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Original Article

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 hydrocephalus. 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.

Keywords: hydrocephalus, epilepsy, infantile spasms, spina bifida, aqueductal stenosis

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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

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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: $\leq$1 unprovoked seizure/year; medically intractable: $\geq$2 unprovoked seizures/year after appropriate trials of two antiseizure medications; and not well controlled/not intractable, $\geq$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).