Clinical and surgical factors associated with increased epilepsy risk in children with hydrocephalus

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ABSTRACT

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BACKGROUND: Children with hydrocephalus are at risk for epilepsy due both to their underlying condition and as a consequence of surgical treatment. **OBJECTIVE:** We sought to characterize epilepsy among children with infancy-onset hydrocephalus and to examine the risks of epilepsy associated with hydrocephalus subtype and with factors related to surgical treatment of hydrocephalus. **METHODS:** Longitudinal cohort study of all children with infancy-onset hydrocephalus treated at a major regional children's hospital during 2002 – 2012, with follow-up to ascertain surgical factors and epilepsy outcome through April, 2015. Poisson regression was used to calculate adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for associations. **RESULTS:** Among 379 children with hydrocephalus, 86 (23%) developed epilepsy (mean onset age 2.7 years), almost one fifth of whom had a history of infantile spasms. The RR for epilepsy associated with having any surgery was 2.8 (95%CI: 1.3-5.8). Among children who had undergone surgery, shunt failure (RR: 1.9, 95%CI: 1.1, 3.3), and infection (RR 1.9, 95%CI: 1.2, 3.0) were independently associated with epilepsy. Relative to spina bifida-associated hydrocephalus, children with other major hydrocephalus subtypes had four- to five-fold increased risks of developing epilepsy. **CONCLUSIONS:** Epilepsy is common among children with hydrocephalus, and more common among those with shunt failure and infection. Relative to children with spina bifida-associated hydrocephalus, children with other major hydrocephalus subtypes have an increased risk of epilepsy.

INTRODUCTION

Hydrocephalus, characterized by progressive accumulation of cerebrospinal fluid (CSF) within the ventricular system of the brain, affects 0.59 to 1.1 per 1000 live births [1, 2] and has many causes, including intraventricular hemorrhage (IVH), infection and trauma. Other common causes include developmental malformations of the central nervous system or skull, which may occur in the setting of a genetic syndrome [3]. When hydrocephalus develops during infancy, significant neurological consequences can result, including abnormal development and epilepsy [4].

Epilepsy, a condition characterized by repeated unprovoked seizures, can be a direct consequence of hydrocephalus or a hydrocephalus-associated syndrome [3]. Several genetic conditions associated with hydrocephalus are also associated with epilepsy. Among children with hydrocephalus, epilepsy may also be treatment-related: Hydrocephalus is most often addressed by surgical placement of a ventriculo-peritoneal shunt (VPS), which reroutes CSF from the ventricles into the peritoneal space, where it is absorbed into the systemic circulation. Although VP shunts are an effective treatment, shunt failure due to mechanical obstruction or infection is common [5], with 84.5% of patients in a recent series requiring at least one shunt revision [6].The extent to which shunt failure and infection convey an increased risk of epilepsy in patients with hydrocephalus is unknown [7].

We followed up a cohort of children diagnosed with hydrocephalus during infancy and treated at a regional children's hospital to determine which individuals had developed epilepsy by the end of the study period. We compared clinical and surgical characteristics (need for initial surgery, total number of surgeries, number of shunt failures and infection) of children who did, and did not, develop epilepsy. We also assessed the characteristics of epilepsy, including seizure type and current level of seizure control.

METHODS

Study overview: We conducted a retrospective cohort study of all children diagnosed with hydrocephalus within the first year of life and treated at Seattle Children's Hospital between 2002 and 2012, with follow-up through April 15, 2015. Epilepsy was defined according to International League Against Epilepsy (ILAE) criteria. Children not meeting these criteria were considered not to have epilepsy only if medical records were sufficiently detailed to confirm absence of seizures; they were otherwise excluded from analysis.

To examine the association of epilepsy with multiple potential risk factors that predated epilepsy onset, we examined medical records of all cohort members and abstracted information on clinical characteristics, surgical history and other potential risk factors.

Study population: This study involves a cohort of children diagnosed with hydrocephalus within the first year of life and treated during 2002-2012. With the approval of the Seattle Children's Hospital Institutional Review Board, individuals were ascertained by the author from the hospital's imaging database. This database contains searchable reports describing the findings of all CT, MRI, ultrasound and X-ray studies performed since 2002, as well as viewable copies of those studies.

Based on the International Hydrocephalus Working Group, hydrocephalus was defined as "an active [and progressive] distension of the ventricular system…resulting from inadequate passage of CSF from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation [8]." Patients in whom excessive CSF was exclusively extra-axial (not within the ventricles), or who had *ex vacuo* ventricular enlargement were excluded. All radiology reports of studies performed on children less than one year of age who were treated in an inpatient or outpatient setting between January 1, 2002 and December 31, 2012 were screened using search terms related to hydrocephalus. If the presence of progressive ventricular enlargement could not be verified on the basis of the report

itself, imaging studies and clinical records were reviewed by the author. Of 424 infants initially identified as having progressive ventricular dilation, detailed medical and imaging records were available for 411; however 13 patients were subsequently excluded because records were insufficient to determine epilepsy. Another 19 were excluded because hydrocephalus subtype could not be determined. Thus, 379 patients were included in this analysis.

Data collection: Data were obtained from existing medical records and imaging studies. Demographic information included sex, date of birth, gestational age, date of hydrocephalus diagnosis (date of birth if the hydrocephalus was diagnosed prenatally, or date of diagnostic imaging study if hydrocephalus developed after birth), date of last follow-up visit, vital status, and date of death as appropriate. Based on diagnosis date, hydrocephalus was classified as pre- or post-natal, and as occurring before or after term gestation equivalent. Hydrocephalus was further assigned to mutually exclusive subtypes, including four subtypes associated with extrinsic etiologies (IVH, neoplasm, infection, trauma), and five subtypes associated with intrinsic physical or functional obstruction of CSF flow (myelomeningocele-associated, proximal obstruction, distal obstruction, cyst- or encephalocele-associated, and communicating [no obstruction]).

Surgical information obtained included surgery type (VPS, subgaleal shunt or reservoir, endoscopic third ventriculostomy, temporary drain, and cyst fenestration); total number of surgeries (continuous); and among those with shunts, history of shunt failure (yes/no) and shunt infection (yes/no). The dates of shunt-related surgical events and of epilepsy diagnoses were recorded so that analysis could be limited to events occurring prior to epilepsy diagnosis, death, or date of last follow-up as appropriate.

Outcome assessment: Epilepsy was defined according to International League Against Epilepsy (ILAE) criteria (at least two unprovoked seizures, a single seizure with a high risk of recurrence, or the diagnosis of an epilepsy syndrome), occurring at any time during the study period. Date of onset was defined as

the date of the first unprovoked seizure (i.e., acute symptomatic seizures were excluded). If this date was not available, date of onset was determined from the date of the first EEG study consistent with epilepsy, or the date of the first clinic visit at which a diagnosis of epilepsy was recorded, whichever was earlier. Also obtained from record review were seizure type, as defined by seizure semiology in conjunction with EEG pattern, including infantile spasms (clusters of flexion or extension movements with hypsarrythmia or modified hypsarthythmia on EEG), focal-onset seizures (focal motor onset seizures or impairment of consciousness and/or focal discharges on EEG), tonic, atonic, or absence (all with generalized discharges) and unspecified convulsions (motor activity without clear focality, with EEG findings that did not allow electrographic onset to be determined). We recorded current seizure control (well-controlled, ≤1 unprovoked seizures/year; medically intractable, ≥2 unprovoked seizures/year after appropriate trials of 2 anti-seizure medications; and not well-controlled/not intractable, ≥2 unprovoked seizures/year, but not meeting criteria for intractability, usually because dosage adjustments were in process).

Follow-up for each hydrocephalus case began at the date of diagnosis and continued through date of death or last indication that the child was alive (clinic visit, emergency department visit or phone call to a nursing line), up to April 15, 2015. Median follow-up time after initial diagnosis of hydrocephalus was 6.1 years (range 0.03-14.9 years) for children with epilepsy and 4.5 years (range 0.11-13.11 years) for those without (5.0 years [range 0.005-14.9 years] overall.)

Statistical Analysis: We compared demographic and clinical characteristics of children who developed epilepsy vs. those who did not develop epilepsy. First we compared bivariate associations or differences between children with and without epilepsy. We subsequently included combinations of variables in Poisson regression analyses to observe their adjusted effects upon risk of epilepsy To estimate the risk of epilepsy in relation to selected pre-specified clinical and surgical factors, we calculated risk ratios (RRs) and 95% confidence intervals (CI) using Poisson regression with robust standard errors [9]. We

considered the potential effects of age at last follow-up and sex in the associations; since sex had no effect on risk estimates, only age was retained in the models.

Epilepsy risk was estimated in relation to any shunt surgery, number of surgeries, and to the four most common hydrocephalus subtypes in the cohort (spina bifida-associated, IVH-associated, proximal obstruction, cysts and celes). Analyses focused on shunt failure and infection included only children with surgical shunt placements. Inferences about the statistical significance of associations were made on the basis of Wald tests in conjunction with the CI. To evaluate whether meaningful differences in these associations differed by hydrocephalus subtype, we compared the results stratified by hydrocephalus subtype.

To investigate whether any identified surgical risks acted independently of others among children who had undergone surgery, a multivariate model was created that included total number of surgical procedures performed, history of shunt failure, history of infection, and age at last follow-up. To investigate the influence of the major hydrocephalus subtypes above and beyond the effect of surgical factors, we created a series of multivariate models that additionally included history of any surgery, history of any shunt failure or infection, and total number of surgeries.
All analyses were performed using Stata 11, StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.

RESULTS

Clinical characteristics: Among 379 children with hydrocephalus, 86 (23%) developed epilepsy during the study period. Compared to children without epilepsy, children with epilepsy were more likely to be female (56 vs 50%) and were slightly older at last follow-up (mean 6.7 vs 5.2 years) (Table 1). The distributions of gestational ages were generally similar. The distributions of hydrocephalus subtypes

differed by epilepsy status, with IVH and proximal obstruction more common among children with epilepsy, and spina bifida and communicating hydrocephalus less common.

Among the 86 patients with epilepsy, the mean age of onset was 2.7 years, but the range was broad, and almost 20% had a history of infantile spasms during the first year of life. Mean elapsed time between initial surgery and epilepsy diagnosis was 2.6 years. The dominant seizure type was focal-onset events, seen as the sole seizure type in 61 children (71%). Fourteen children (16%) had multiple seizure types; 10 of these had a history of infantile spasms that predated their current form of epilepsy. Seizures were well-controlled in 55%, but were medically intractable in 20%. Notably, two patients who would have been categorized as having medically intractable epilepsy at earlier time points became seizure-free after epilepsy surgery.

History of any surgery (RR: 2.8, 95%CI: 1.3-5.8), shunt failure (RR 2.0, 95%CI: 1.2-3.1), and shunt infection (RR 2.0, 95%CI: 1.4-3.0) were all associated with epilepsy (Table 2). Each surgical procedure was associated with a 7% increase in risk of epilepsy (RR 1.07, 95%CI: 1.001-1.14). Because the median age of children with epilepsy was older than those without, we performed the same analyses limited to children <6 years old by the end of the study follow-up; results for all estimates remained generally increased, with the exception of the RR for total surgeries; however confidence intervals included one, and our ability to examine this was limited by small numbers (data not shown). Our ability to examine hydrocephalus subtype-specific RRs was also limited by small numbers; however, for each of the four hydrocephalus subtypes examined, epilepsy occurred more often in children with surgical complications than in children without (Table 3).

We examined whether, among surgically-treated children, these surgical factors were independently associated with a risk of epilepsy. After adjusting for the other surgical risk factors, the risks associated with history of shunt failure and of infection were essentially unchanged from previous estimates (RR:

1.91, 95%CI 1.11, 3.30, RR: 1.87, 95%CI 1.15, 3.03, respectively), but the risk of epilepsy associated with each additional surgical procedure was no longer apparent (RR: 0.95, 95%CI 0.86-1.06).

Relative to children with spina bifida, the risk of epilepsy was significantly greater in children with the other major hydrocephalus subtypes, including IVH (RR 4.20, 95%CI 1.74-10.1), proximal obstruction (RR 4.94, 95%CI 2.00-12.20), and cysts and celes (RR 4.59, 95%CI 1.77-11.88). Adjustment for history of surgery or surgical complications did not alter the magnitude of these associations (data not shown).**DISCUSSION:** We evaluated a cohort of children with hydrocephalus to determine whether selected clinical and surgical features were associated with increased epilepsy risk. In 2015, the prevalence of epilepsy was estimated at 8.5 in 1,000 Americans [10]; it was present in almost a quarter of children with infancy-onset hydrocephalus. Strikingly, one in five patients with epilepsy had a history of infantile spasms, usually considered to be a rare seizure type, and one that may escape detection by families and clinicians since it can be clinically subtle. Observational evidence suggests that early treatment of infantile spasms may improve clinical outcome [11]. Therefore, the relatively common occurrence of this potentially devastating form of childhood epilepsy among children with hydrocephalus deserves emphasis, since it may be under-recognized by clinicians.

History of any surgery, history of shunt failure and history of shunt infection increased the risk of epilepsy in children with hydrocephalus. The risk associated with undergoing any surgery could reflect confounding by indication (i.e., more severely affected children were more likely to require surgery and were also more likely to develop epilepsy). We therefore limited our analyses of the risks associated with shunt failure and infection to those children who had undergone surgery and found that the risks associated with these surgical complications may act independently.

In our exploratory analysis, hydrocephalus subtype demonstrated an association with epilepsy above and beyond what was mediated by surgical risk factors. The risk of epilepsy was markedly greater in

children with subtypes of hydrocephalus other than that associated with spina bifida, which we set as the reference category because it is associated with the Chiari II, an obstructive brain malformation of the brainstem and cerebellum, areas not generally considered to act as epileptic foci. Other hydrocephalus subtypes are characterized by varying combinations of malformations or injury in supratentorial structures, where epilepsy originates. Spina bifida therefore allows an approximation of the baseline risk of epilepsy associated with hydrocephalus and its surgical correction; the increased risk seen in other subtypes presumably reflects the additional contribution of supratentorial malformations or injury.

This study has several limitations. As with any observational study, our ability to determine causality is imperfect. However, the nature of the cohort design allows a temporal relationship to be determined, and our analyses were limited to factors that preceded each child's diagnosis of epilepsy.

This study is also limited by its use of existing data, which may not be consistently complete. Surgical procedures are reliably documented in medical records, but clinical events such as seizures may not be specifically addressed in clinical notes. Several children were excluded from analysis because we could not determine from their records whether they had epilepsy. If those excluded children did not have epilepsy, this would lead to an overestimation of the incidence of epilepsy in our cohort.

This study is also limited by missing data, usually reflecting loss to follow-up. Most data is likely to be missing at random, due to children moving from the area. Our assumption is that these children would be no more likely to develop epilepsy than children who remained. However, some children may have been lost to follow-up specifically because they had fewer medical complications, including epilepsy and shunt failure, and therefore received less medical care. This would bias our estimates of the proportions of individuals with these complications, but its effect upon risk estimates should be less differential, since outcome and risk factor data would both be missing.

Though the number of patients is relatively large compared to existing studies of infantile hydrocephalus, we still had limited statistical power for some analyses. In particular, the small numbers of patients with certain subtypes of hydrocephalus meant that possible differences in associations by subtype could not be fully explored.

CONCLUSIONS: Epilepsy is common among children with hydrocephalus. Infantile spasms are a surprisingly frequent seizure type, one that may not be well recognized by clinicians. Subtype influences the risk of epilepsy, which is lowest in patients with spina bifida. Shunt failure and shunt infection independently raise the risk of epilepsy.

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TABLES

Table 1. Characteristics of hydrocephalic children with and without epilepsy[1]

		Epilepsy (n=86)	No epilepsy (n=293)
Patient characteristics			
Male		43 (50.0)	166 (56.7)
Gestational age (wks)	<28	10 (13.0)	27 (11.2)
	28-31	8 (10.4)	25 (10.4)
	32-36	22 (28.6)	54 (22.4)
	37+	37 (56.0)	135 (56.0)
Age at last visit (yrs) mean +/- SD (min, max)		6.7 +/- 3.6 (0.04, 14.9)	5.2 +/- 3.4 (0.03, 13.6)
Hydrocephalus characteristics			
Age at diagnosis	Prenatal/preterm[2]	58 (68.2)	189 (66.1)
	1w-6m	24 (28.2)	56 (19.6)
	>6m-12mo	3 (3.5)	41 (14.3)
Subtype	Spina bifida	5 (6.1)	72 (24.9)
	IVH	28 (34.2)	72 (24.9)
	Proximal obstruction	20 (24.4)	40 (13.8)
	Communicating	2 (2.4)	29 (10.0)
	Cysts and celes	11 (13.4)	27 (9.3)
	Distal obstruction	2 (2.4)	23 (8.0)
	Neoplasm	4 (4.9)	13 (4.5)
	Infection	7 (8.5)	9 (3.1)
	Trauma	3 (3.7)	4 (1.4)
Epilepsy characteristics			
Age of onset (yrs) mean ±SD (min, max)		2.7 ± 2.9 (0.0, 12.2)	
Years between first surgery and epilepsy diagnosis mean ±SD (min, max)		2.6 ± 2.9 (0.0, 12.2)	
Current seizure type	Infantile spasms	2 (2.3)	
	Focal onset or focal discharges on EEG	61 (70.9)	
	Unclear onset with generalized/multifocal discharges on EEG	6 (7.0)	
	Tonic +/- myoclonic	14 (16.3)	
History of infantile spasms		16 (19.0)	
Seizure control	Well-controlled	44 (55.0)	
	Not controlled, not medically intractable	20 (25.0)	
	Medically intractable	16 (20.0)	

[1]Numbers that add to less than column total reflect missing data.
[2]Onset at <37 weeks gestational age, seen on prenatal ultrasound, or diagnosed within one week of a term birth.

Table 2. Adjusted[1] risks for epilepsy among children with hydrocephalus

	Epilepsy (n=86)	No epilepsy (n=293)	RR (95%CI)
Surgical factors			
Any surgery[2, 3]	78 (91.8)	215 (73.4)	2.76 (1.32, 5.75)
History of shunt failure[2, 4, 5]	54 (72.9)	93 (48.4)	1.97 (1.24, 3.12)
History of shunt infection[2, 4, 6]	22 (29.3)	17 (8.1)	2.02 (1.37, 2.97)
Total surgeries (mean± SD [range]) [2, 3, 7, 8]	4.1 ± 3.7 (0, 17)	2.2 ± 1.8 (1, 12)	1.07 (1.001, 1.14)
Subtype[9]			
Spina bifida	5 (7.8)	72 (34.1)	1 (ref)
IVH	28 (43.8)	72 (34.1)	4.20 (1.74, 10.1)
Proximal obstruction	20 (31.3)	40 (19.0)	4.94 (2.00, 12.2)
Cysts and celes	11 (17.2)	27 (12.8)	4.59 (1.77, 11.88)

[1] Adjusted for age at most recent follow-up.
[2] Prior to onset of epilepsy or more recent follow-up, whichever came first.
[3] Includes VP shunt, VA shunt, subgaleal shunt or reservoir, EVD, ETC with or without CPC, and cyst fenestration.
[4] Limited to those with shunt
[5] Includes mechanical failure and shunt infection.
[6] Includes any culture-proven or presumed infection associated with one-of the hydrocephalus-related surgeries described above.
[7] Limited to those who underwent surgery.
[8] RR for each additional surgical procedure.
[9] Limited to four most common subtypes.

Table 3. Risk of epilepsy in relation to shunt surgery and selected surgical factors among children with different subtypes of hydrocephalus.

IVH-associated hydrocephalus			
	Epilepsy (n=28)	**No epilepsy (n=72)**	**RR[1] (95%CI)**
Any surgery[2, 3]	27 (96.4)	58 (80.6)	3.77 (0.54, 26.5)
History of shunt failure[2, 4, 5]	21 (80.8)	29 (58.0)	2.15 (0.90, 5.15)
History of shunt infection[2, 4, 6]	7 (28.0)	7 (12.5)	1.70 (0.88, 3.29)
Total surgeries [2, 3, 7, 8]	3.8 ± 3.4 (0,14)	2.7 ± 2.5 (1,13)	1.06 (0.97, 1.16)
Spina bifida-associated hydrocephalus			
	Epilepsy (n=5)	**No epilepsy (n=72)**	**RR[1] (95%CI)**
Any surgery[2, 3]	5 (100.0)	62 (86.1)	- -
History of shunt failure[2, 4, 5]	5 (100.0)	33 (54.1)	- -
History of shunt infection[2, 4, 6]	3 (60.0)	4 (6.5)	6.7 (1.6, 28.4)
Total surgeries [2, 3, 7, 8]	6.3 ± 2.2	1.9 ± 1.2	1.57 (1.29, 1.91)

	(4, 9)	(1, 6)	
Proximal obstruction			
	Epilepsy (n=20)	**No epilepsy (n=40)**	**RR[1] (95%CI)**
Any surgery[2, 3]	19 (95.0)	1 (5.0)	4.39 (0.64, 29.9)
History of shunt failure[2, 4, 5]	14 (73.7)	13 (44.8)	1.95 (0.80, 4.80)
History of shunt infection[2, 4, 6]	6 (31.6)	3 (10.3)	1.89 (0.98, 1.16)
Total surgeries [2, 3, 7, 8]	2.1 ± 1.3 (1, 5)	1.9 ± 1.1 (1, 4)	1.05 (0.80, 1.39)
Cysts and celes			
	Epilepsy (n=11)	**No epilepsy (n=27)**	**RR[1] (95%CI)**
Any surgery[2, 3]	10 (90.9)	23 (85.2)	1.17 (0.18, 7.78)
History of shunt failure[2, 4, 5]	7 (77.8)	8 (44.4)	2.70 (0.67, 11.0)
History of shunt infection[2, 4, 6]	1 (10.0)	3 (13.6)	0.77 (1.12, 4.85)
Total surgeries [2, 3, 7, 8]	1.9 ± 1.8 (0,5)	2.7 ± 2.0 (1, 8)	0.83 (0.60, 1.16)

[1] Adjusted for age at most recent follow-up.
[2] Prior to onset of epilepsy or more recent follow-up, whichever came first.
[3] Includes VP shunt, VA shunt, subgaleal shunt or reservoir, EVD, ETC with or without CPC, and cyst fenestration.
[4] Limited to those with shunt
[5] Includes mechanical failure and shunt infection.
[6] Includes any culture-proven or presumed infection associated with one-of the hydrocephalus-related surgeries described above.
[7] Limited to those who underwent surgery.
[8] RR for each additional surgical procedure.

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