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# Clinical and Surgical Factors Associated With Increased Epilepsy Risk in Children With Hydrocephalus

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## Abstract

**BACKGROUND:** Children with hydrocephalus are at risk for epilepsy both due to their underlying condition and as a consequence of surgical treatment; however, the relative contributions of these factors remain unknown.

**OBJECTIVE:** The authors 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.

**METHODS:** We conducted a longitudinal cohort study of all children with infancy-onset hydrocephalus treated at a major regional children's hospital during 2002 to 2012, with follow-up to ascertain risk factors and epilepsy outcome through April 2015. Poisson regression was used to calculate adjusted risk ratios and 95% confidence intervals 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. Relative to spina bifida-associated hydrocephalus, children with other major hydrocephalus subtypes had fourfold higher risks of developing epilepsy. Among children who underwent surgery, surgical infection doubled the risk of epilepsy (risk ratio = 2.0, 95% confidence interval = 1.4 to 3.0). Epilepsy was associated with surgical failure for intracranial reasons but not extracranial reasons (risk ratio = 1.7, 95% confidence interval = 1.1 to 2.7; risk ratio = 1.1, 95% confidence interval = 0.7 to 1.9, respectively).

**CONCLUSIONS:** Epilepsy is common among children with hydro-cephalus. Compared with children with spina bifida–associated hydrocephalus, children with other major hydrocephalus subtypes have a markedly increased risk of epilepsy. Surgical infection doubles the risk of epilepsy.

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**Keywords**

hydrocephalus; epilepsy; infantile spasms; spina bifida; aqueductal stenosis

## 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), meningitis, and trauma. Other common causes include developmental malformations of the central nervous system, 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, 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 ventriculoperitoneal shunt, which reroutes CSF from the ventricles into the peritoneal space, where it is absorbed into the systemic circulation. Although ventriculoperitoneal (VP) shunts are effective, 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] Alternative surgical treatments such as endoscopic third ventriculostomy (ETV) may also be associated with high failure rates in infants.[7] The extent to which surgical complications convey an increased risk of epilepsy in patients with hydrocephalus is unknown.[8]

We monitored 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 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.

## Materials and 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 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 to 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 computed tomography, magnetic resonance imaging, ultrasound, and x-ray studies performed since 2002, as well as viewable copies of those studies.

Based on the International Hydrocephalus Working Group definition, hydrocephalus was characterized 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."[9] 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 aged less than one year 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 dilatation, detailed medical and imaging records were available for 411; however, 13 patients were subsequently excluded because records were insufficient to establish whether epilepsy was present. Another 19 were excluded because the 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. Hydrocephalus was 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, aqueductal obstruction, posterior fossa crowding, cyst or encephalocele associated, and communicating [no obstruction]).

Surgical information obtained included definitive surgery type (ventriculoperitoneal shunt, subgaleal shunt or reservoir, ETV, temporary drain, and cyst fenestration); total number of surgeries (continuous); and among those treated surgically, history of surgical failure (yes/no) and infection (yes/no). Surgical failure was further classified as intracranial (failure of ventricular shunt catheter, hardware removal necessitated by infection, failed ETV, or failed cyst fenestration) or extracranial (failure of shunt valve, distal catheter or abdominal pseudocyst). The dates of surgical events and of epilepsy diagnoses were recorded, so that analysis could be limited to events occurring before epilepsy diagnosis, death, or date of last follow-up as appropriate.

## Outcome assessment

Epilepsy was defined according to International League Against Epilepsy 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 electroencephalograph (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 hypsarrhythmia or modified hypsarrhythmia 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 seizures (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 seizure/year; medically intractable: ≥2 unprovoked seizures/year after appropriate trials of two antiseizure medications; and not well controlled/not intractable, ≥2 unprovoked seizures/year, but not meeting criteria for intractability, usually because medication adjustments were in process).

Follow-up for each hydrocephalus patient 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 the initial diagnosis of hydrocephalus was 6.1 years (range = 0.03 to 14.9 years) for children with epilepsy and 4.5 years (range = 0.11 to 13.11 years) for those without (5.0 years [range = 0.005 to 14.9 years] overall).

## Statistical analysis

We compared demographic and clinical characteristics of children who developed epilepsy and 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 on risk of epilepsy. To estimate the risk of epilepsy in relation to selected prespecified clinical and surgical factors, we calculated risk ratios (RRs) and 95% confidence intervals (CIs) using Poisson regression with robust standard errors.[10] We considered the potential effects of age at last follow-up and sex in the associations; because sex had no effect on risk estimates, only age was retained in the models.

Epilepsy risk was estimated in relation to the four most common hydrocephalus subtypes in the cohort (spina bifida associated, IVH associated, aqueductal obstruction, cysts and celes), to any hydrocephalus-related surgery, and to a history of surgical failure and infection. Inferences about the statistical significance of associations were made on the basis of Wald tests in conjunction with the CI.

All analyses were performed using Stata14 (StataCorp, 2015, *Stata Statistical Software: Release 14*, College Station, TX: StataCorp LP).

## Results

### Clinical characteristics

Among 379 children with hydrocephalus, 86 (23%) developed epilepsy during the study period. Compared with 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 versus 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 aqueductal obstruction more common among children with epilepsy, and spina bifida and communicating hydrocephalus less common.

VP shunt placement was by far the most common type of hydrocephalus treatment. Among surgically treated children, VP shunts were placed in 96% of children with epilepsy and 90% without. Compared with children without epilepsy, children with epilepsy underwent more hydrocephalus-related surgical procedures overall (mean = 3.3 versus 2.2 procedures).

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, observed as the sole seizure type in 61 children (71%). Fourteen children (16%) had multiple seizure types; ten 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.

Relative to children with spina bifida the risk of epilepsy was at least fourfold higher in children with other major hydrocephalus subtypes, including IVH, aqueductal obstruction, and cysts and celes (Table 2). Adjustment for history of surgery or surgical complications did not alter the magnitude of these associations (data not included).

History of any surgery, any surgical failure, and surgical infection were all associated with a higher risk of epilepsy. Surgical failure for intracranial reasons was four times as common as surgical failure for extracranial reasons, and only intracranial surgical failure was associated with an increased risk of epilepsy. In an analysis limited to the subset of children without a history of surgical infection the risk associated with intracranial surgical failure was still increased but no longer statistically significant (RR = 1.5, 95% CI = 0.88 to 2.52).

Because the median age of children with epilepsy was older than those without, we performed the same analyses limited to children less than six years old by the end of the study follow-up; results for all estimates remained similar; however, CIs 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 substantially more often in children with surgical complications than that in children without.

## 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[11]; 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 nonneurologist clinicians because it can be clinically subtle. Observational evidence suggests that early treatment of infantile spasms may improve clinical outcome.[12] Therefore the relatively common occurrence of this potentially devastating form of childhood epilepsy among children with hydrocephalus deserves emphasis because it may be under-recognized in these patients.

Hydrocephalus subtype demonstrated a strong association with epilepsy. We set spina bifida 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 usually originates. Spina bifida therefore allows an approximation of the baseline risk of epilepsy associated with hydrocephalus and its surgical correction. Compared with these children, other forms of hydrocephalus were associated with risks of epilepsy at least four times higher, presumably reflecting the additional contribution of supratentorial malformations or injury.

History of any surgery was associated with increased risk of epilepsy. This fact 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 surgical failure and infection to surgically treated children and evident that both these complications were associated with increased epilepsy risk.

The association between epilepsy and surgical failure was statistically significant for intracranial but not extra-cranial surgical failures. This fact could conceivably reflect the specific effect of surgical procedures on the brain (as opposed to the more general effect of elevated intracranial pressure). However, extracranial failures were relatively uncommon, so we may have lacked the power to detect an association. We also examined whether the risk of epilepsy associated with intracranial failures was independent from the risk associated with surgical infection (which necessitates additional intracranial surgical procedures). In an analysis limited to the subset of children with no history of surgical infection the observed risk of epilepsy associated with intracranial surgical failures was still increased to a similar extent to that observed in the cohort as a whole but was no longer statistically significant. Smaller numbers in that subset of children also limit our ability to draw definitive conclusions from those results.

This study has several additional 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 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 are likely to be missing at random because of 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 fact would bias our estimates of the proportions of individuals with these complications, but its effect on risk estimates should be less differential because outcome and risk factor data would both be missing.

Although the number of patients in this cohort is relatively large compared with 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 caregivers and non-neurologist clinicians. Hydrocephalus subtype markedly influences the risk of epilepsy, which is fourfold greater in patients with IVH, aqueductal obstruction, and cystic malformations compared with children with spina bifida. Surgical complications—most notably surgical infection-further increase that risk.

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**TABLE 1.**

Characteristics of Hydrocephalic Children With and Without Epilepsy*

| | Epilepsy (n = 86); n (%) | No Epilepsy (n = 293); n (%) |
|---|---|---|
| **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 +/− S.D. (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*† | 58 (68.2) | 189 (66.1) |
| *1 wk to 6 mo* | 24 (28.2) | 56 (19.6) |
| *>6–12 mo* | 3 (3.5) | 41 (14.3) |
| Subtype | | |
| *Spina bifida* | 5 (6.1) | 72 (24.9) |
| *IVH* | 28 (34.2) | 72 (24.9) |
| *Aqueductal obstruction* | 20 (24.4) | 40 (13.8) |
| *Communicating* | 2 (2.4) | 29 (10.0) |
| *Cysts and celes* | 11 (13.4) | 27 (9.3) |
| *Posterior fossa crowding* | 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) |
| Surgery type‡ | | |
| *VP shunt* | 75 (96.2) | 194 (90.2) |
| *Subgaleal shunt*§ | 0 (0.0) | 4 (1.9) |
| *ETV*§ | 0 (0.0) | 4 (1.9) |

| | Epilepsy (n = 86); n (%) | No Epilepsy (n = 293); n (%) |
|---|---|---|
| *Temporary drain*[§] | 2 (2.6) | 10 (4.7) |
| *Cyst fenestration*[§] | 1 (1.3) | 3 (1.4) |
| Total number of hydrocephalus-related surgical procedures; mean ± S.D. (min, max) | 3.32 ± 3.26 (1, 18) | 2.21 ± 1.82 (1, 13) |
| **Epilepsy characteristics** | | |
| Age of onset (yr); mean ± S.D. (min, max) | 2.7 ± 2.9 (0.0, 12.2) | |
| Years between first surgery and epilepsy diagnosis; mean ± S.D. (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 +/−atonic* | 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) | |

Abbreviations:

EEG = electroencephalograph

ETV = endoscopic third ventriculostomy

IVH = intraventricular hemorrhage

[*] Numbers that add to less than column total reflect missing data.

[†] Onset at less than 37 weeks gestational age, observed on prenatal ultrasound, or diagnosed within 1 week of a term birth.

[‡] Surgically treated children only. Each child was assigned to a single category based on the procedure that was ultimately successful in treating their hydrocephalus.

[§] Without subsequent VP shunt placement.

**TABLE 2.**

Adjusted* Risks for Epilepsy Among Children With Hydrocephalus

| | Epilepsy (n = 86); n (%) | No Epilepsy (n = 293); (n%) | RR (95% CI) |
|---|---|---|---|
| **Subtype**† | | | |
| *Spina bifida* | 5 (7.8) | 72 (34.1) | 1 (ref) |
| *IVH* | 28 (43.8) | 72 (34.1) | 4.20 (1.74–10.14) |
| *Aqueductal obstruction* | 20 (31.3) | 40 (19.0) | 4.94 (2.01–12.17) |
| *Cysts and celes* | 11 (17.2) | 27 (12.8) | 4.59 (1.77–11.88) |
| **Surgical factors**‡ | | | |
| Any hydrocephalus-related surgery§ | 78 (91.8) | 215 (73.4) | 2.76 (1.32–5.75) |
| History of any surgical failure‖ | 45 (67.2) | 105 (50.0) | 1.56 (1.01–2.55) |
| *Intracranial failure*‖,¶ | 43 (65.2) | 90 (44.6) | 1.71 (1.08–2.68) |
| *Extracranial failure*‖,# | 11 (13.8) | 22 (7.8) | 1.11 (0.66–1.88) |
| History of surgical infection‖,** | 18 (24.0) | 17 (8.0) | 2.02 (1.37–2.97) |

Abbreviations:

CI = confidence interval

IVH = intraventricular hemorrhage

RR = risk ratio

*Adjusted for age at most recent follow-up.

†Limited to four most common subtypes.

‡Before onset of epilepsy or more recent follow-up, whichever came first.

§Includes placement of VP shunt, subgaleal shunt, or temporary external ventricular drain (EVD); endoscopic third ventriculostomy (ETV); and cyst fenestration (EVD).

‖Limited to children who underwent surgery.

¶Any surgical failure requiring revision of proximal shunt or EVD catheter, or failure of ETV or cyst fenestration.

#Any failure of shunt valve or distal catheter, or abdominal pseudocyst.

**Includes any culture-proven or presumed infection.