Pediatric Neurosurgery at Seattle Childrens Hospital

Clinical Research → Better Understanding, Better Outcomes

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Our Mission

Clinical Excellence

Compassionate Care

Research disease

Innovative Therapy

- History of Contributions to the Understanding Of Disease

A clinically applicable functional MRI memory paradigm for use with pediatric patients

Hillary A. Shurtleff [a, b], Andrew Poliakov [c], Dwight Barry [d], Jason N. Wright [c, e], Molly H. Warner [a, b], Edward J. Novotny [a, b, f, g], Ahmad Marashly [a, b, f, g], Robert Buckley [h], Hannah E. Goldstein [a, h, i], Jason S. Hauptman [a, h, i], Jeffrey G. Ojemann [a, b, h, i], Dennis W.W. Shaw [c, e]

Robot-assisted stereoelectroencephalography in young children: technical challenges and considerations

Scott Boop, Ariana Barkley, Samuel Emerson, Laura M. Prolo, Hannah Goldstein, Jeffrey G. Ojemann & Jason S. Hauptman

Child's Nervous System **38**, 263–267 (2022) | Cite this article

Review > Neurology. 2021 Nov 2;97(18):864-873. doi: 10.1212/WNL.0000000000012773. Epub 2021 Oct 4.

Hypothalamic Hamartomas: Evolving Understanding and Management

Nathan T Cohen [1], J Helen Cross [2], Alexis Arzimanoglou [2], Samuel F Berkovic [2], John F Kerrigan [2], Ilene Penn Miller [2], Erica Webster [2], Lisa Soeby [2], Arthur Cukiert [2], Dale K Hesdorffer [2], Barbara L Kroner [2], Clifford B Saper [2], Andreas Schulze-Bonhage [2], William D Gaillard [2], Hypothalamic Hamartoma Writing Group

> Neurosurg Focus. 2020 Apr 1;48(4):E9. doi: 10.3171/2020.1.FOCUS19889.

Pediatric functional hemispherectomy: operative techniques and complication avoidance

Christopher C Young [1], John R Williams [1], Abdullah H Feroze [1], Margaret McGrath [1], Ali C Ravanpay [1 2], Richard G Ellenbogen [1 3], Jeffrey G Ojemann [1 3], Jason S Hauptman [1 3]

> Epilepsy Behav. 2021 Sep 16;124:108298. doi: 10.1016/j.yebeh.2021.108298. Online ahead of print.

Pediatric hemispherectomy outcome: Adaptive functioning, intelligence, and memory

Hillary A Shurtleff [1], Emma A Roberts [2], Christopher C Young [3], Dwight Barry [4], Mary H Warner [5], Russell P Saneto [6], Robert Buckley [3], Timothy Firman [7], Andrew V Poliakov [8], Richard G Ellenbogen [9], Jason S Hauptman [9], Jeffrey G Ojemann [9], Ahmad Marashly [6]

Review > Front Neurol. 2021 Feb 12;12:639319. doi: 10.3389/fneur.2021.639319. eCollection 2021.

The Putative Role of mTOR Inhibitors in Non-tuberous Sclerosis Complex-Related Epilepsy

Hannah E Goldstein [1 2], Jason S Hauptman [1 2]

> Neuroradiology. 2020 Nov;62(11):1467-1474. doi: 10.1007/s00234-020-02491-z. Epub 2020 Jul 10.

Structural MRI and tract-based spatial statistical analysis of diffusion tensor imaging in children with hemimegalencephaly

Tae Yeon Jeon [1], Andrew V Poliakov [2], Seth D Friedman [2], Xiuhua L Bozarth [3], Edward J Novotny [3], Jason S Hauptman [4], Sung-Hoon Moon [5], Dennis W W Shaw [2]

Overview

Hydrocephalus

- HCRN Prospective Registry
- ESTHI

Epilepsy

- Clinical trials
- Genetics

HCRN registry

- Prospective study documenting every hydrocephalus surgical event and evaluation
- Informed consent waived
- Current patient enrollment at SCH: 1,239
- The Registry has provided descriptive data to generate sub-studies under the HCRN

hydrocephalus
clinical research network

HCRN registry

- We are a principal site for over a decade
- Wide range of patient data collected
- Allowed for over 20 publications to help us understand risk factors for failure and infection
- Contributed to infection reduction

hydrocephalus
clinical research network

Registry enrollment

Site Enrollment Summary

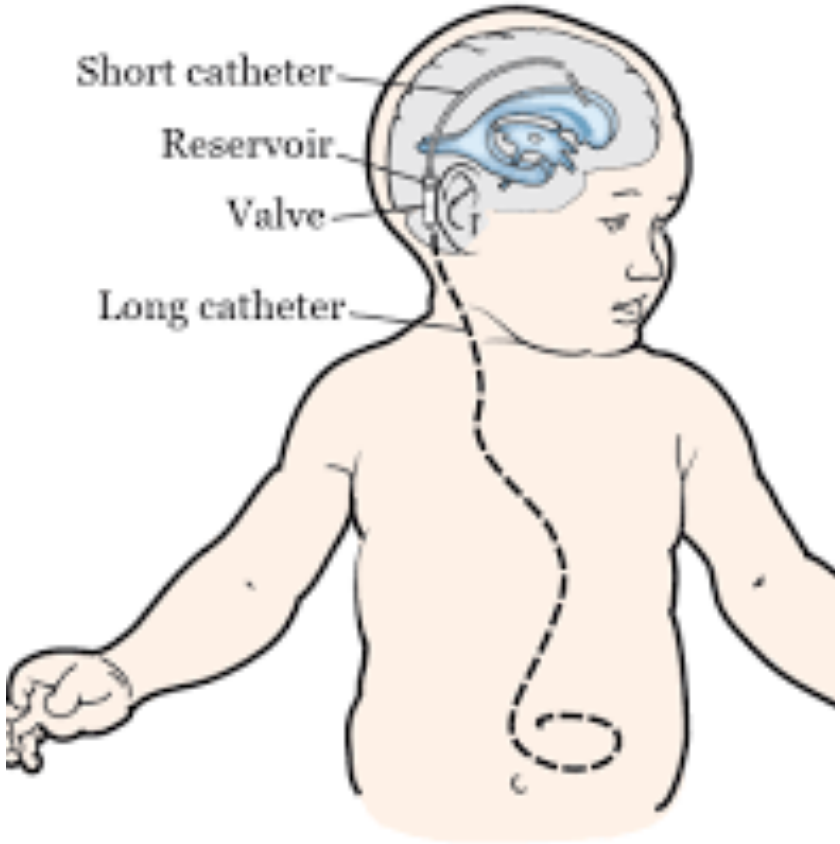
Site	Enrolled - Comprehensive	Enrolled - Non-comprehensive	Total
ALPE	78	41	119
BHEM	489	287	776
CHMW	459	324	783
DLTE	281	194	475
ELXA	812	470	1282
EPOC	44	45	89
FAPS	483	305	788
JAMN	241	174	415
NWCH	758	481	1239
OYBD	171	66	237
RHMT	1482	532	2014
SUPT	990	624	1614
WHIQ	3	0	3
XETA	1	0	1
YWLT	984	644	1628
ZOLT	276	250	526
Total	7552	4437	11989

ESTHI
Hydrocephalus and ETV-CPC An Prospective, Randomized Controlled Trial

Overall Rationale

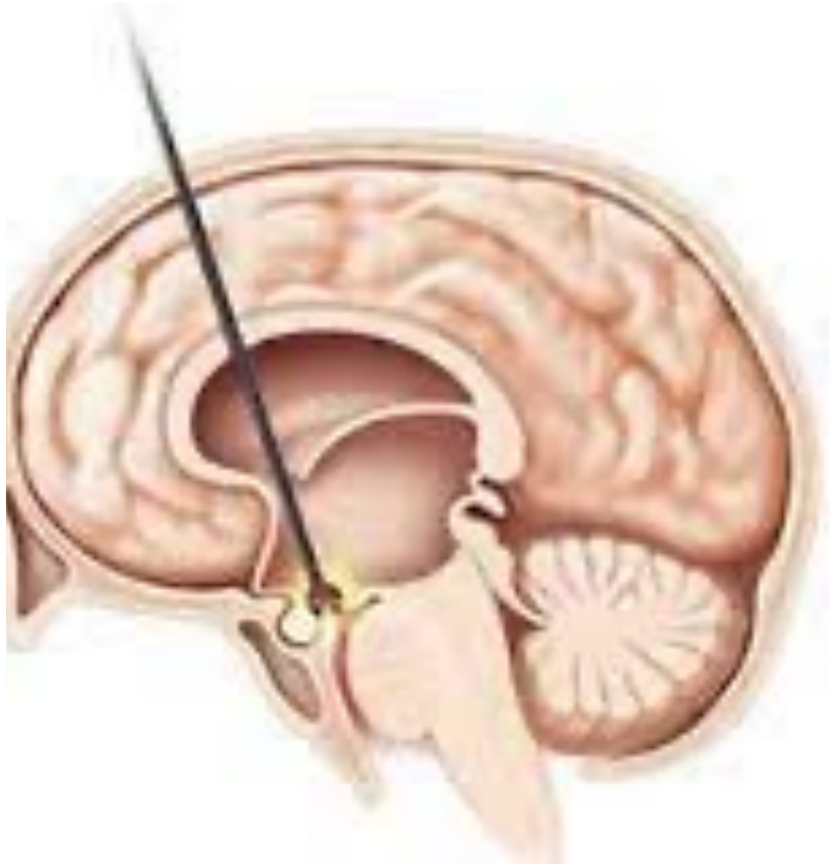
- Shunting remains the most common treatment for pediatric hydrocephalus
  - Associated with short- and long-term complications

- Complications of shunt surgery in infants are especially high



Overall Rationale

- The most promising alternatives have been endoscopic surgical options (ETV)
  - ETV alone has poor success in infants
  - Single largest age group for new onset HCP
  - Addition of choroid plexus cauterization (CPC) to ETV may augment the ETV

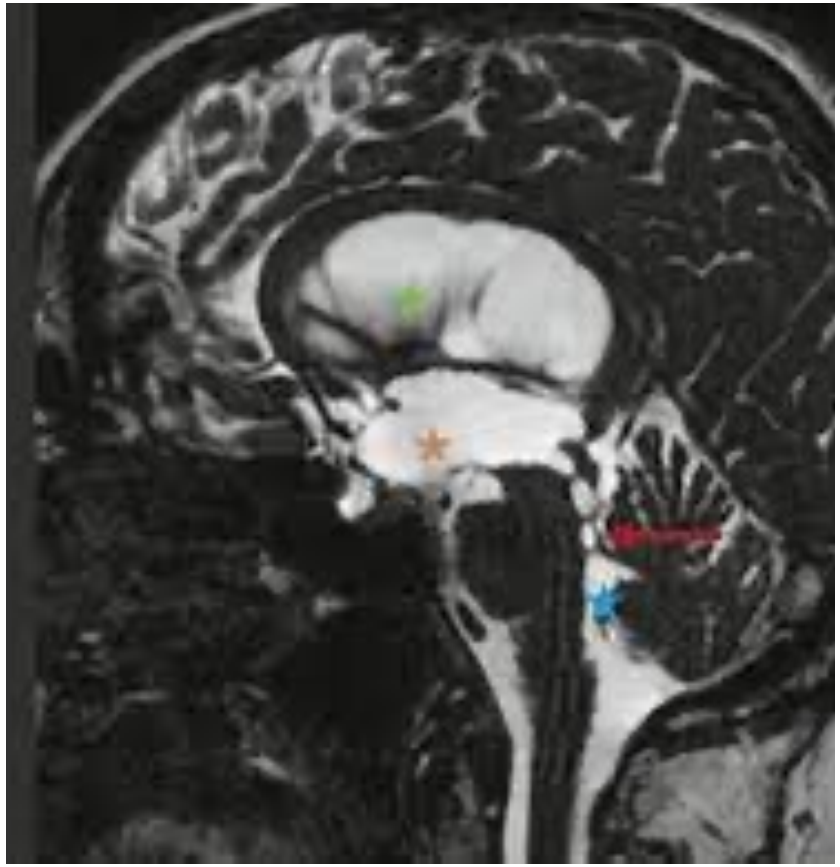


Hydrocephalus and Shunting

- Common causes of hydrocephalus in children include
  - myelomeningocele,
  - PHH,
  - congenital aqueductal stenosis,
  - brain tumors,
  - infection, and
  - other congenital anomalies.

- The majority of children with newly diagnosed hydrocephalus are infants **under 2 years old**.

- The most common treatment for hydrocephalus has been VPS, which has been in popular use for over 50 years.



VPS is not the perfect solution

- Complications of shunting are substantial
  - Shunt infection (5-10%),
  - Shunt obstruction (30-40% in the first 2 years), and
  - Shunt overdrainage (10-15%)

- Shunt complications can occur anytime during life and requires on-going surveillance.

- Each year there are over 38,000 admissions, nearly 400,000 hospital days, and total hospital charges of $1.4-2.0 billion for pediatric hydrocephalus, accounting for 3.1% of all pediatric hospital charges.
  - Most of these are related to shunts and their complications.

VPS is not the perfect solution

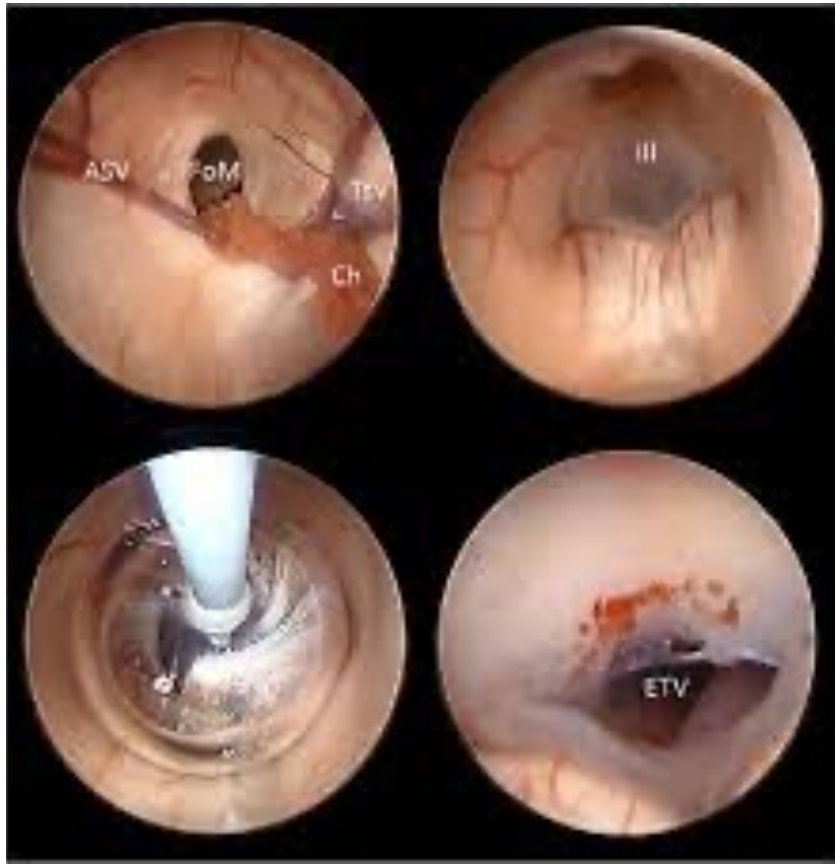
Aside from their medical morbidity and economic cost, shunt complications also adversely impact **QOL**.

Worse QOL associated with:

- Any history of shunt infection,
- A history of 2 or more shunt revisions, and
- Longer hospital stay for treatment of shunt complications

So how about ETV?

- Since the early 1990s, ETV has become the main alternative to shunting for hydrocephalus.
- This procedure involves placing an endoscopic camera into the ventricles of the brain and creating a hole in the floor of the third ventricle to act as an internal bypass for obstructed CSF.
- Avoidance of any implanted foreign shunt material = lower infection rate.
- Because there is no hardware, it may have better longevity.

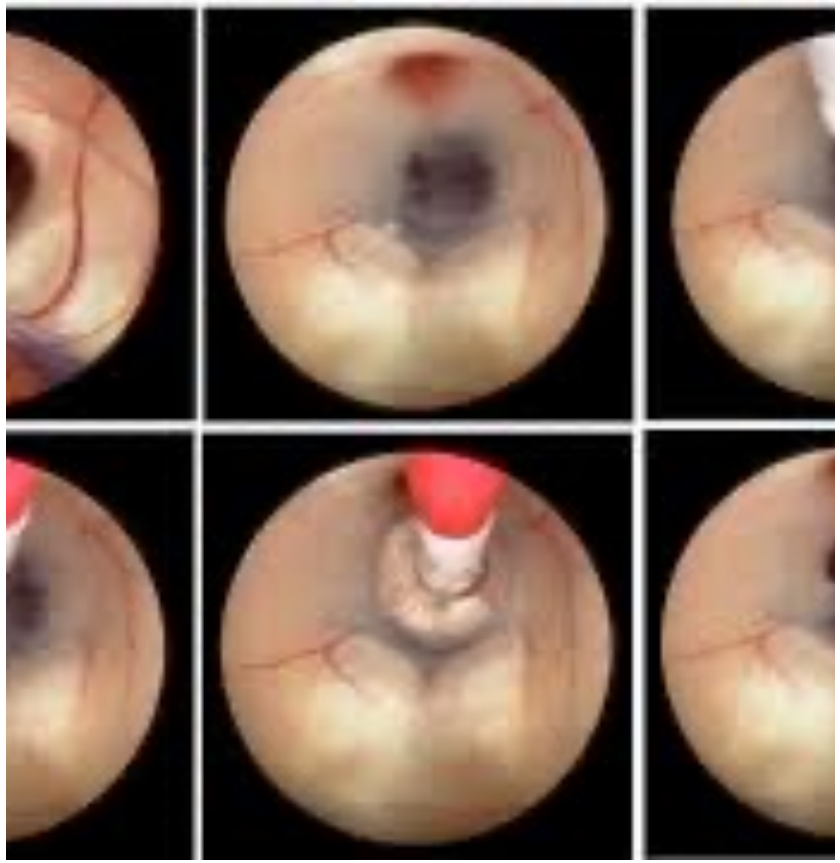


So how about ETV?

- The vast majority of ETV failures occur in 3-6 months
  - If an ETV remains complication-free at 6 months, then late complication rates are lower than compared to shunt.
  - Significant lifetime benefit

- Currently, ETV is a very routine procedure
  - 10-15% of new HCP cases are treated with ETV as the first-line therapy.

- The problem with ETV, however, is that many patients have a high rate of early failure.
  - Especially infants

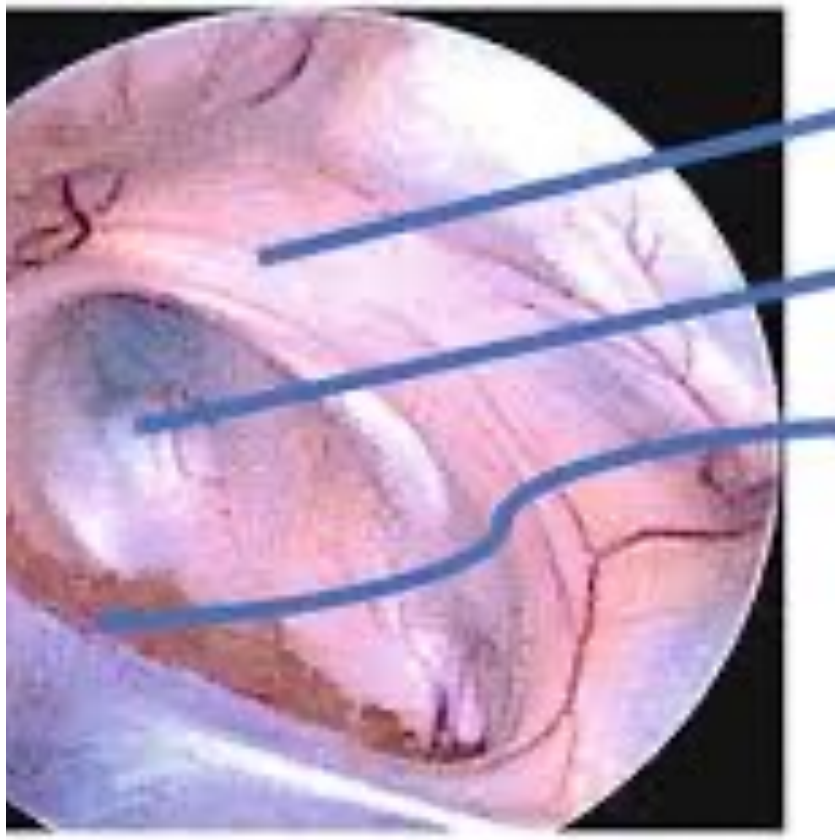


Why CPC? - Animal Work

- In rhesus monkeys, removing the choroid plexus of both lateral ventricles results in 33-40% reduction in CSF production up to 9 months after the procedure

- When the choroid plexus is removed and the foramen of Monro occluded, the ventricle doesn't enlarge (Dandy, Bering)

- When the choroid plexus is ablated, the CSF pulse pressure is lower (Wilson)
  - Pulse pressure waves caused by choroid plexus are a main driver of ventriculomegaly
  - Reducing choroid plexus pulsatility can reduce ventriculomegaly



Early Human Experience

- Scarff (1970) reported on a 23 year experience (1942-1965) of 39 cases of communicating hydrocephalus treated with CPC.
  - Overall, 26 cases (67%) had successful treatment of hydrocephalus, with >10 year follow-up and no long-term complications

- Pople et al in Bristol, UK
  - Performed CPC on 116 patients, with data for 104
  - Median age 5 months, mean f/u 10.5 year
  - There were no deaths or serious morbidity and complications
  - Overall success rate was 35% (long-term shunt-free)
    - Best results were in children with sub-acute communicating hydrocephalus (64% success)
    - Noted a lower incidence of seizures and better educational outcome than those who failed CPC and needed shunt

Modern African Experience

- The modern experience with CPC has largely been in its combined use with ETV, as pioneered by Warf in the early 2000s and published in 2005.
- 66% success rate compared to 47% for ETV alone in those <1 year old
- Predictors of successful outcome include
  - older age
  - myelomeningocele etiology (rather than post-infectious)
  - the degree of CPC performed
- “Dose-response" effect
  - partial CPC was beneficial (OR=2.0 versus ETV alone)
  - complete lateral ventricular CPC was even more beneficial (OR=4.8)

Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy

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Object. The aim of this prospective study was to investigate the causes of hydrocephalus in Uganda, the efficacy of endoscopic third ventriculostomy (ETV) in this environment, and whether existing parameters could be used to guide patient selection.

Methods. Three hundred consecutive children, 81.3% of whom were younger than 1 year of age, underwent ventriculoscopy preceding ETV as an initial treatment for hydrocephalus. In 179 patients (60%) the hydrocephalus was caused by a cerebrospinal fluid infection; in 76% of patients the infection had occurred in the 1st month of life. In 229 patients (76.3%) ETV was performed; 2% of patients were lost to follow up after less than 1 month and the surgical mortality rate was 1.8%. The first ETV was successful in 115 patients (52%); the mean follow-up period was 15.2 months. The mean time to repeated operation following a failed ETV was 1.5 months. Sixty-five patients underwent a second endoscopy; 37 underwent a second ETV, of which 14 procedures (38%) were successful (mean follow-up period 12.25 months). The overall success rate for ETV was 59%. Among patients older than 1 year of age, the procedure was successful in 22 (81%) of 27 with postinfectious hydrocephalus (PIHC) and 18 (90%) of 20 with nonpostinfectious hydrocephalus (NPIHC). The success rate of ETV among those patients younger than 1 year of age was 59% (60 of 101) for patients suffering from PIHC and 40% (21 of 52) for those suffering from NPIHC. Age correlated with success for NPIHC ($p = 0.0002$) and PIHC ($p = 0.0421$). The success rate of the surgery for patients with myelomeningocele and hydrocephalus who were younger than 1 year of age was 40% (eight of 20). The success rate of the surgery for PIHC in infants younger than 1 year of age was 70% (44 of 63) among patients with aqueductal obstruction but 45% (16 of 31) among patients with aqueductal patency ($p = 0.0254$). Fourth ventricular size as demonstrated on cranial ultrasonography or computerized tomography scanning predicted whether the aqueduct was patent ($p = 0.0001$).

Conclusions. Infection is the most common cause of hydrocephalus in Uganda. In all children older than 1 year of age and in those younger than 1 year of age with PICH and aqueductal obstruction, which was reliably predicted by cranial ultrasonography, ETV was effective.

KEY WORDS • **endoscopic third ventriculostomy** • **hydrocephalus** • **neonatal meningitis** • **ventriculitis** • **myelomeningocele** • **developing country** • **pediatric neurosurgery**

THE incidence of hydrocephalus in East Africa is very high. The use of shunts in a developing country—even if the difficulties of cost and availability are surmounted—presents unique problems. The complications of shunt malfunction and infection are manageable when competent neurosurgical care is available on an urgent basis; in a situation like that in Uganda, however, ready access to such care is impossible for most patients because of financial and logistical barriers. Long-term shunt dependency is more dangerous under these circumstances than it is in the developed world.

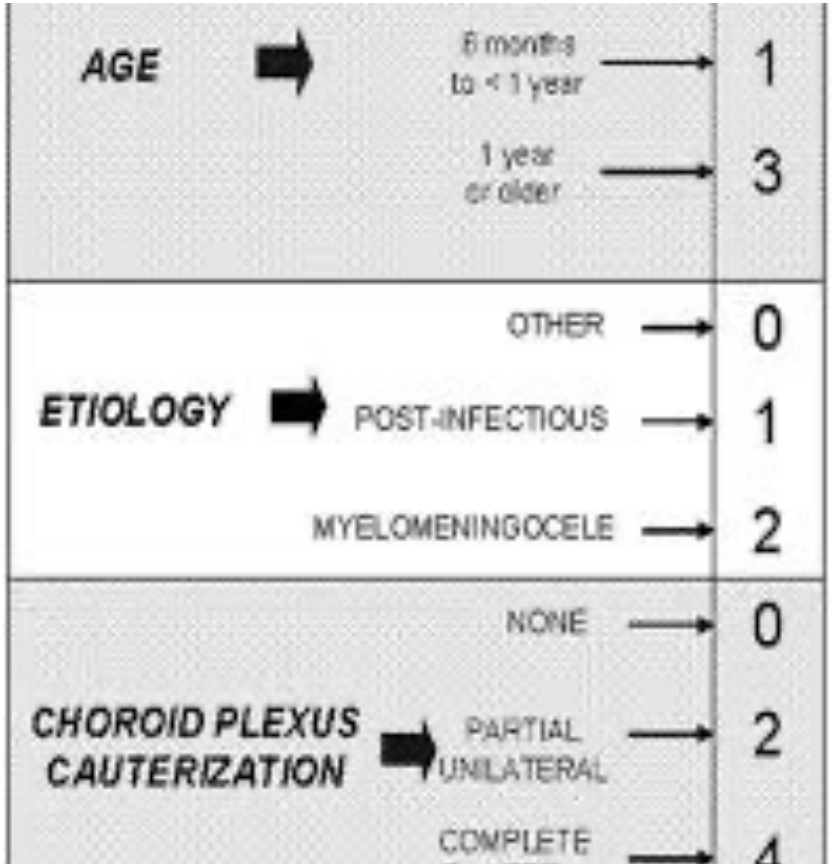
Abbreviations used in this paper: AIDS = acquired immunodeficiency syndrome; BA = basilar artery; CSF = cerebrospinal fluid; CPX = choroid plexus cauterization; ETV = endoscopic third ventriculostomy; HIV = human immunodeficiency virus; NPIHC = nonpostinfectious hydrocephalus; PIHC = postinfectious hydrocephalus; VP = ventriculoperitoneal.

In a developing country, ETV presents an attractive option for potentially treating hydrocephalus in a permanent way without the use of a shunt and its attendant expense, risks of infection and malfunction, and the need for life-long maintenance. The usefulness of ETV has been clearly demonstrated in cases of aqueductal stenosis in older children and adults;[4,9,13] however, questions have lingered concerning its use in infants,[4,13,29] in cases of hydrocephalus secondary to infection,[6,21,22] and in those associated with a myelomeningocele.[4,13,29] The majority of our patients present for treatment when they are younger than 1 year old, and the most common cause of hydrocephalus appears to be infections such as ventriculitis and meningitis. From the outset, therefore, the usefulness of ETV in our setting was uncertain. Nonetheless, the difficulty and danger of maintaining shunts in the environment of a developing country provided compelling reasons to study the efficacy of ETV as the initial treatment for hydrocephalus of all origins in children of all ages.

Modern African Experience

- Subgroups by etiology
  - congenital communicating HCP (72% vs 20% success)
  - congenital aqueductal stenosis (82% vs 49% success)
  - Myelomeningocele and Dandy-Walker complex, the rsuccess rates of roughly 75%

- In a retrospective multicenter study comparing ETV+CPC in Africa to ETV alone performed in other countries, Kulkarni et al. showed that the superior success rates in the African patients could be entirely explained by known **patient prognostic factors** and the advantages conferred by **CPC**.



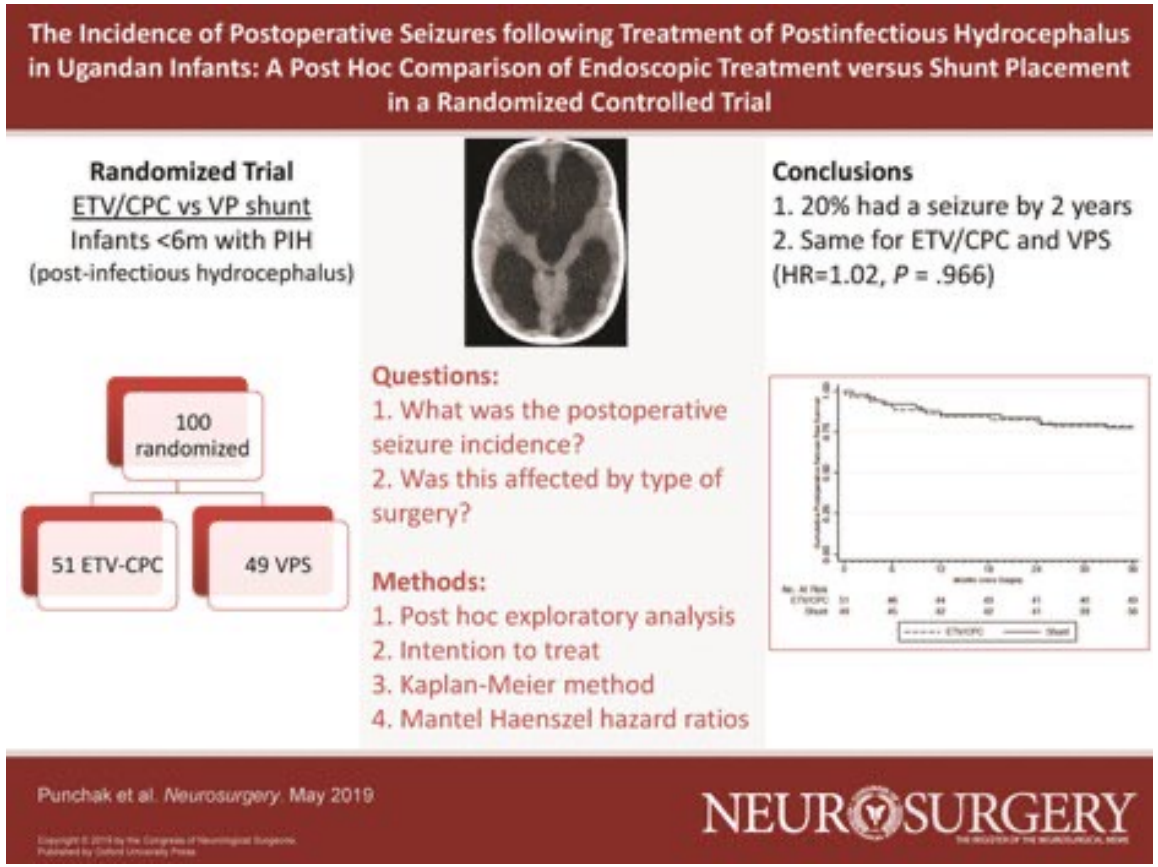
Modern African Experience

- Cognitive outcomes in myelomeningocele:
  - Those treated with ETV+CPC, those treated with shunt, and those requiring no treatment for hydrocephalus.
  - The Bayley-III scores were similar amongst all 3 groups
  - Mean Bayley-III Cognitive Scale scores 8.0 for treatment by ETV+CPC and 6.7 for treatment by shunt

- No difference in shunt survival or shunt infection between those treated with a primary shunt compared to those who were shunted after failure of ETV+CPC.
  - To date, over 4000 children in Africa have been treated with ETV+CPC.

Modern African Experience

- Randomized trial in Uganda specifically compared ETV+CPC versus shunt for post-infectious hydrocephalus
  - Cognitive outcome was no different
  - The success rate for ETV+CPC was non-significantly lower than shunt
    - 1 year success rates of 64% for ETV+CPC vs 73% for shunt, p=0.24
  - No difference in brain volume between ETV+CPC and shunt at 12 months
  - Proportion of children ultimately achieving normal brain volume was numerically similar



How about outside of Africa?

- Ogiwara et al. (Japan) reported 50% success in 18 children treated with CPC, of whom 12 also had ETV.

- Chamiraju et al. (Miami) reported 37% success in 27 infants with post-hemorrhage hydrocephalus of prematurity with ETV+CPC.
  - Rigid endoscope prohibiting complete CPC
  - Most of the failures occurring in the very youngest patients and those with narrow prepontine cisterns on MRI.
  - 83% of their ETV+CPC failures occurred in the first 3 months

- Recently, Zandian et al. performed a literature review and meta-analysis of ETV+CPC compared to ETV alone for pediatric hydrocephalus, utilizing the entire global experience from Africa and elsewhere.
  - Overall success rate in the pediatric population is 55% for ETV alone (534 cases) compared to 67% for ETV+CPC (164 cases).

How about outside of Africa?

- One of the largest published North American experiences to date comes from Warf himself (now Boston).

- Warf et al. reported their very early experience with 10 infants with intraventricular hemorrhage (IVH) of prematurity treated with ETV+CPC.
  - A total of 6 failed the procedure, all of whom had demonstrated prepontine cisternal scarring at surgery and on pre-operative MRI.

- Warf then published his larger series:
  - Of 91 infants treated with ETV+CPC, the success rate was 57%.
  - Some of the initial failures responded to repeat ETV, bringing the overall “shunt-free" rate to 65%.
  - Predictors of failed ETV+CPC included: post-infectious etiology, age at treatment younger than 6 months, presence of prepontine cistern scarring, and prior CSF diversion.

HCRN Retrospective Data

First 36 infants treated with ETV+CPC within 7 centers of the HCRN

No major peri-operative morbidities or mortalities and the procedure was successful in 52% at 1 year.

Disproportionately difficult, "salvage"-type cases

Second review of 192 cases in infants.

Over the course of 8 years, more frequently used and is being used in younger infants, broader range of etiologies

Median age was 3.6 months, with 92% under 12 months, 73% under 6 months, and 25% under 1 month.

MMC (26%), PHH (24%), AS(17%).

The 1 year success rate for ETV+CPC was 46%

Very low incidence of intra-operative and post-operative complications

<1 month with PHH = poor success rates

HCRN Prospective Data

- Beginning in 2014, the HCRN started recruiting for a prospective study of ETV+CPC in infants
  - 118 patients
  - Consensus a priori eligibility criteria (96% compliance) and failure criteria
  - The median corrected age was 1.3 months
  - MMC (30.5%), PIH (22.9%), and AS (21.2%).
  - The most common complications included seizures (5.1%) and CSF leak (3.4%).
  - The 6-month success rate was 36%.
- Important predictors of treatment success included older age ($p = 0.002$), smaller preoperative ventricle size ($p = 0.009$), and greater degree of CPC ($p = 0.02$).
- Age- and etiology-matching algorithm
  - Amongst 112 matched pairs, ETV+CPC was found to have signicantly higher failure rate than shunt ($p < 0.001$).

So why an RCT?

- Despite higher failure rates than a shunt, there is strong parental interest in pursuing this line of surgical treatment
  - NOT a shunt
  - Publicized at certain institutions
  - Not a strong understanding of Africa vs. North American outcomes

ESTHI Trial

- The Primary Hypothesis
  - Initial treatment of hydrocephalus with ETV+CPC will result in 12-month cognitive outcome, as assessed by Bayley-III, that is **not inferior** to cognitive outcome achieved with initial treatment with shunt, among infants eligible for either procedure.

- Non-inferiority is defined as rejection of the null hypothesis that 12-month Bayley-III Cognitive Scale score is at least 1.5 points lower among infants randomized to ETV+CPC versus those randomized to shunt.

Who is eligible?

All infants <52 weeks corrected age requiring a first-time permanent procedure for the treatment of hydrocephalus will be screened for the study.

Inclusion Criteria

- Hydrocephalus due to myelomeningocele in a child >37 weeks

  OR hydrocephalus due to other etiology in a child who is 30 days corrected age,

- Symptomatic hydrocephalus

  - Ventriculomegaly (frontal-occipital horn ratio (FOR) >0.45) **and** at least **one** of the following:
  - Head circumference >98th percentile for corrected age with bulging fontanelle or splayed sutures
  - Upgaze paresis/palsy (sundowning)
  - CSF leak
  - Papilledema
  - Tense pseudomeningocele
  - Vomiting or irritability, with no other attributable cause
  - Bradycardias or apneas, with no other attributable cause
  - Intracranial pressure (ICP) monitoring showing persistent elevation

- No prior history of shunt or ETV (VSGS OK)

- Corrected age <52 weeks

Exclusion Criteria

- Hydrocephalus due to intraventricular hemorrhage born <37 weeks
- Anatomy not suitable for ETV+CPC or anteriorly placed VPS
- Underlying condition with a high chance of mortality within 12 months
- Hydrocephalus with loculated CSF compartments
- Peritoneal cavity not suitable for distal shunt placement
- Active CSF infection
- Hydranencephaly
- Child requires an intraventricular procedure (e.g. endoscopic biopsy) in addition to hydrocephalus surgery

Let’s switch gears and talk about epilepsy

Phase 1 study of ABI-009 (*nab*-rapamycin) for Surgically-Refractory Epilepsy (RaSuRE) and RaSuRE Open Label Extension

10/31/2018 - Present

Big Picture

Epilepsy: 5 out of every 10,000 children per year

Up to 1/3 are medically refractory

- Surgical outcomes are highly variable despite evolving technique
  - Hemis, lesional temporal lobes do great
  - Non lesional extratemporal do not do as great
  - Lesional cases generally do better than non-lesional cases

Big Picture

- What is a lesion?
  - Limits of our detection by ultrastructural imaging
  - Diagnostic improvements
    - Higher field MRI, new sequences, functional connectivity, white matter connectivity will broaden lesional definitions
  - Type 1 cortical dysplasia being a prototypical example of this dilemma
  - Isn’t the “lesion” really genomic/proteomic/metabolomic?

What happens to our surgical failures?

Continue cycling through ASMs

VNS, RNS, DBS (by definition palliative)

Give up on the notion of improved control

Succumb to the natural history

SUDEP

Neurodevelopmental decline/epileptic encephalopathy

Mammalian Target of Rapamycin (mTOR)

- mTOR is a ubiquitous 289kDa serine/threonine kinase in the phosphatidylinositol 3-kinase (PI3K)-related kinases (PIKK) family
  - Dysregulated in a number of human diseases, including tuberous sclerosis complex (TSC) and epilepsy

Analysis of common PI3K-AKT-MTOR mutations in pediatric surgical epilepsy by droplet digital PCR reveals novel clinical and molecular insights

Filomena Pirozzi, Matthew Berkseth, Rylee Shear, Lorenzo Gonzalez, Andrew E. Timms, Josef Sulc, Emily Pao, Nora Oyama, Francesca Forzano, Valerio Conti, Renzo Guerrini, Emily S. Doherty, Sulagna C. Saitta, William B. Dobyns, Edward Novotny, Jason N.N. Wright, Russell P. Saneto, Seth Friedman, Jason Hauptman, Jeffrey Ojemann, Raj P. Kapur, Ghayda M. Mirzaa

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PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia

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ABI-009 (Nab-rapamycin) for Surgically-Refractory Epilepsy (RaSURE)

- Intravenous albumin-bound mTOR inhibitor, ABI-009
- Hypotheses:
  1. ABI-009 is **safe** and **well-tolerated** in children with medically- and surgically-refractory epilepsy
  2. The addition of ABI-009 therapy results in improved seizure control
- Unique among trials of antiepileptic medications – mTOR inhibition in both a TSC and non-TSC population

Objectives and Endpoints

- Primary Objectives:
  1. Determine dose-limiting toxicities (**DLTs**) and maximum tolerated dose (**MTD**) of ABI- 009
  2. Record the **adverse events** (AEs)
  3. Record medication **compliance**
- Secondary Objectives:
  1. Drug **efficacy**

     - percent reduction in seizure rate, median percent reduction, treatment response rate, seizure frequency, and number of seizure-free days
  2. Rapamycin **levels** were measured to assess a relationship to response

Prospective, single-center, phase 1 safety study

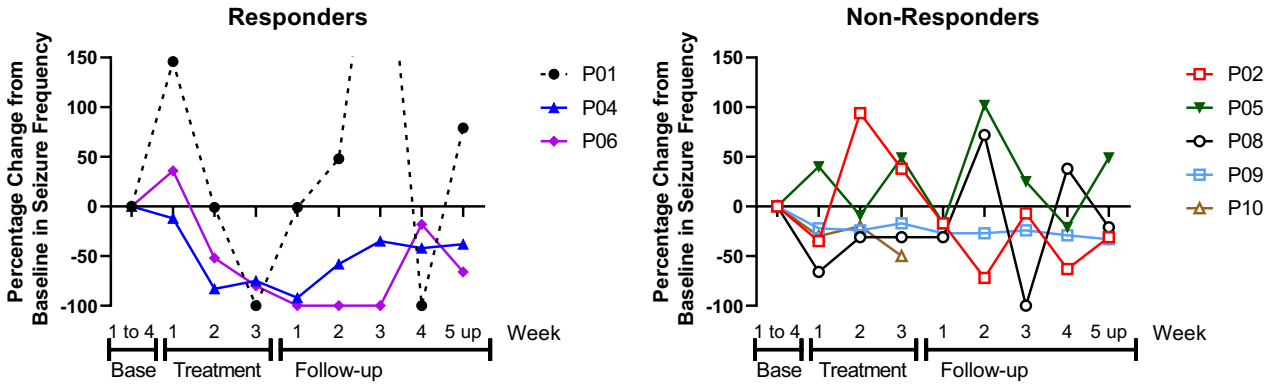
Screening/Enrollment	3-26 years of age Continued seizures despite being at least 3 months post-epilepsy surgery (resective surgery with an intent to cure) without additional resective options
Participants observed on their preexisting antiepileptic drug regimen for 1 month	Epilepsy diary Behavioral indices Labs
ABI-009 IV at different dose levels of 5, 10 or 20 mg/m^2 in cohorts of 3 participants each, weekly for a total of 3 weeks.	Epilepsy diary Behavioral indices Labs
ABI-009 is then discontinued and the participants observed for an additional 3 months	Epilepsy diary Behavioral indices Labs

Where we are at

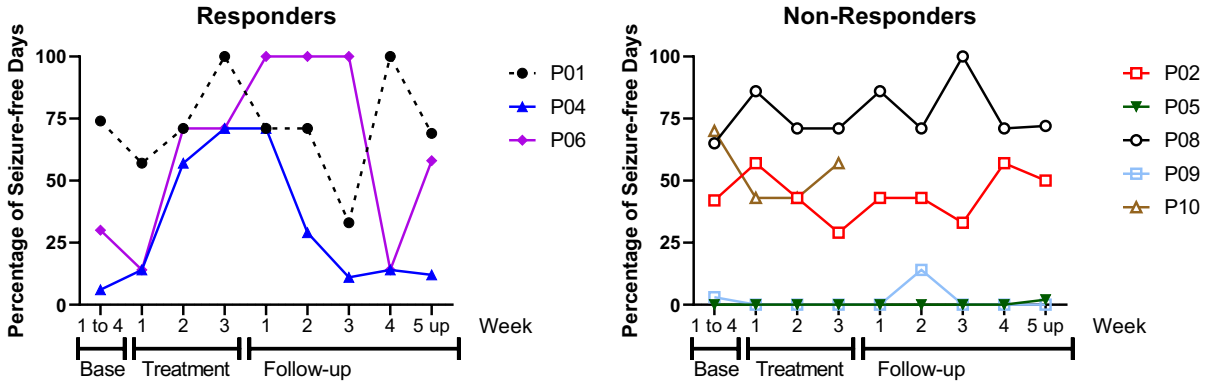
- Enrollment status
  - 3 patients completed cohort 1 at 5 mg/m^2
  - 3 patients completed cohort 2 at 10 mg/m^2
  - 3 patients completed cohort 3 at 20 mg/m^2
  - Have an additional 3 at 20mg/m2 with TS
  - All patients compliant; none have withdrawn during or after treatment
- Safety: No dose limiting toxicity to date
  - Common AEs: asymptomatic mild thrombocytopenia, mild epistaxis, and skin rash – all easily managed without dosing modification
  - Moderate Grade AEs of dermatitis and oral mucositis seen at 20 mg/m^2
  - No increased risk of suicidality during or after treatment

First 8 Patients (non-TS)

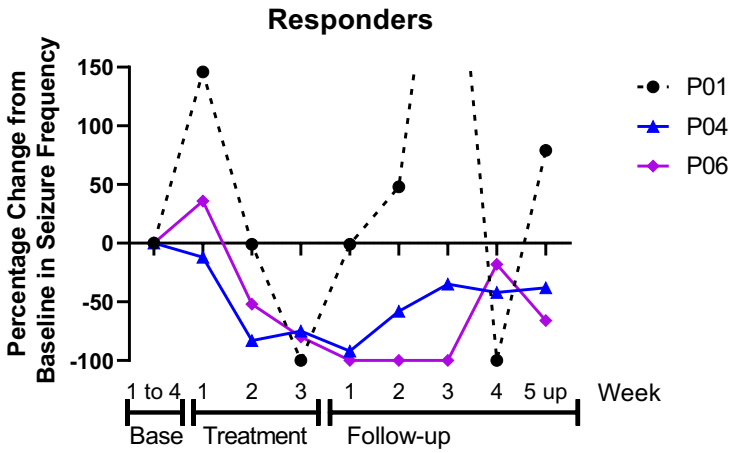
Change in Seizure Frequency



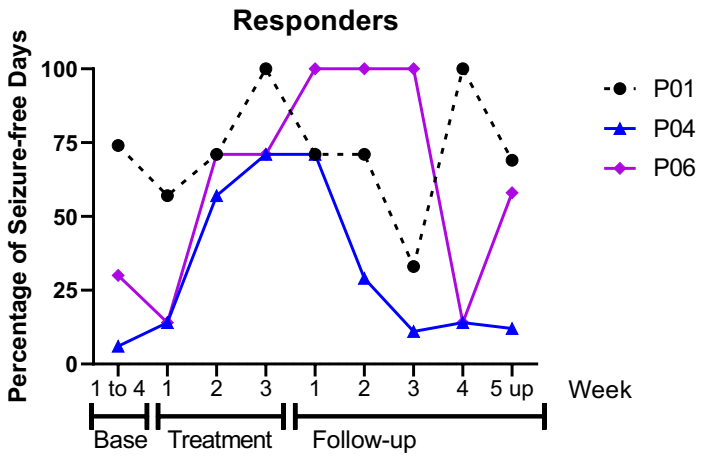
Percentage of Seizure Free Days



Responder Cohort

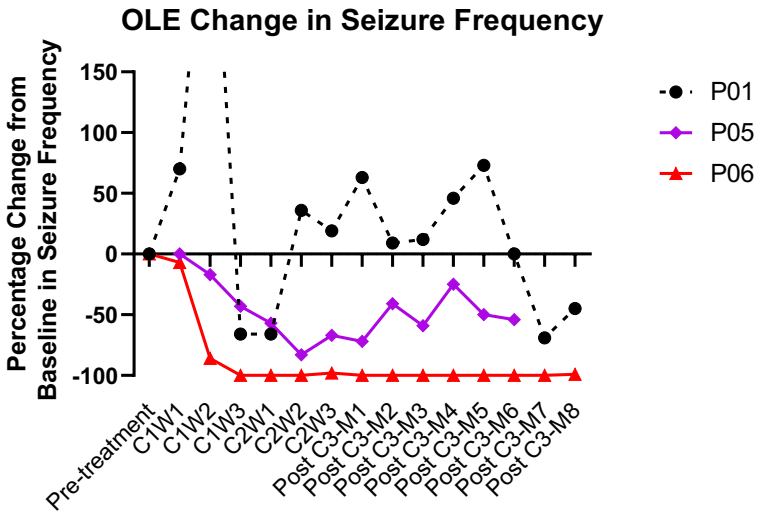


Reduction in average weekly seizure frequency

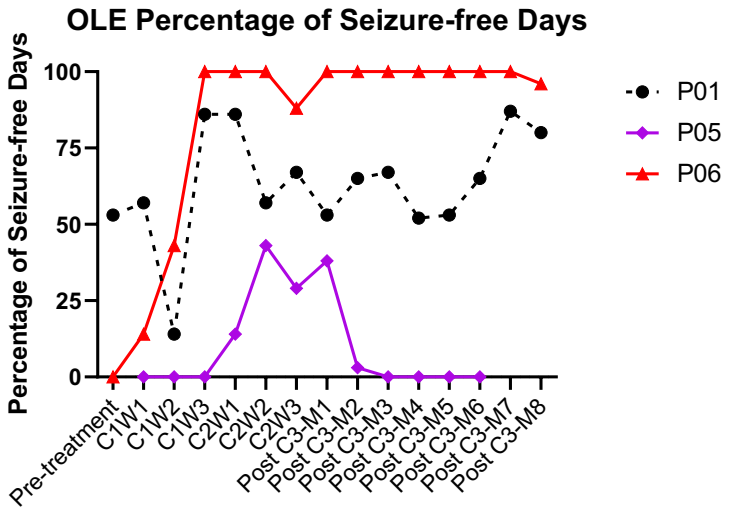


Increased percentage of seizure free days

OLE (first 3, non TS)



Reduction in average weekly seizure frequency



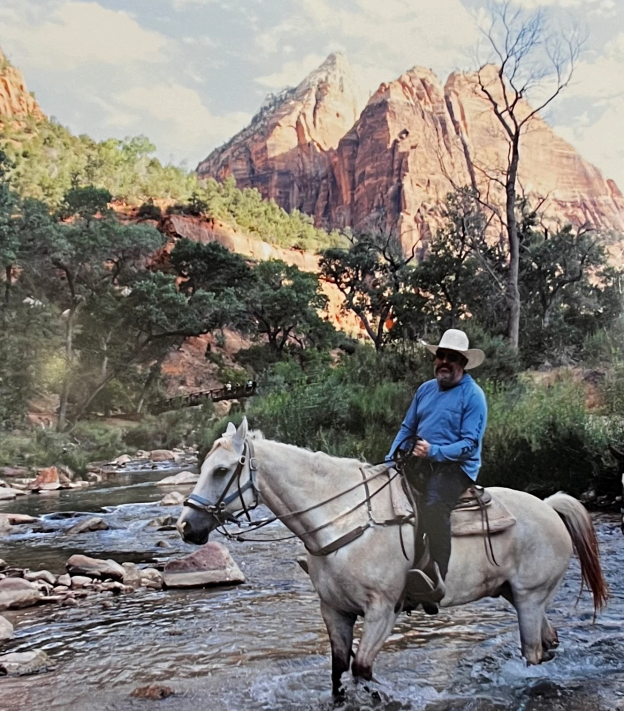
Increased percentage of seizure free days

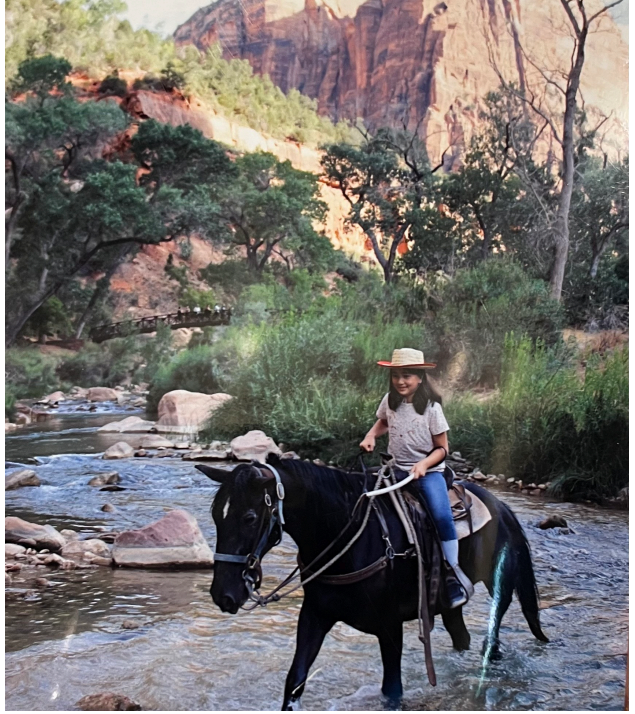
Conclusions so far

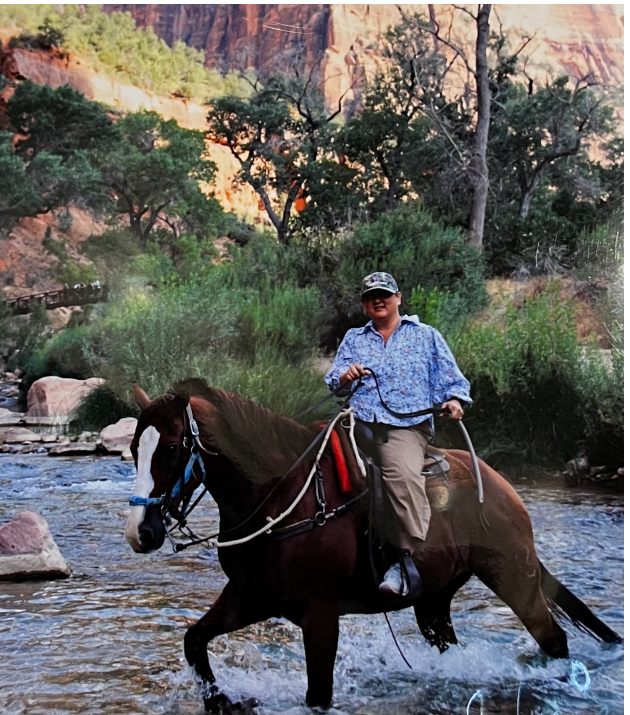
- ABI-009 is safe and well tolerated
- Evidence of efficacy in a subset of patients
    - Justification for an open-label extension
        - 5 patients currently enrolled (two with TS)
- Further work needed
    - Understand optimal dose
    - Phase 2 multi-institutional study
        - Determine efficacy
        - Better understand which patients benefit most

Future Directions

- Currently developing phase 2
  - Likely multi-institutional
  - Duration of dosing?
  - Placebo arm?
  - Making sure we are measuring the right endpoints
  - Making sure we are including the right patients
  - **Biorepository? Sequencing??**







Thank you!