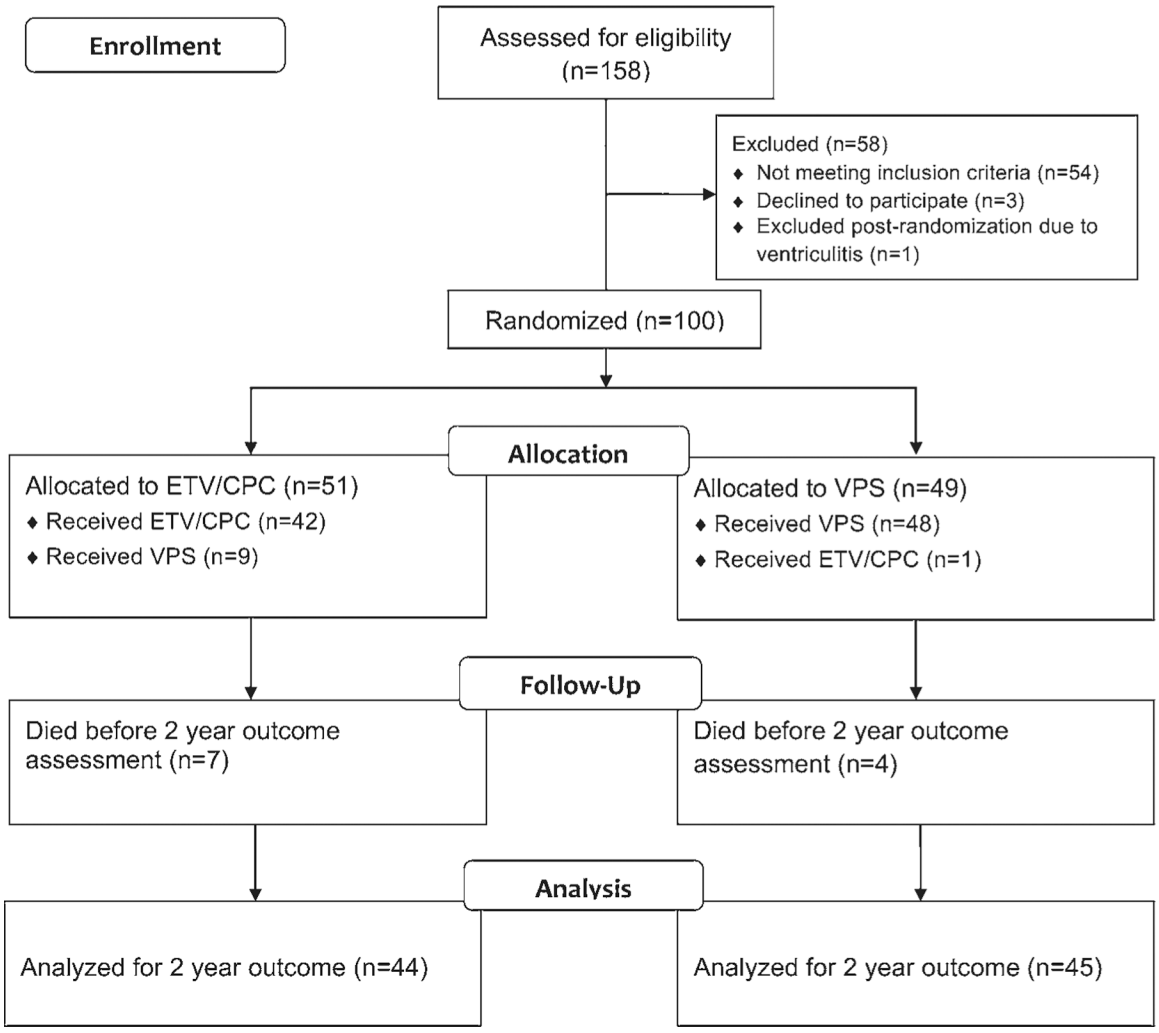

FIG. 1.
Flowchart showing enrollment, randomization, treatment, and follow-up.

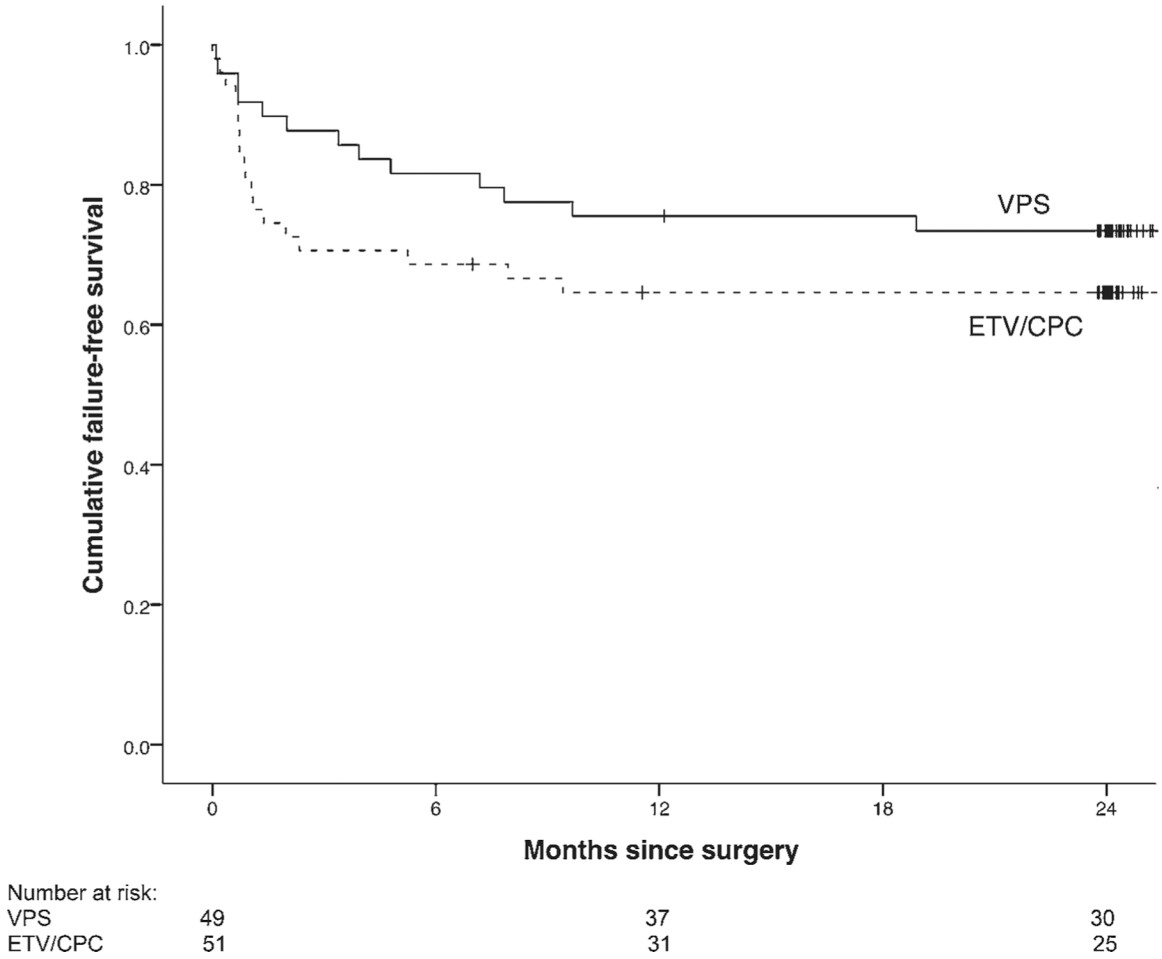

FIG. 2.

Kaplan-Meier survival curves for time to first treatment failure, grouped by intention to treat.

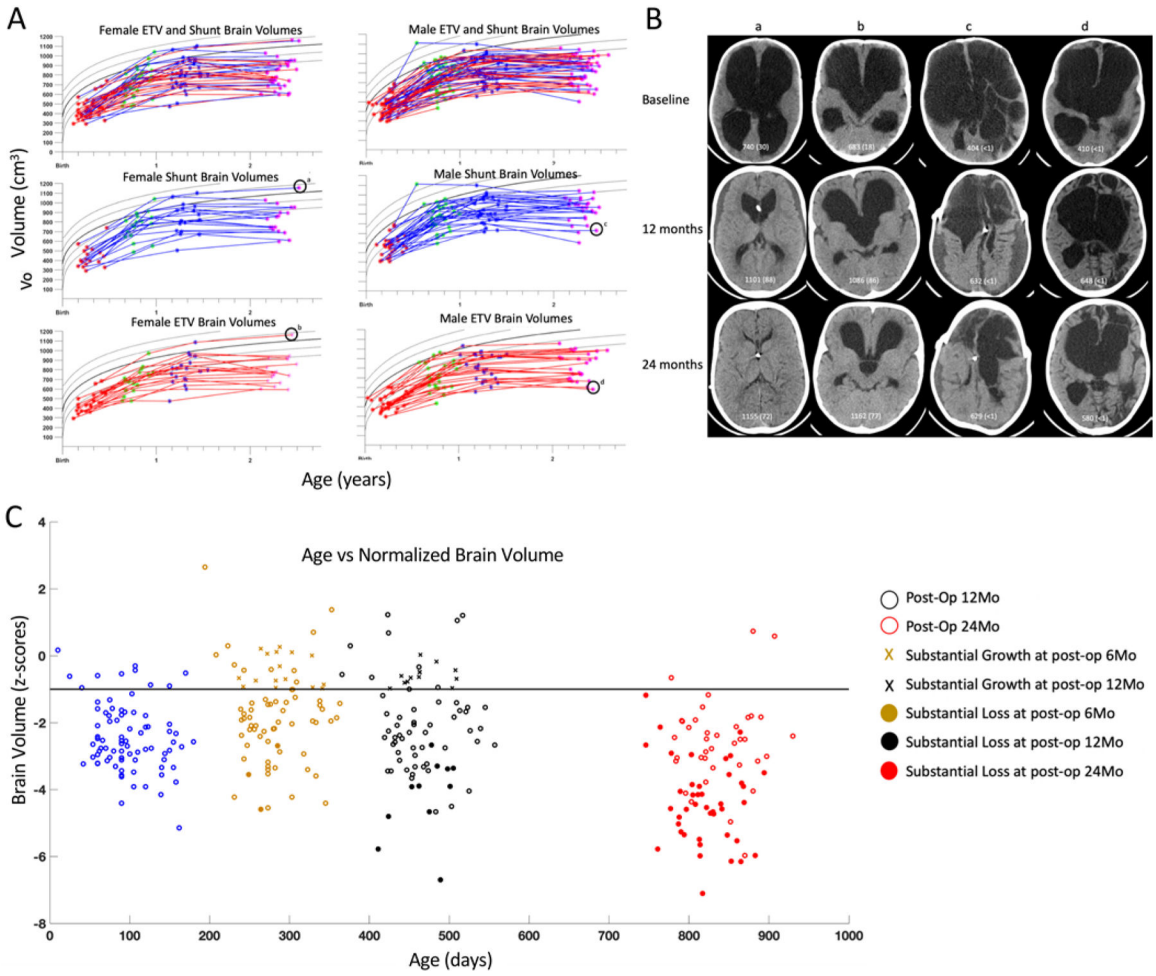

FIG. 3.

A: Raw brain volumes, in cm^3, stratified by males, females, shunts, and ETV intention to treat. **B:** Representative CT images for cases of normal brain volume at 24 months for female shunt (a) and female ETV (b) and growth failure at 24 months for male shunt (c) and male ETV (d). Brain volume (and normalized percentage) is given on each image shown. **C:** Normalized brain volumes, age adjusted and plotted as z-scores, for volumes measured before surgery and 6, 12, and 24 months following surgery. Cases with substantial growth are indicated with x's, and *filled colored circles* indicate substantial volume loss. The *horizontal line* at z = −1 indicates the threshold of normal age-adjusted volume (above) and volume less than normal for age (below).

TABLE 1.

Patient characteristics at baseline

Variable	Overall	Randomized to ETV+CPC	Randomized to VPS
Age at randomization in mos	3.1 (2.6, 4.1)	3.1 (2.2, 4.2)	3.1 (2.7, 3.9)
Female sex	39 (39.0%)	21 (41.2%)	18 (36.7%)
Weight in kg	6.0 (5.0, 7.0)	5.6 (4.5, 7.0)	6.2 (5.4, 7.2)
Head circumference in cm	48.5 (45.2, 50.8)	48.1 (44.5, 50.0)	48.7 (45.8, 53.5)
BSID-III scaled scores			
Cognitive	1 (1, 5)	1 (1, 5)	1 (1, 5)
Expressive language	3 (1, 6)	3 (1, 7)	2 (1, 6)
Receptive language	6 (1, 8)	6 (2, 9)	5 (1, 8)
Gross motor	3 (1, 5)	3 (1, 6)	2 (1, 4)
Fine motor	3 (1, 5)	4 (1, 6)	3 (1, 4)
Brain & CSF vol			
CSF vol in cm^3	783 (570, 1050)	741 (542, 992)	824 (639, 1345)
Raw brain vol in cm^3	448 (379, 514)	435 (378, 510)	461 (382, 518)
Normalized brain vol z-score	−2.2 (−4.4, −1.8))	−3.3 (−4.2, −1.7)	−2.8 (−4.6, −1.8)
Normal brain vol	15/99 (15.2%)	7/50 (14.0%)	8/49 (16.3%)

Data are expressed as median (interquartile range) or number (percent). Brain and CSF volume data were available for 50 ETV+CPC and 49 VPS infants. There were no significant between-group differences in the characteristics listed except for head circumference (p = 0.03, Mann-Whitney U-test) and CSF volume (p = 0.05, Mann-Whitney U-test).

TABLE 2.

Outcome results at 24 months

Variable	Overall	Randomized to ETV+CPC	Randomized to VPS	p Value	Difference (95% CI) for ETV+CPC vs VPS
Head circumference in cm	49.5 (46.9, 51.5)	50.0 (48.2, 52.9)	48.0 (46.1, 51.3)	0.008	2.0 (0.5, 3.4)
Treatment failure	33/100 (33.0%)	18/51 (35.3%)	15/49 (30.6%)	0.67	4.7% (−13.7%, 23.1%)
Infection	4 (4.0%)	2 (3.9%)	2 (4.1%)	>0.99	−0.2% (−7.8%, 7.5%)
All-cause mortality	15 (15.0%)	9 (17.6%)	6 (12.2%)	0.58	5.4% (−8.5%, 19.3%)
BSID-III scaled scores					
Cognitive, primary outcome	4 (1, 5)	4 (1, 6)	3 (1, 5)	0.17	0 (0, 2)
Gross motor	1 (1, 5)	1 (1, 9)	1 (1, 3)	0.07	0 (0, 1)
Fine motor	5 (1, 8)	6 (1, 9)	5 (1, 7)	0.31	0 (0, 2)
Change in BSID-III scaled scores from baseline					
Cognitive	0 (−2, 3)	1 (−2, 4)	0 (−2, 3)	0.64	0 (−1, 2)
Gross motor	0 (−3, 1)	0 (−3, 4)	0 (−2, 0)	0.62	0 (−1, 2)
Fine motor	2 (−2, 4)	2 (−3, 4)	1 (−2, 4)	0.67	0 (−2, 1)
Brain vol: raw, in cm^3					
At baseline	448 (379, 514)	435 (379, 510)	461 (382, 518)	0.84	−5 (−43, 34)
At 12 mos	813 (709, 941)	809 (692, 937)	821 (741, 956)	0.21	−33 (−97, 19)
At 24 mos	831 (725, 923)	774 (688, 920)	863 (740, 948)	0.36	−30 (−95, 30)
Brain vol: normalized for age and sex					
Normalized brain vol at 24 mos, z-score	−2.6 (−3.9, −1.4)	−3.0 (−4.1, −1.4)	−2.4 (−3.6, −1.4)	0.40	−0.3 (−1.1, 0.5)
Normal brain vol at 24 mos	16/90 (17.8%)	9/45 (20.0%)	7/45 (15.6%)	0.78	4.0% (−11.0%, 20.0%)
Substantial brain growth from baseline to 24 mos	23/89 (25.8%)	7/44 (15.9%)	16/45 (35.6%)	0.05	−20.0% (−38.0%, −1.0%)
Substantial brain vol loss from baseline to 24 mos	19/89 (21.3%)	9/44 (20.5%)	10/45 (22.2%)	>0.99	−2.0% (−19.0, 15.0%)
Substantial brain vol loss from 12 to 24 mos	69/90 (76.7%)	34/45 (75.6%)	35/45 (77.8%)	>0.99	−2.0% (−20.0%, 15.0%)
Substantial brain growth from 12 to 24 mos	2/90 (2.2%)	1/45 (2.2%)	1/45 (2.2%)	>0.99	−0% (−6.0%, 6.0%)

Data are expressed as median (interquartile range) or number (percent), unless indicated otherwise. The p values were derived from the Mann-Whitney U-test or Fisher's exact test. Twenty-four–month data for head circumference were available for 90 patients (45 ETV+CPC, 45 VPS), and data for BSID-III scores and volumes were available for 89 patients (44 ETV+CPC, 45 VPS). Hodges-Lehmann estimates and 95% confidence intervals were used for differences in medians and normal approximation for differences in proportions.

TABLE 3.

Correlation of 24-month outcome with brain and fluid volume

Variable	Raw Brain Vol	Normalized Brain Vol	CSF Vol
BSID-III scaled scores at 24 mos			
Cognitive	0.63, <0.001	0.64, <0.001	−0.29, 0.006
Gross motor	0.52, <0.001	0.52, <0.001	−0.31, 0.003
Fine motor	0.58, <0.001	0.61, <0.001	−0.23, 0.03
Change in BSID-III scaled scores at 24 mos, from baseline			
Cognitive	0.48, <0.001	0.48, <0.001	−0.06, 0.61
Gross motor	0.45, <0.001	0.46, <0.001	−0.25, 0.02
Fine motor	0.55, <0.001	0.56, <0.001	−0.08, 0.44

Data are expressed as Spearman correlation, p value. Data were available for 88 patients.