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Original Article

Maternal and Infant Factors Associated With Infancy-Onset Hydrocephalus in Washington State

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ABSTRACT

OBJECTIVE: Hydrocephalus, a complex condition characterized by progressive accumulation of cerebrospinal fluid within the ventricular system of the brain, affects ~6 in 10,000 infants and is heterogeneous in nature. Previous investigations of risk factors have not considered etiologic heterogeneity. **METHODS:** We conducted a case-control study of 1748 children with hydrocephalus identified through birth certificate check boxes and ICD-9 codes of linked hospital discharge records through the first year of life. Control infants were identified from birth records (N = 19,700), frequency matched to cases by year of birth. Three mutually exclusive, nonexhaustive subgroups were identified: hydrocephalus associated with a neural tube defect (n = 332); prenatal-onset hydrocephalus (n = 402); and hydrocephalus associated with intracranial hemorrhage (n = 446). Within each group, we examined associations with maternal age, race/ethnicity, parity, diabetes and hypertension, and infant sex and gestation. We used logistic regression to calculate odds ratios and 95% confidence intervals. **RESULTS:** Asian ethnicity was independently associated with an inverse risk of all subtypes of hydrocephalus (hydrocephalus associated with a neural tube defect: odds ratio, 0.44; 95% confidence interval, 0.23 to 0.84; prenatal-onset hydrocephalus: odds ratio, 0.47; 95% confidence interval, 0.27 to 0.83; hydrocephalus associated with intracranial hemorrhage: odds ratio, 0.59; 95% confidence interval, 0.33 to 1.07) compared with whites. Pre-existing diabetes was associated to varying degrees with all three subtypes (hydrocephalus associated with a neural tube defect: odds ratio, 1.94; 95% confidence interval, 0.61 to 6.17; prenatal-onset hydrocephalus: odds ratio, 5.20; 95% confidence interval, 2.60 to 10.40; hydrocephalus associated with intracranial hemorrhage: odds ratio, 5.26; 95% confidence intervals, 2.85 to 9.69). Hypertension had a positive association with hydrocephalus associated with intracranial hemorrhage (odds ratio, 1.91; 95% confidence interval, 1.46 to 2.52) but an inverse association with hydrocephalus associated with a neural tube defect (odds ratio, 0.59; 95% confidence interval, 0.36 to 0.98). Gestation ≤30 weeks was associated with all three subgroups, most notably hydrocephalus associated with intracranial hemorrhage (odds ratio, 443.56; 95% confidence intervals, 326.34 to 602.87); nearly two-thirds (64%) of hydrocephalus associated with intracranial hemorrhage infants were born ≤30 weeks. Male gender was independently associated only with hydrocephalus associated with intracranial hemorrhage (odds ratio, 1.82; 95% confidence interval, 1.40 to 2.39). No associations were observed with advanced or young maternal age or with parity. **CONCLUSIONS:** The different risk profiles seen among these three subgroups support the biologically heterogeneous nature of infantile hydrocephalus. Future research should take specific etiologic subtypes into account.

Keywords: hydrocephalus, epidemiology, myelomeningocele, intraventricular hemorrhage

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Introduction

Hydrocephalus is a common but complex condition characterized by progressive accumulation of cerebrospinal fluid within the ventricular system of the brain. Hydrocephalus can develop at any age, including during the prenatal period. Congenital hydrocephalus, which has been defined variably as hydrocephalus that is present at birth or that develops during the first year of life, was recently estimated to affect 5.9 in 10,000 infants during their initial birth hospitalization.[1]

Hydrocephalus that develops during infancy is heterogeneous in nature, and can accompany a neural tube defect (NTD) or other central nervous system (CNS) malformation,[2] in which case it usually develops in the second or third trimester and is present at birth. Infantile hydrocephalus can also be the result of extrinsic causes such as intracranial hemorrhage (ICH) or infection.[3] In those situations, it is usually not present at birth, but develops later in the first year of life. Previous investigations of the risks for infancy-onset hydrocephalus have assessed both maternal and infant risk factors such as ethnicity, parity, and infant gender, but analyses were limited by broad case definitions that did not take etiologic heterogeneity into account.[1,4,5] As a result, risk factors have neither been defined for subtypes of hydrocephalus nor have they been compared across subtypes.

In the current analysis, we evaluated selected maternal and infant factors associated with hydrocephalus diagnosed in Washington State infants during their first year of life, compared with control infants without hydrocephalus. Because infantile hydrocephalus is heterogeneous, we hypothesized that risk factors would depend on the etiology; we chose to evaluate risk factors within three discrete, biologically related subgroups: hydrocephalus associated with an underlying NTD; hydrocephalus present at birth but unrelated to NTD or ICH; and hydrocephalus associated with ICH.

Methods

The Human Subjects Protection Review Boards at the University of Washington and the Washington State Department of Health approved the procedures used in the conduct of this study and determined that it was exempt from review.

Data sources

We conducted a population-based case-control study using the Birth Event Records Database, which contains linked hospital discharge-birth certificate data from Washington State from 1987 to 2012. Additional information was obtained from the Comprehensive Hospital Abstract Report System, a statewide longitudinal inpatient hospital discharge database.

Selection of cases and controls

Cases were ascertained on the basis of ICD-9 codes for hydrocephalus-related diagnoses and procedures captured in inpatient hospital billing records from the first year of life, as well as data reported on the birth certificate. Infants with hydrocephalus were identified using ICD-9 codes for hydrocephalus-related diagnoses recorded on hospital discharge, including 331.3 and 331.4 (communicating hydrocephalus, obstructive hydrocephalus), 741.0 (spina bifida [NTD] with hydrocephalus), and 742.3 (congenital hydrocephalus), and several hydrocephalus-related procedure codes, including 002.2 (ventriculostomy), 002.3 (ventricular shunt placement), and 002.4 (ventricular shunt revision). In addition to identifying cases on the basis of diagnosis and procedure codes from hospital discharge data, potential cases were identified through birth certificates. From 1980 to 2002, Washington State birth certificates contained a check box for hydrocephalus. Infants with a birth certificate diagnosis of hydrocephalus but without one of the diagnosis or procedure codes that had been used for primary ascertainment were also included if they had an ICD-9 diagnosis code of 741 (spina bifida) or 742 (other congenital anomalies of the nervous system). Those who had a birth certificate report of hydrocephalus but no accompanying procedure or diagnosis code consistent with this diagnosis were excluded. We initially identified 1970 infants with hydrocephalus that had been born in Washington State between 1985 and 2002. We subsequently excluded 222 patients because they had a birth certificate check box but no compatible diagnosis or procedure code, which left 1748 cases for analysis.

For comparison, controls (infants with no record of hydrocephalus) were randomly selected from the Washington State birth certificate database at a control:case ratio of 10:1 and frequency matched to cases by birth year.

Delineation of subgroups

Using information from hospital discharge records, including ICD-9 diagnosis and procedure codes as well as length of stay, we defined three mutually exclusive but nonexhaustive subgroups as follows:

1. NTD-associated hydrocephalus (NTD-H) subgroup: all patients had an NTD-related ICD-9 diagnosis code (741: spina bifida) or underwent an NTD-related procedure (03.51: repair of spinal meningocele or 03.52: repair of spinal myelomeningocele). Because of the specificity of these diagnosis and procedure codes, we assume that this group consists entirely of patients with spinal myelomeningocele; however, these codes do not allow us to distinguish whether the NTD occurred in isolation or in conjunction with other physical anomalies or an underlying syndrome.
2. Prenatal-onset hydrocephalus (PO-H) subgroup: all patients had hydrocephalus designated on their birth certificates, had a hydrocephalus-related diagnosis code given within the first 7 days of life, or underwent a hydrocephalus-related surgical procedure within the first 14 days of life, and did not meet criteria for inclusion in one of the other two subgroups. We assume that most patients within this group have developmental brain malformations such as aqueductal stenosis or obstructive intracranial cysts, although a small proportion could have had an unrecognized intrauterine infection or hemorrhage that led to hydrocephalus.[6]
3. ICH-associated hydrocephalus (ICH-H) subgroup: all patients had a hemorrhage-related ICD-9 diagnosis code (772.1: intraventricular hemorrhage (IVH) or 767.0: subdural or cerebral hemorrhage, newborn only). We presume that most of the ICH identified in this group was peri or postnatal in onset, although some may have been prenatal in onset.

Using these criteria, we identified 332 patients with NTD-H, 402 patients with PO-H (not associated with NTD or ICH), and 446 patients with ICH-H. Of these patients with ICH, 387 (87%) had been assigned diagnosis codes indicating IVH; the other 59 had been assigned codes indicating ICH (which may also include IVH).

The remaining 578 infants did not fall into one of these three categories and were therefore not included in the subgroup analyses. Our presumption is that most uncategorized patients had other forms of acquired hydrocephalus (especially postinfectious and post-traumatic), later-onset developmental forms, and hydrocephalus that truly belonged in one of the three defined subgroups, but which had not been assigned the specific diagnosis or procedure codes to enable it to be categorized as such.

Demographic information and risk factors

Maternal age (<20, 20-34, 35+ years), number of prior births (0, 1, 2+), and maternal race/ethnicity (white, black, Hispanic, Asian,