Child's Nervous System (2020) 36:1407–1414
https://doi.org/10.1007/s00381-020-04503-y

ORIGINAL ARTICLE

Cranial and ventricular size following shunting or endoscopic third ventriculostomy (ETV) in infants with aqueductal stenosis: further insights from the International Infant Hydrocephalus Study (IIHS)

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Received: 1 December 2019 / Accepted: 2 January 2020 / Published online: 21 January 2020

Abstract

Purpose The craniometrics of head circumference (HC) and ventricular size are part of the clinical assessment of infants with hydrocephalus and are often utilized in conjunction with other clinical and radiological parameters to determine the success of treatment. We aimed to assess the effect of endoscopic third ventriculostomy (ETV) and shunting on craniometric measurements during the follow-up of a cohort of infants with symptomatic triventricular hydrocephalus secondary to aqueductal stenosis.

Methods We performed a post hoc analysis of data from the International Infant Hydrocephalus Study (IIHS)—a prospective, multicenter study of infants (< 24 months old) with hydrocephalus from aqueductal stenosis who were treated with either an ETV or shunt. During various stages of a 5-year follow-up period, the following craniometrics were measured: HC, HC centile, HC *z*-score, and frontal-occipital horn ratio (FOR). Data were compared in an analysis of covariance, adjusting for baseline variables including age at surgery and sex.

Results Of 158 enrolled patients, 115 underwent an ETV, while 43 received a shunt. Both procedures led to improvements in the mean HC centile position and *z*-score, a trend which continued until the 5-year assessment point. A similar trend was noted for FOR which was measured at 12 months and 3 years following initial treatment. Although the values were consistently higher for ETV compared with shunt, the differences in HC value, centile, and *z*-score were not significant. ETV was associated with a significantly higher FOR compared with shunting at 12 months (0.52 vs 0.44; $p = 0.002$) and 3 years (0.46 vs 0.38; $p = 0.03$) of follow-up.

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Conclusion ETV and shunting led to improvements in HC centile, *z*-score, and FOR measurements during long-term follow-up of infants with hydrocephalus secondary to aqueductal stenosis. Head size did not significantly differ between the treatment groups during follow-up, however ventricle size was greater in those undergoing ETV when measured at 1 and 3 years following treatment.

Keywords International Infant Hydrocephalus Study · Infant hydrocephalus · Endoscopic third ventriculostomy · Shunt

Introduction

The pre- and post-operative assessment of infants with hydrocephalus typically includes measurements of head circumference (HC) and ventricular size. Together with other clinical and radiological parameters, such craniometrics may be helpful in determining the success of treatment. Changes in ventricular size following shunting or endoscopic third ventriculostomy (ETV) have been studied widely in the pediatric population, with successful shunting able to decrease ventricular size relatively quickly, while successful ETV also decreases ventricular size, but less consistently so [1–4]. A decrease or stabilization of HC *z*-score is typically expected following successful treatment [2]. However, despite the ubiquitous practice of measuring HC, the effect of treatment on the rate of head growth remains an understudied metric, particularly in the infant population.

The International Infant Hydrocephalus Study (IIHS) was a multicenter prospective study of infants (< 24 months old) with symptomatic triventricular hydrocephalus from aqueductal stenosis [5–7]. It is the first prospective study directly comparing the long-term outcomes of shunting and ETV for infant hydrocephalus. No significant difference in overall health status and quality of life was observed which was the primary outcome measure, reported in 2018 [7]. Herein, we present our findings of a post hoc analysis that examined the effect of shunting and ETV on ventricular size and HC during follow-up.

Methods

Descriptions of the IIHS have been published previously [5–7]. Centers experienced in pediatric neuroendoscopy prospectively enrolled infants with hydrocephalus secondary to aqueductal stenosis that was amenable to treatment with a ventriculoperitoneal shunt (VPS) or ETV. Initially, the study included both randomized and non-randomized arms, but poor recruitment into the randomized arm led to analyses being performed on the combined cohort [8]. Recruitment occurred between 2004 and 2013.

The following inclusion criteria were applied: < 24 months of age at time of operation; symptomatic triventricular hydrocephalus requiring primary treatment; gestational age > 36 weeks at birth; pre-operative magnetic resonance imaging (MRI) showing aqueductal stenosis with no other major brain anomalies. Patients with a history of intraventricular hemorrhage (intra-uterine or post-natal) or intracranial infection were included, unless this related to prematurity. Patients with the following conditions were excluded: open spina bifida; Dandy Walker syndrome with vermian agenesis/dysgenesis; perinatal asphyxia; severe brain dysmorphic anatomical features; known chromosomal abnormalities; or intracranial tumor.

Treatment failure was defined as the need for any repeat intervention for CSF diversion (including ETV or shunt insertion/revision) determined by the treating surgeon, following standard clinical practice, or death related to hydrocephalus. The treating surgeon then decided whether to repeat the primary surgery or try the alternative treatment, essentially "crossing-over" the patient from their primary treatment.

Craniometrics

Measurements at enrolment and during follow-up were performed in the following manner:

- Head circumference: Measurements performed at the bedside in the standard manner were recorded in centimeters (cm) to calculate percentile positions and *z*-scores at several stages of follow-up. The *z*-scores are an age-corrected unit describing the HC deviance from the mean value of the reference population divided by the standard deviation for the reference population based upon the 2006 WHO Child Growth Standards (https://www.who.int/childgrowth/en/). A *z*-score of −2, −1, 1, and 2 approximately correspond to the 2.5th, 15th, 85th, and 98th centiles, respectively. The *z*-scores are advantageous in that they provide a single directional unit reflecting deviation of HC, facilitating comparisons at the extremes of distribution.
- Ventricular size: MRIs performed pre-operatively and at 12 months and 3 years of follow-up were utilized to calculate the frontal-occipital horn ratio (FOR). FOR is a validated ratio in pediatric hydrocephalus that has been demonstrated to have a high degree of inter-observer reliability [9, 10]. The normal ventricle size is 0.37 ± 0.03 [9].

Analysis

Data collected from the randomized and non-randomized arms of the study were pooled to compare craniometric measurements for those undergoing ETV versus shunt as their primary surgery. Descriptive data are presented as mean and standard deviation (SD) or median and inter-quartile range (IQR) where appropriate. Comparisons of baseline data to determine potential imbalances in pre-operative measurements were undertaken using chi-square or Mann-Whitney tests, as appropriate.

An analysis of covariance (ANCOVA) was undertaken using HC, HC percentile, HC *z*-score, and FOR as dependent variables to compare measurements at various stages of follow-up for infants undergoing ETV or shunt, adjusting for patient age at first surgery (months), sex, history of infection or hemorrhage, and geographical continent. An intention to treat analysis was performed, whereby data collected at each stage of follow-up was analyzed based on the primary treatment modality. Recognizing that some of these patients will have crossed-over to the other treatment arm, thus clouding the interpretation of the data, the analyses were repeated by limiting the cohort to only those patients who did not experience any treatment failure and, therefore, remained with their primary treatment modality throughout without crossing-over.

The IIHS was publicly registered (NCT00652470) and received ethics approval from all participating institutions. Participating investigators and other trial personnel are listed in the Acknowledgments.

Results

One hundred and fifty eight eligible patients were previously analyzed, of whom 115 underwent ETV and 43 had a shunt as the primary intervention. Patients were enrolled from 27 centers in 4 continents (see [6] for breakdown of centers per continent). Infants undergoing ETV were slightly older than shunted patients (4.3 versus 2.2 months, $p = 0.007$) and had slightly lower mean HC percentile values (86.3 versus 93.4; $p = 0.03$) and *z*-scores (2.35 versus 3.98; $p = 0.02$) than shunted patients, but otherwise the baseline characteristics were similar (Table 1).

During a median follow-up period of 35 months (IQR 22–57), 47 patients (29.7%; 38 ETV patients and 9 shunt patients) failed primary treatment. Among these failures, there was 1 hydrocephalus-related death (in the primary shunt group) due to presumed shunt failure in a child who died prior to being transferred to the treating neurosurgical center. The remaining majority went on to receive a second procedure (ETV or shunt). Data analysis pertaining to treatment failure has previously been reported [11].

Table 2 illustrates the mean craniometric measurements obtained during follow-up for patients in each treatment cohort. Both procedures led to reductions in HC percentile, *z*-scores, and FOR during the 5-year study period. Head size metrics were not significantly different between treatment groups at any assessment point; however, ventricular size (FOR) was significantly greater in the ETV cohort at 1 (0.52 versus 0.44; $p = 0.002$) and 3 years (0.46 versus 0.38; $p = 0.03$) of follow-up (Table 2, Figs. 1 and 2). The mean ventricular size of shunted patients was near normal when measured at 3 years (Fig. 2).

Re-defining the cohort further such that any patient experiencing treatment failure was excluded from analysis (cohort sizes with complete data at 5 years; ETV, 42, shunt, 13), the findings were similar in that cranial size metrics did not significantly differ between treatment modalities at the 5-year follow-up point, while FOR remained greater in the ETV cohort at 12 months

Table 1 Baseline characteristics (adapted from [6]). *HC*, head circumference; *FOR*, frontal-occipital horn ratio, *%tile*, percentile

	Overall	ETV ($n = 115$)	Shunt ($n = 43$)	*p* value
Age in months (median, IQR)	3.6 (1.6–6.6)	4.3 (1.8–7.7)	2.2 (0.6–5.3)	0.007
Age categories (number, %)				
< 30 days	29 (18.4%)	15 (13.0%)	14 (32.6%)	
30 days to < 6 months	83 (52.5%)	60 (52.2%)	23 (53.5%)	
6 to < 12 months	28 (17.7%)	24 (20.9%)	4 (9.3%)	
12 to < 24 months	18 (11.4%)	16 (13.9%)	2 (4.7%)	
Sex (M/F)	100/58	74/41	26/17	0.71
History of infection (number, %)	9 (5.7%)	4 (3.5%)	5 (11.6%)	0.06
History of hemorrhage (number, %)	9 (5.7%)	8 (7.0%)	1 (2.3%)	0.44
Treatment failure (number, %)	47 (29.7%)	38 (33.0%)	9 (20.9%)	0.17
Length of follow-up, months (median, IQR)	35 (22–57)	37 (24–56)	34 (11–59)	0.36
HC %tile ($n = 157$) (mean, SD)	88.2 (22.6)	86.3 (24.8)	93.4 (14.3)	0.03
z-score ($n = 157$) (mean, SD)	2.8 (2.96)	2.35 (2.18)	3.98 (4.23)	0.02
FOR ($n = 148$) (mean, SD)	0.61 (0.09)	0.61 (0.08)	0.62 (0.12)	0.33

Table 2 Craniometric data measured during follow-up

Metric	ETV	Shunt	Adjusted difference between ETV and shunt (95% confidence interval)*	Adjusted *p* value*
12 months				
N	85	32		
HC in cm (mean, SD)	48.8 (3.3)	48.6 (3.5)	− 0.225 (− 1.5 to 1.1)	0.73
HC %tile (mean, SD)	80.1 (31.2)	79.9 (28.5)	− 2.925 (− 15.4 to 9.6)	0.64
HC *z*-score (mean, SD)	2.0 (2.3)	2.0 (2.4)	− 0.3 (− 1.3 to 0.6)	0.49
FOR (mean, SD)	0.52 (0.11)	0.44 (0.13)	0.08 (0.03 to 0.12)	*0.002*
18 months				
N	86	30		
HC in cm (mean, SD)	50.0 (2.8)	49.1 (2.5)	0.6 (− 0.6 to 1.7)	0.32
HC %tile (mean, SD)	81.4 (28.3)	71.1 (31.5)	6.4 (− 6.1 to 18.9)	0.31
HC *z*-score (mean, SD)	1.84 (2.0)	1.21 (1.75)	0.41 (− 0.42 to 1.24)	0.33
2 years				
N	93	28		
HC in cm (mean, SD)	50.9 (2.9)	49.7 (2.6)	1.1 (− 0.2 to 2.3)	0.09
HC %tile (mean, SD)	82.4 (27.8)	71.7 (33.0)	9.2 (− 3.6 to 22.0)	0.16
HC *z*-score (mean, SD)	1.88 (2.0)	1.14 (1.74)	0.74 (− 0.14 to 1.61)	0.10
3 years				
N	85	27		
HC in cm (mean, SD)	51.5 (3.1)	50.4 (2.8)	1.1 (− 0.2 to 2.4)	0.09
HC %tile (mean, SD)	78.3 (31.6)	65.3 (33.9)	11.9 (− 2.33 to 26.1)	0.10
HC *z*-score (mean, SD)	1.67 (2.31)	0.86 (1.89)	0.87 (− 0.11 to 1.84)	0.08
FOR (mean, SD)	0.46 (0.12)	0.38 (0.08)	0.07 (0.01 to 0.13)	*0.03*
5 years				
N	62	17		
HC in cm (mean, SD)	52.5 (2.96)	51.6 (2.02)	0.82 (− 0.71 to 2.34)	0.29
HC %tile (mean, SD)	71.3 (31.9)	64.4 (33.2)	5.4 (− 12.6 to 23.4)	0.55
HC *z*-score (mean, SD)	1.29 (2.19)	0.62 (1.42)	0.59 (− 0.55 to 1.73)	0.30

N, cohort size with complete data; *ETV*, endoscopic third ventriculostomy; *HC*, head circumference; *FOR*, frontal-occipital ratio, *%tile*, percentile.

*Adjusted *p* values and adjusted mean differences were derived from ANCOVA models, adjusted for age, sex, history of infection/hemorrhage, and geographical continent. *P* values in italics were deemed statistically significant

and 3 years (0.49 versus 0.38; $p = 0.002$) (Table 3). The mean HC measurement and *z*-score value were significantly greater in the ETV group at 2 years of follow-up, though this difference did not persist at 3 and 5 years (Table 3).

Discussion

This post hoc analysis of the IIHS cohort of infants with aqueductal stenosis treated with either ETV or shunt has demonstrated some important findings. First, the data show that both ETV and shunting led to improvements in HC percentile, HC *z*-score, and FOR measurements during long-term follow-up, including measurements obtained at the 5 year post-treatment stage. Second, cranial size, although numerically greater for ETV, did not significantly differ between the treatment cohorts during follow-up; however, ventricular size remained significantly greater in those undergoing ETV compared with shunted patients when measured at 1 and 3 years following treatment (Figs. 1 and 2).

The latter observation is in keeping with other studies where shunting has been more reliable at decreasing ventricular size than ETV [12, 13]. The addition of choroid plexus cauterization (CPC) to ETV adds the potential of reducing CSF production; but its true effect and outcomes remain understudied. Dewan et al. recently compared 6-month craniometric outcomes in an infant cohort with a range of pathologies undergoing successful treatment with VPS or ETV/CPC [14]. Ventricle size (FOR) was also observed to decrease significantly more following VPS insertion compared with ETV/CPC. Six months following treatments, ventricular size remained unchanged in the ETV/CPC group while a 27% decrease was observed in the VPS treated group

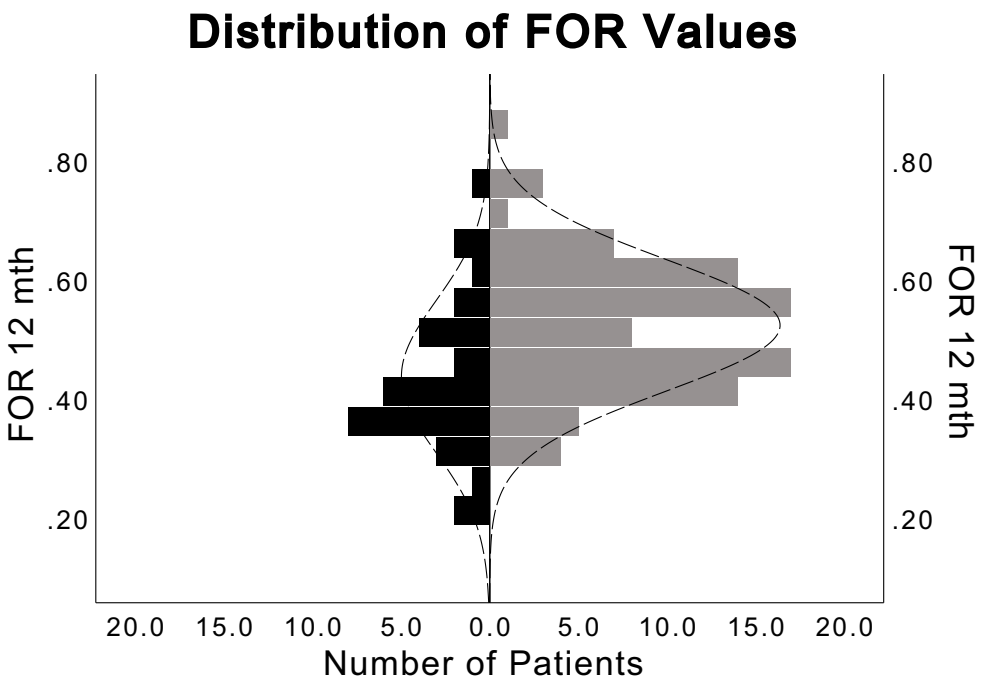

Fig. 1 Population pyramid demonstrating frequency and distribution of FOR values measured 12 months following shunt (black) or ETV (gray). FOR, frontal-occipital horn ratio

(to near normal). Absolute HC values at 6 months did not differ between the treatment groups, though the average HC centile was higher in the ETV/CPC group at 6 months post-operatively (76th vs 54th percentile for ETV/CPC and shunted patients respectively; $p = 0.046$). Their study was limited by its short follow-up period and heterogeneous cohort mix with regard to hydrocephalus etiology. Further work analyzing the success/failure of ETV/CPC suggests the collective assessment of metrics is necessary and advisable when making treatment decisions [15].

Although taking repeated measurements of HC is a simple and safe method for monitoring infant head growth, there is a

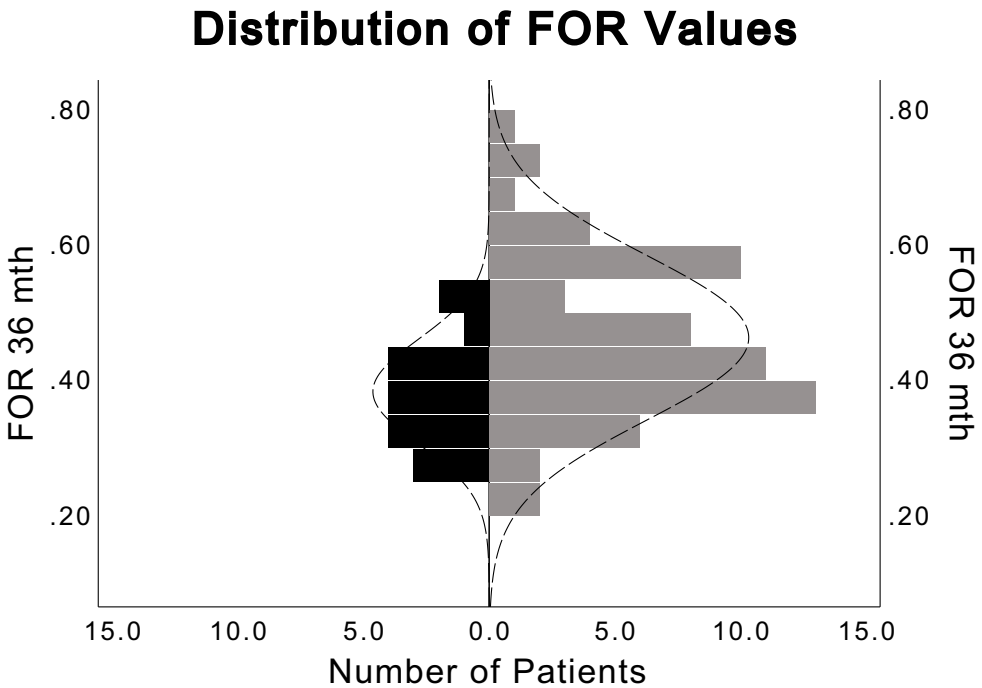

Fig. 2 Population pyramid demonstrating frequency and distribution of FOR values measured 3 years following shunt (black) or ETV (gray). FOR, frontal-occipital horn ratio

Table 3 Craniometric data measured during follow-up, excluding cases experiencing treatment failure

Metric	ETV	Shunt	Adjusted difference between ETV and shunt (95% confidence interval)*	Adjusted *p* value*
12 months				
N	50	26		
HC in cm (mean, SD)	49.4 (3.6)	48.8 (3.7)	−0.2 (−1.8 to 1.5)	0.86
HC %tile (mean, SD)	83.5 (30.3)	81.5 (29.4)	−1.3 (−16.2 to 13.7)	0.87
HC *z*-score (mean, SD)	2.4 (2.5)	2.2 (2.5)	−0.3 (−1.5 to 0.9)	0.67
FOR (mean, SD)	0.54 (0.1)	0.43 (0.12)	0.09 (0.04 to 0.14)	*0.001*
18 months				
N	58	24		
HC in cm (mean, SD)	50.5 (2.9)	49.3 (2.7)	0.9 (−0.5 to 2.2)	0.22
HC %tile (mean, SD)	86.1 (25.6)	73.7 (30.7)	9.4 (−4.5 to 23.4)	0.18
HC *z*-score (mean, SD)	2.2 (2.0)	1.4 (1.8)	0.6 (−0.4 to 1.7)	0.21
2 years				
N	65	21		
HC in cm (mean, SD)	51.5 (3.0)	49.9 (2.7)	1.5 (0.01 to 3.1)	*0.048*
HC %tile (mean, SD)	87.9 (22.9)	74.3 (33.1)	12.6 (−1.4 to 26.5)	0.08
HC *z*-score (mean, SD)	2.3 (2.1)	1.3 (1.8)	1.1 (0.02 to 2.2)	*0.047*
3 years				
N	59	21		
HC in cm (mean, SD)	51.9 (3.4)	50.5 (3.0)	1.2 (−0.4 to 2.9)	0.14
HC %tile (mean, SD)	79.4 (31.7)	67.8 (34.7)	9.1 (−7.9 to 26.1)	0.29
HC *z*-score (mean, SD)	1.9 (2.6)	1.0 (2.1)	0.904 (−0.4 to 2.2)	0.16
FOR (mean, SD)	0.49 (0.11)	0.38 (0.08)	0.11 (0.04 to 0.18)	*0.002*
5 years				
N	43	13		
HC in cm (mean, SD)	52.9 (3.3)	52.0 (2.0)	0.6 (−1.4 to 2.6)	0.56
HC %tile (mean, SD)	75.1 (31.8)	72.0 (28.9)	0.5 (−20.5 to 21.4)	0.96
HC *z*-score (mean, SD)	1.6 (2.4)	0.9 (1.3)	0.5 (−1.0 to 1.9)	0.54

N, cohort size with complete data; *ETV*, endoscopic third ventriculostomy; *HC*, head circumference, *FOR*, frontal-occipital ratio; *%tile*, percentile

*Adjusted *p* values and adjusted mean differences were derived from ANCOVA models, adjusted for age, sex, history of infection/hemorrhage, and geographical continent. *P* values in italics were deemed statistically significant

paucity of such data in ETV and shunt-treated patients, particularly in the infant population. HC serves as a surrogate clinical marker of brain growth, and infancy is when up to two thirds of brain growth occurs, highlighting its importance and those of its derived measures, such as percentile and *z*-score, in clinical practice. Nilsson et al. demonstrated the capability of shunting to decrease HC in an infant cohort (< 12 months) with a range of underlying pathologies and found that HC decreased in comparison with a reference population of healthy children at the ages of 2 and 3 years [16]. Head size was typically normalized compared with the reference population by 1 year. Although we did not include a control cohort, we similarly observed an improvement in cranial size metrics derived from HC measurements over a 5-year period in both shunt and ETV treated patients. We did find however, that these values were consistently greater in the ETV group, although the differences were small and non-significant. We acknowledge that our analyses are post hoc, and the study was not powered to detect such small differences.

While shunting more reliably decreases ventricular size in hydrocephalic patients than ETV, we are still trying to understand the neurocognitive implications of ventricular size during childhood development [12]. The primary analysis of the IIHS suggested long term overall health status and quality of life for the cohort was, in general, high and that there was no difference between those treated initially with ETV and shunt [7]. This is despite ETV patients in general having slightly larger ventricles by comparison. In a cohort of 93 children with spina bifida and hydrocephalus, Warf et al. found that FOR did not significantly differ between patients treated with VPS, ETV/CPC or managed conservatively, though cognitive performance was significantly better in those not requiring treatment, suggesting that ventricle size itself does not consistently correlate with cognitive performance [17]. Kulkarni

et al. recently corroborated this observation in a randomized trial that assessed the cognitive outcomes of Ugandan infants with post-infectious hydrocephalus following treatment with VPS or ETV/CPC. Brain volumes and cognitive performance measured at 12 months did not significantly differ between the treatment groups, even though ventricle size was significantly greater in the ETV/CPC group suggesting ventricle size is not the predominant determinant of cognitive function [18]. In the current study, brain volume was not quantified, although it may represent a more accurate surrogate marker of cognitive abilities than ventricular size alone [19], and therefore, its measurement should be considered in future work.

In this analysis, FOR was found to be significantly larger in the ETV treated group both at 1 and 3 years of follow-up. This differs slightly from the IIHS primary outcome analysis, however, where the difference in ventricle size between the ETV and shunt groups was not significant [7]. This may be explained by the variation in cohort size analyzed; the primary outcome analysis [7] investigated health status and quality of life, thus excluding patients with incomplete health outcome measures at 5 years of follow-up. That cohort was therefore slightly smaller than the one analyzed herein.

The IIHS has proved valuable in many respects since its conception [5], continuing to yield data from a relatively understudied group (infants < 24 months). Other strengths of the study include its prospective, international, multicenter nature and homogenous patient cohort, based on age and pathology. As such, some valuable insights into differences between shunting and ETV in infants have been derived [6, 7, 11]. Herein, further insights into how ETV and shunting may affect cranial growth and ventricle size for infants with aqueductal stenosis has been provided, which serves to further guide preoperative counseling and post-operative decision making.

This study is limited in several respects. We performed an intention to treat analysis such that cases were analyzed during follow-up based on their initial treatment. Almost one third of the cohort failed treatment (29%) at various stages of follow-up. Of these, the majority failed ETV treatment and went on to receive a shunt [11]. As such, crossing-over has served to increase the heterogeneity of the treatment cohort groups. Excluding cases failing primary treatment substantially reduced the cohort sizes for comparisons in the latter years of follow-up; however, the main observations and differences between treatment groups were similar (Table 3). The relatively small sample size allows the possibility that our study was under-powered to demonstrate significant differences in cranial size metrics. It is possible therefore, that the lack of statistically significant difference in these comparisons is simply related to lack of power. Furthermore, potential differences in cranial size metrics in the youngest patients (< 6 months at the time of treatment) may have been missed as the cohort was not divided based on age. However, we did adjust for age at treatment in our comparative analyses. In addition, FOR measurements at 5 years were not available for most of the cohort. Nevertheless, it is a reasonable assumption that most children would have reached a stable ventricle size by 3 years that would be consistent at 5 years of age. Although we independently adjudicated eligibility criteria for the study, treatment failure was diagnosed by the treating surgeon, thus introducing the possibility of bias. Moreover, as our cohort only included infants with aqueductal stenosis, the findings may not be applicable to the wider population.

Conclusions

Further analysis of the IIHS cohort of infants treated with ETV or shunting for aqueductal stenosis and symptomatic triventricular hydrocephalus has yielded valuable insights into cranial growth and ventricular size during long-term follow-up. Both ETV and shunting led to improvements in HC centile, HC *z*-score, and FOR measurements during long-term follow-up. Cranial size did not significantly differ between the treatment groups during follow-up; however, mean ventricle size was greater in those undergoing ETV when measured at 1 and 3 years following initial treatment. Larger studies on broader populations are required to establish the true impact of successful hydrocephalus treatments on cranial size, ventricular size, brain volume, and ultimately neurocognitive outcomes.

Acknowledgments The authors would like to extend a special thanks to Adina Sherer, who ran the organizational logistics of this study and without whom, the IIHS would not have been possible.

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Author contributions AVK, SS, CS, and ICC contributed to the study conception and design. Data collection was performed by AVK, SS, CS, and collaborators from the IIHS. Material preparation and data analysis were performed by ICC and AVK. The first draft of the manuscript was written by ICC, and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

The IIHS was publicly registered (clinicaltrials.gov, NCT00652470) and received ethics approval from all participating institutions.

Conflict of interest The members of the Steering Committee have no conflicts of interest with respect to this work.

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