HCRN Update

Curtis J. Rozzelle, MD

Department of Neurosurgery, Pediatric Section; University of Alabama at Birmingham School of Medicine

Disclosures

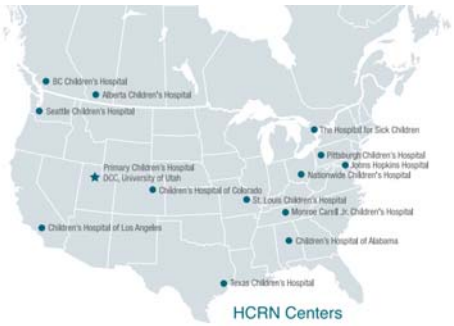
- *No personal "Conflicts of Interest."*
- *Hydrocephalus Clinical Research Network operations are funded by the Hydrocephalus Association*
- *Entry Site RCT funded by PCORI*

Introduction

- HCRN overview
- Recent Publications
- Entry Site Trial
- ETV+CPC Research Plan Progress

- Multi-site collaborative clinical research effort
  - In 2006: 5 busy pediatric neurosurgery programs
  - Now grown to 14 participating centers
  - Prospective registry of all CSF Shunt + ETV procedures performed at all sites
- Collect, analyze, & report on high volume rigorous studies to improve diagnosis, treatment, and outcomes for HCP patients
- Provide research-based evidence to support a standard of care.
- www.hcrn.org

Network Map



Recent HCRN Publications

- Registry studies
  - Shunt malfunction risk factors
  - CSF shunt infection & reinfection
- SOPPH
- Entry Site
- ETV+CPC Studies

JNS PEDIATRICS CLINICAL ARTICLE
J Neurosurg Pediatr 17:382–390, 2016

Risk factors for shunt malfunction in pediatric hydrocephalus: a multicenter prospective cohort study

Jay Riva-Cambrin, MD, MSc,[1] John R. W. Kestle, MD,[1] Richard Holubkov, PhD,[2] Jerry Butler, MSc,[2] Abhaya V. Kulkarni, MD, PhD,[3] James Drake, MBBCh, MSc,[3] William E. Whitehead, MD,[4] John C. Wellons III, MD, MSPH,[5] Chevis N. Shannon, MBA, MPH, DrPH,[5] Mandeep S. Tamber, MD, PhD,[6] David D. Limbrick Jr., MD, PhD,[7] Curtis Rozzelle, MD,[8] Samuel R. Browd, MD, PhD,[9] and Tamara D. Simon, MD, MSPH,[10] for the Hydrocephalus Clinical Research Network

- Prospective cohort study of first time shunt insertion in patients <19 y.o. (6 sites, 2008-11, mean F/U = 400d).
- N = 1036: Malfunctions = 265, Infections = 79.
- Failure associated with:
  - Age < 6 mos.; HR = 1.6 (95% CI: 1.1-2.1)
  - Cardiac comorbidity; HR = 1.4 (95% CI: 1.0-2.1)
  - Endoscopic shunt placement; HR = 1.9 (95% CI: 1.2-2.9)

JNS PEDIATRICS CLINICAL ARTICLE
J Neurosurg Pediatr 17:391–396, 2016

A new Hydrocephalus Clinical Research Network protocol to reduce cerebrospinal fluid shunt infection

John R. W. Kestle, MD,[1] Richard Holubkov, PhD,[2] D. Douglas Cochrane, MD,[3] Abhaya V. Kulkarni, MD,[3] David D. Limbrick Jr., MD, PhD,[4] Thomas G. Luerssen, MD,[5] W. Jerry Oakes, MD,[6] Jay Riva-Cambrin, MD, MSc,[1] Curtis Rozzelle, MD,[6] Tamara D. Simon, MD, MSPH,[7] Marion L. Walker, MD,[1] John C. Wellons III, MD, MSPH,[8] Samuel R. Browd, MD, PhD,[7] James M. Drake, MBBCh,[3] Chevis N. Shannon, MBA, MPH, DrPH,[8] Mandeep S. Tamber, MD, PhD,[9] and William E. Whitehead, MD, MPH,[9] for the Hydrocephalus Clinical Research Network

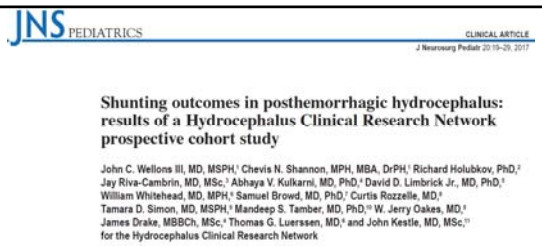
- First protocol reduced VPS infection rate from 8.7% to 5.7%.
- New protocol added *Antibiotic Impreg. Caths.* on Jan. 1, 2012.
- Overall infection rate among 1935 procedures was 6.0%.
  - New insertion = 5.0%; Revision = 5.4%.
  - Insertion after EVD = 8.3%; After infection = 12.6%.
- Protocol compliance (77% overall) was associated with a lower infection risk:
  - Compliant rate = 5.0%; non-compliant = 8.7% (p = 0.005).

JNS PEDIATRICS CLINICAL ARTICLE
J Neurosurg Pediatr 21:340–358, 2018

Reinfection after treatment of first cerebrospinal fluid shunt infection: a prospective observational cohort study

Tamara D. Simon, MD, MSPH,[1,2] Matthew P. Kronman, MD, MSCE,[1,3] Kathryn B. Whitlock, MS,[1] Nancy E. Gove, PhD,[1] Nicole Mayer-Hamblett, PhD,[1,3] Samuel R. Browd, MD, PhD,[2] D. Douglas Cochrane, MD,[4] Richard Holubkov, PhD,[5] Abhaya V. Kulkarni, MD, PhD,[4] Marcie Langley, BS,[5] David D. Limbrick Jr., MD, PhD,[7] Thomas G. Luerssen, MD,[8] W. Jerry Oakes, MD,[9] Jay Riva-Cambrin, MD, MSc,[10] Curtis Rozzelle, MD,[9] Chevis Shannon, DrPH,[11] Mandeep Tamber, MD, PhD,[12] John C. Wellons III, MD, MSPH,[11] William E. Whitehead, MD, MPH,[9] and John R. W. Kestle, MD,[9] on behalf of the Hydrocephalus Clinical Research Network

- Prospective cohort study of surgical management & antibiotic therapy for first VPS infection @ 7 sites (2008-12).
- Reinfection rate was 16% (38/233) @ median of 44 days with no sig. risk factors identified.


JNS PEDIATRICS

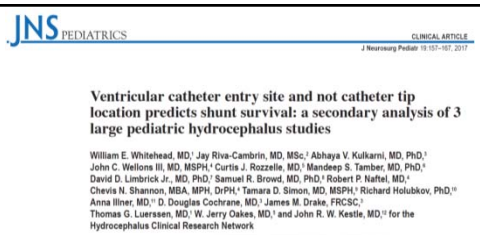
CLINICAL ARTICLE

J Neurosurg Pediatr 20:19–29, 2017

Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study

John C. Wellons III, MD, MSPH,[1] Chevis N. Shannon, MPH, MBA, DrPH,[1] Richard Holubkov, PhD,[2] Jay Riva-Cambrin, MD, MSc,[3] Abhaya V. Kulkarni, MD, PhD,[4] David D. Limbrick Jr., MD, PhD,[5] William Whitehead, MD, MPH,[6] Samuel Browd, MD, PhD,[7] Curtis Rozzelle, MD,[8] Tamara D. Simon, MD, MSPH,[9] Mandeep S. Tamber, MD, PhD,[10] W. Jerry Oakes, MD,[8] James Drake, MBBCh, MSc,[4] Thomas G. Luerssen, MD,[8] and John Kestle, MD, MSc,[11] for the Hydrocephalus Clinical Research Network

- Prospective cohort study @ 6 sites of premature infants with PHH, standardizing criteria for initial treatment (Reservoir or VSGS) and conversion to VPS.
- Surgeon compliance with protocol was 90%(!).
- No significant differences found in infection or VPS conversion rates for reservoir vs. VSGS.


JNS PEDIATRICS

CLINICAL ARTICLE

J Neurosurg Pediatr 19:157–167, 2017

Ventricular catheter entry site and not catheter tip location predicts shunt survival: a secondary analysis of 3 large pediatric hydrocephalus studies

William E. Whitehead, MD,[1] Jay Riva-Cambrin, MD, MSc,[2] Abhaya V. Kulkarni, MD, PhD,[3] John C. Wellons III, MD, MSPH,[4] Curtis J. Rozzelle, MD,[5] Mandeep S. Tamber, MD, PhD,[6] David D. Limbrick Jr., MD, PhD,[7] Samuel R. Browd, MD, PhD,[8] Robert P. Naftel, MD,[9] Chevis N. Shannon, MBA, MPH, DrPH,[4] Tamara D. Simon, MD, MSPH,[2] Richard Holubkov, PhD,[10] Anna Illner, MD,[11] D. Douglas Cochrane, MD,[3] James M. Drake, FRCSC,[3] Thomas G. Luerssen, MD,[7] W. Jerry Oakes, MD,[3] and John R. W. Kestle, MD,[12] for the Hydrocephalus Clinical Research Network

- Shunt Survival analysis of catheter tip location in 858 cases from 3 large studies found no significant differences unless outside ventricle (bad).
- Anterior entry site associated with ~1/3 lower risk of shunt failure (HR=0.65, 95% CI 0.51-0.83).
- Laid foundation for Entry Site RCT (ongoing).

Entry Site RCT

- New VPS for HCP in pts. < 19y.o. @ all 14 sites.
  - Prior EVD, Reservoir, or VSGS okay
  - Prior ETV (+/-CPC) okay
- Randomize Ant. vs. Post. Entry site
  - Stratify by surgeon & etiology
- Outcome measures:
  - Quality of Life (survey)
  - Shunt failure (survival curves)
- Enrolled 402 of 448 planned
- Minimum F/U of 18 mos. required

HCRN ETV+CPC Studies

- ~~Retrospective Review~~ Done
- ~~Investigator Training (hands-on)~~ Done
- ~~Prospective Cohort Study~~ Done
- Randomized Controlled Trial
  - ETV+CPC vs. VPS for initial mgmt of infant HCP
  - R01 application scored, not funded
  - Revised application submitted 2 weeks ago.

Benjamin Warf, MD*

*2012 MacArthur Fellow (www.macfound.org)

CURE Children's Hospital: Uganda

Comparison of endoscopic third ventriculostomy alone and combined with choroid plexus cauterization in infants younger than 1 year of age: a prospective study in 550 African children

BENJAMIN C. WARF, M.D.

CURE Children's Hospital of Uganda, Mbale, Republic of Uganda

Object. The aim of this prospective study was to determine whether, and in which patients, the outcome for bilateral choroid plexus cauterization (CPC) in combination with endoscopic third ventriculostomy (ETV) was superior to ETV alone.

Methods. A total of 710 children underwent ventriculoscopy as candidates for ETV as the primary treatment for hydrocephalus. The ETV was accomplished in 550 children: 266 underwent a combined ETV–CPC procedure and 284 underwent ETV alone. The mean and median ages were 14 and 5 months, respectively, and 443 patients (81%) were younger than 1 year of age. The hydrocephalus was postinfectious (PIH) in 320 patients (58%), nonpostinfectious (NPIH) in 152 (28%), posthemorrhagic in five (1%), and associated with myelomeningocele in 73 (13%). The mean follow up was 19 months for ETV and 9.2 months for ETV–CPC. Overall, the success rate of ETV–CPC (66%) was superior to that of ETV alone (47%) among infants younger than 1 year of age ($p < 0.0001$). The ETV–CPC combined procedure was superior in patients with a myelomeningocele (76% compared with 35% success, $p = 0.0045$) and those with NPIH (70% compared with 38% success, $p = 0.00025$). Although the difference was not significant for PIH (62% compared with 52% success, $p = 0.1607$), a benefit was not ruled out (power = 0.3). For patients at least 1 year of age, there was no difference between the two procedures (80% success for each, $p = 1.0000$). The overall surgical mortality rate was 1.3%, and the infection rate was less than 1%.

Conclusions. The ETV–CPC was more successful than ETV alone in infants younger than 1 year of age. In developing countries in which a dependence on shunts is dangerous, ETV–CPC may be the best option for treating hydrocephalus in infants, particularly for those with NPIH and myelomeningocele.

KEY WORDS • hydrocephalus • myelomeningocele • endoscopic third ventriculostomy • choroid plexus cauterization • developing country • pediatric neurosurgery

Long-term outcome for endoscopic third ventriculostomy alone or in combination with choroid plexus cauterization for congenital aqueductal stenosis in African infants

Clinical article

BENJAMIN C. WARF, M.D.,[1,2] SARAH TRACY, B.A.,[2] AND JOHN MUGAMBA, M.D.[3]

[1]Department of Neurosurgery, Children's Hospital Boston; [2]Department of Global Health and Social Medicine, Harvard Medical School, Boston; [3]University of Massachusetts School of Medicine, Worcester, Massachusetts; and [4]CURE Children's Hospital of Uganda, Mbale, Uganda

Object. The authors have previously reported on the overall improved efficacy of endoscopic third ventriculostomy (ETV) combined with choroid plexus cauterization (CPC) for infants younger than 1 year of age. In the present study they specifically examined the long-term efficacy of ETV with or without CPC in 35 infants with congenital aqueduct stenosis treated at CURE Children's Hospital of Uganda during the years 2001–2006.

Methods. Infants with congenital aqueductal stenosis were treated during 2 distinct treatment epochs: all underwent ETV alone, and subsequently all underwent ETV-CPC. Prospectively collected data in the clinical database were reviewed for all infants with an age < 1 year who had been treated for hydrocephalus due to congenital aqueductal stenosis. Study exclusion criteria included: 1) a history or findings on imaging or at the time of ventriculoscopy that suggested a possible infectious cause of the hydrocephalus, including scarred choroid plexus; 2) an open aqueduct or an aqueduct obstructed by a membrane or cyst rather than by stenosis; 3) severe malformations of the cerebral hemispheres including hydranencephaly, significant segments of undeveloped brain, or schizencephaly; 4) myelomeningocele, encephalocele, Dandy-Walker complex, or tumor; or 5) previous shunt insertion. The time to treatment failure was analyzed using the Kaplan-Meier method to construct survival curves. Log-rank (Mantel-Cox) and Gehan-Breslow-Wilcoxon tests were used to determine whether differences between the 2 treatment groups were significant.

Results. Thirty-five patients met the study criteria. Endoscopic third ventriculostomy alone was performed in 12 patients (mean age 4.7 months), and combined ETV-CPC was performed in 23 patients (mean age 3.5 months). For patients without treatment failure, the mean and median follow-ups were, respectively, 51.6 and 48.0 months in the ETV group and 31.2 and 26.4 months in the ETV-CPC group. Treatment was successful in 48.6% of the patients who underwent ETV alone, as accurately predicted by the Endoscopic Third Ventriculostomy Success Score (ETVSS), and in 81.9% of the patients who underwent ETV-CPC ($p = 0.0119$, log-rank test; $p = 0.0041$, Gehan-Breslow-Wilcoxon test; HR 6.42 [95% CI 1.51–27.36]).

Conclusions. Combined ETV-CPC is significantly superior to ETV alone for infants younger than 1 year of age with congenital aqueductal stenosis. The fact that the outcome for ETV alone was accurately predicted by the ETVSS suggests that these results are applicable in developed countries.

(http://thepns.org/doi/abs/10.3171/2012.4.PEDS12253)

JNS PEDIATRICS

CLINICAL ARTICLE

J Neurosurg Pediatr 21:214–223, 2018

Endoscopic third ventriculostomy and choroid plexus cauterization in infant hydrocephalus: a prospective study by the Hydrocephalus Clinical Research Network

Abhaya V. Kulkarni, MD, PhD,[1] Jay Riva-Cambrin, MD, MSc,[2] Curtis J. Rozzelle, MD,[3] Robert P. Naftel, MD,[4] Jessica S. Alvey, MSc,[1] Ron W. Reeder, PhD,[1] Richard Holubkov, PhD,[5] Samuel R. Browd, MD, PhD,[6] D. Douglas Cochrane, MD,[7] David D. Limbrick Jr., MD, PhD,[8] Tamara D. Simon, MD, MSPH,[9] Mandeep Tamber, MD, PhD,[3] John C. Wellons III, MD, MSPH,[4] William E. Whitehead, MD,[10] and John R. W. Kestle, MD, MSc,[11] for the Hydrocephalus Clinical Research Network

- Prospective cohort of 118 ETV+CPC for infant HCP @ 9 sites over 16 mos. c/w VPS (n=112) & ETV (n=74) infants matched for age & etiology.
- ETV+CPC success @ 6 mos. = 36% (varies with CPC %age).
- ETV+CPC failure > VPS ($p<0.001$) but NS r.e. ETV ($p=0.73$).

Predictors of ETV+CPC Success

- Prospective cohort (registry) study
  - All ETV+CPC pts. <2y.o. @ 8 sites; 6/06-3/15.
  - Analyze pre- & intra-op factors.
  - Assess effect of "formal ETV+CPC training."
- Primary ETV+CPC in 191 pts. by 17 surgeons.
  - Age < 6 mos. comprised 79%
  - MMC = 26%; Prem. IVH = 24%; AS = 17%
- Independent Predictors of Failure:
  - Younger age (p=0.08) & Etiology (p=0.007)
  - Specific age groups in each etiology had higher success rates

Predictors of ETV+CPC Success

- 60% performed by "trained" surgeons.
  - Training assoc. with use of flexible endoscope (p<0.001)
  - And with more complete CPC; >90% (p<0.001)
- Trained surgeons' success rates NOT assoc. with ETC+CPC success (p=0.63).
- Subgroups identified as more favorable inform RCT.
  - MMC - term age – 12 mos.
  - Prem. IVH - > 6 – 12 mos. (corrected)
  - All others - >1 – 12 mos. (corrected)
- NIH R01 Grant (Re-) Application under review.