Risk factors of congenital hydrocephalus: a 10 year retrospective study

M Van Landingham, T V Nguyen, A Roberts, A D Parent, J Zhang

Department of Neurosurgery, University of Mississippi Medical Center, Jackson, Mississippi, USA

Correspondence to: Dr J Zhang, Department of Neurosurgery, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216-4505, USA; jhzhang@neurosurgery.umsmed.edu

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ABSTRACT

Objective: To evaluate and identify the risk factors associated with the pathogenesis of congenital hydrocephalus in a large specific population.

Methods: An International Classification of Diseases (ICD)-9 database search of patients with congenital hydrocephalus treated at the University of Mississippi Medical Center between 1998 and 2007 was performed. All recruited patients were interviewed, assessing maternal age, onset of prenatal care, geographic location of pregnancy, maternal diabetes and chronic hypertension, pregnancy induced hypertension, pre-eclampsia, eclampsia, single or multiparous gestation, maternal alcohol, tobacco and drug use, infection and trauma during gestation, trauma or sexually transmitted disease at parturition, and other family members with hydrocephalus.

Results: In this 10 year retrospective study, several significant risk factors were identified among 596 well defined cases of congenital hydrocephalus. The identified risk factors included lack of prenatal care, multiparous gestation, maternal diabetes, maternal chronic hypertension, maternal hypertension during gestation and alcohol use during pregnancy. Of these patients with congenital hydrocephalus, 12.1% identified an additional family member also diagnosed with hydrocephalus. No differences in risk factors were identified between sporadic and familial congenital hydrocephalus cases except for an increased incidence of multiparous pregnancies and prenatal care in the first trimester in familial cases.

Conclusions: A number of key risk factors have been identified to be strongly associated with the development of congenital hydrocephalus in an infant. The prevalence of familial patterns of inheritance for congenital hydrocephalus suggests a broader role for genetic factors in the pathogenesis of congenital hydrocephalus.

The diversity of pathological conditions that cause hydrocephalus in neonates has rendered a precise characterisation of the disease inherently difficult. Traditionally, hydrocephalus has been categorised as congenital (primary) or acquired (secondary), but in neonates this clinical distinction is often difficult to make because hydrocephalus may be present at birth and secondary to another pathology. Furthermore, hydrocephalus present at birth could remain subclinical until aging or trauma causes the disease to become symptomatic.[1–3] Depending on how a study defines "congenital hydrocephalus" (CH) as well as the geographic and ethnic makeup of the study population, the reported incidence of CH ranges between 0.4 and 3.16 per 1000 live births.[4–6]

A wide variety of environmental factors have been demonstrated to cause hydrocephalus in animal models, including alcohol consumption,[7 8] *x* ray radiation,[9] infections, nutritional abnormalities and chemical exposure during gestation.[10] In addition, a number of therapeutic drugs administered during pregnancy can cause an increased risk of CH.[11–13]

Only one gene (L1 at Xq28, coding for L1CAM) has been linked to CH in humans. Although X linked CH makes up approximately 2–7% of all cases of CH,[14] L1CAM has been estimated to be mutated in approximately 15% of sporadic cases.[15 16] L1CAM mutations are strongly associated with aqueductal stenosis, the primary pathological insult that causes hydrocephalus in these patients. A study of 35 patients with congenital hydrocephalus and aqueductal stenosis found that nearly 40% of this subset of patients had a genetic aetiology of their hydrocephalus.[17] Several other reports of human kindreds harbouring an autosomal recessive, autosomal dominant and mitochondrial patterns of inheritance have been reported, but the genes and loci responsible for these forms of transmission have not been fully identified.[18–26] Studies in animal models support the hypothesis that multiple genes play a role in the expression of the hydrocephalus phenotype.[26]

The current study aims to provide a detailed epidemiological examination of a geographically limited cohort of congenital hydrocephalics and their prenatal risk factors. By improving our understanding of the comorbidities associated with CH, we hope to further specify neonates at high risk for having CH and provide a foundation for analysis of the role of genetics in the pathogenesis of the condition.

METHODS

Patient acquisition

The University of Mississippi Medical Center (UMMC) is the primary neurosurgical referral centre for the state of Mississippi (MS). After obtaining approval from the institutional review board, we compiled a single institutional database of patients treated at UMMC between 1998 and 2007 with International Classification of Diseases (ICD)-9 diagnostic codes for congenital hydrocephalus (742.3), spina bifida with hydrocephalus (741.0), communicating hydrocephalus (331.3) and obstructive hydrocephalus (331.4). Demographic information, age at time of treatment and treatment dates were obtained for all individuals. Using Excel software, we stored all clinical data in the neurosurgery research centre. Furthermore, to comply with the Health Insurance Portability and Accountability Act (HIPAA), confidentiality of information was ensured by utilising text

encryption, password protection and limited personnel involvement. All methods were performed according to the Declaration of Helsinki.

Data acquisition

Qualified patients were contacted to ask a standardised set of questions for pre-screening evaluation. Regardless of their ICD-9 diagnostic code, we excluded patients that reported never receiving a diagnosis of CH and who failed to meet diagnostic criteria for CH during review of their medical records. We defined CH as hydrocephalus present at birth or secondary to pathology present at birth. If patients could not provide adequate medical history in response to our questions, we followed-up by using the patients' medical records. If a patient reported a relative with CH, then we considered this patient a familial CH case. All screened patients for whom data could not be completely confirmed by interview or medical records were excluded from further analysis.

Data reported by the Mississippi Department of Health from 1998 to 2006 were used to perform statistical analysis, documenting the state-wide incidence of advanced maternal age, prenatal care, maternal diabetes mellitus, maternal chronic hypertension, maternal pregnancy induced hypertension, and tobacco and alcohol use during pregnancy. Demographic information was also acquired from this source.

Data analysis

Comparisons between proportions were assessed by χ^2 goodness of fit test. The χ^2 test, or Fisher's exact test when applicable, was used for multiple comparisons. Bivariate analysis was performed to identify possible risk factors represented as odds ratio (OR) and risk ratio (RR) with 95% confidence interval (CI).

Data analyses were performed with STATA 8 (StataCorp, College Station, Texas, USA) statistical software.

RESULTS

A 10 year retrospective database search of patients with CH treated at UMMC between 1998 and 2007 yielded a total of 4312 patients: 710 patients corresponding to ICD-9 code 742.3, 499 patients to 741.0, 170 patients to 331.3 and 2933 patients to 331.4. This initial patient cohort contained 841 duplicate assignments to the above mentioned ICD-9 codes. Of the remaining 3471 unique patients, we were able to contact 1108 patients, with all other patients being unreachable via the contact information acquired. After further exclusions because of non-congenital hydrocephalus, miscoded diagnoses and unwillingness to participate in the study, we positively identified 596 cases of CH (fig 1).

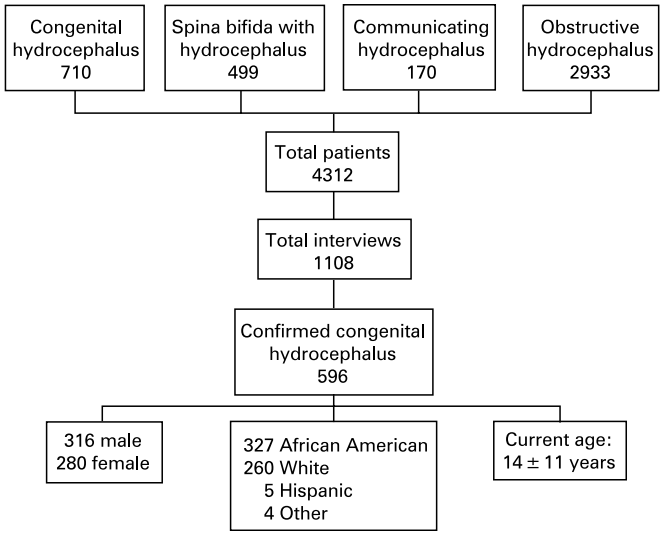

Figure 1 Flow diagram of patient acquisition and demographics.

The geographic distribution of where each CH patient was carried to term demonstrated no statistically significant localisation.

Prenatal risk factors associated with CH were analysed with respect to the incidence of these risk factors in Mississippi's general population (table 1). Advanced maternal age was not associated with the occurrence of CH ($\chi^2 = 0.001$, $p = 0.976$). Although the onset of prenatal care during the pregnancy was not significantly associated with CH, the complete lack of prenatal care was highly correlated with CH ($\chi^2 = 62.78$, $p<0.0001$). Maternal hypertension during pregnancy was significantly associated with CH ($\chi^2 = 16.3$, $p<0.0001$). Further differentiation of the type of maternal hypertension during pregnancy revealed that both pregnancy induced hypertension and pre-eclampsia correlated well with the subsequent development of CH in the child ($\chi^2 = 18.51$, $p<0.0001$). We could not demonstrate this same correlation with eclampsia ($\chi^2 = 0.116$, $p = 0.733$) which only one mother of a CH patient experienced prior to delivery.

Tobacco use during pregnancy did not vary significantly between mothers of the CH population and mothers in the general Mississippi population, but alcohol use during gestation was significantly greater among mothers of CH children ($\chi^2 = 54.33$, $p<0.0001$). No difference between the genders of the hydrocephalic population and the general Mississippi population was found ($\chi^2 = 0.775$, $p = 0.3787$). Although a notable difference in the racial composition of the CH cohort compared with the state's general population was found, this difference did not reach statistical significance ($\chi^2 = 7.087$, $p = 0.0692$). African American patients constituted a disproportionately large percentage of the CH cohort ($\chi^2 = 13.963$, $p = 0.0001$). Although no comparable information is reported by the State Department of Health, the following risk factors were also noted in CH pregnancies: traumatic birth (19.5%), infection (9.0%), sexually transmitted disease at the time of delivery (1.2%), trauma to the mother during gestation (3.0%) and illicit drug use during the pregnancy (3.9%).

In total, 72 of our 596 patients (12.1%) reported at least one additional family member with hydrocephalus. By comparing prenatal risk factors between familial and sporadic CH patients, we have identified some significant differences between the two cohorts (table 2). The odds of a multiparous pregnancy occurring in a CH mother were significantly greater in familial cases than sporadic cases ($p<0.0001$). Familial CH mothers were also much more likely to have received prenatal care during the first trimester of pregnancy than mothers of sporadic CH offspring ($p = 0.0292$). Sporadic and familial CH patients were equally likely to have been exposed to all other prenatal risk factors assessed.

DISCUSSION

CH is the ultimate outcome of a variety of neuropathological insults; however, the risk factors associated with the condition are not well established. Familial patterns of CH inheritance have not yet been examined in a large subject group. Although we were only able to assess 1108 patients from our initial database of 3471 patients, it is unlikely that further patient

Table 1 Risk factors among patients with hydrocephalus

Risk factor	Hydrocephalus patients (%)	Mississippi general population (%)	p Value
Advanced maternal age	7.425	7.347	0.976
Prenatal care			
Within first trimester	78.169	83.042	0.195
Within second trimester	9.859	13.718	0.262
Within third trimester	2.817	2.184	0.665
None	9.155	1.056	<0.0001***
Pregnancy			0.015*
Uniparous	92.678	96.9	
Multiparous	7.322	3.1	
Pre-existing maternal diabetes mellitus	6.032	2.801	0.05*
Maternal chronic hypertension	5.399	1.714	0.005**
Maternal HTN during pregnancy	15.496	5.948	<0.0001***
PIH and pre-eclampsia	15.254	5.471	<0.0001***
Eclampsia	0.242	0.477	0.733
Alcohol use during pregnancy	6.019	0.553	<0.0001***
Smoked during pregnancy	15.081	12.296	0.396
Gender			0.379
Female	47	51.4	
Male	53	48.6	
Race			0.069*
White	43.6	61.2	
Black	54.9	36.9	
Hispanic	0.8	1.7	
Other	0.7	0.2	

PIH and pre-eclampsia were considered together because the Mississippi Department of Health does not distinguish between the two in their data collection. Within the CH population, 9.93% of CH mothers had PIH and 5.33% had pre-eclampsia.
*p<0.05; **p<0.01; ***p<0.0001.
CH, congenital hydrocephalus; HTN, hypertension; PIH, pregnancy induced hypertension.

recruitment would have had a significant effect on our results. Although contact information from patients treated earlier in the timeline of the database are more likely to be inaccurate and the patient unreachable, there is no reason to suspect a tendency towards recruiting more recently treated patients would have impacted on the incidence of risk factors assessed, as these factors exhibited minimal temporal trends during the study period in Mississippi.

Table 2 Risk factors and their odds ratio and risk ratio among familial hydrocephalus cases compared with sporadic congenital hydrocephalus

Risk factors	OR (95% CI)	RR (95% CI)	p Value
Advanced maternal age	0.2201 (0.0294–1.6476)	0.2445 (0.0349–1.7117)	0.1552
Prenatal care			
Within first trimester	2.8209 (1.0873–7.3185)	2.5694 (1.0511–6.281)	0.0292*
Within second trimester	0.5385 (0.1601–1.8105)	0.5714 (0.1861–1.755)	0.3404
None	0.3729 (0.0871–1.5961)	0.4050 (0.1024–1.602)	0.2039
Pregnancy			
Uniparous	0.1571 (0.0744–0.3317)	0.237 (0.1441–0.3898)	<0.0001***
Multiparous	6.3651 (3.0149–13.4378)	4.2190 (2.5656–6.9382)	<0.0001***
Maternal diabetes mellitus	1.3523 (0.4469–4.0917)	1.2981 (0.5072–3.3223)	0.7556
Maternal chronic hypertension	2.1558 (0.764–6.0828)	1.9045 (0.8374–4.3318)	0.1757
Maternal HTN during pregnancy	1.6497 (0.7952–3.4227)	1.5381 (0.8326–2.8414)	0.2088
PIH	1.2779 (0.5085–3.2113)	1.2373 (0.5617–2.7252)	0.6133
Pre-eclampsia	2.2614 (0.7958–6.4263)	1.9747 (0.8714–4.475)	0.1668
Infection during pregnancy	0.8436 (0.2865–2.4841)	0.8600 (0.3277–2.2572)	1.0000
Alcohol use during pregnancy	0.5673 (0.1302–2.4713)	0.6006 (0.1548–2.3296)	0.5584
Smoked during pregnancy	1.2412 (0.591–2.6069)	1.2072 (0.636–2.2917)	0.6904
Illicit drug use during pregnancy	0.9333 (0.2075–4.1987)	0.9412 (0.2498–3.546)	1.0000
Trauma during pregnancy	2.2531 (0.5993–8.4697)	1.9639 (0.7034–5.4831)	0.3819
Traumatic birth	1.0090 (0.4829–2.1086)	1.0079 (0.5271–1.9276)	1.0000
Maternal STI at time of delivery	1.8878 (0.2068–17.2343)	1.7102 (0.2905–10.0676)	1.0000
Race	1.1824 (0.7186–1.9455)	1.1601 (0.7458–1.8045)	0.5301

A bivariate analysis was performed to estimate odds ratio and risk ratio. The difference between measures was tested.
*p<0.05; ***p<0.0001.
HTN, hypertension; PIH, pregnancy induced hypertension; STI, sexually transmitted infection.

The early diagnosis and treatment of CH is critical to the outcome of the patient. Although sonography can identify ventriculomegaly antenatally, only certain aetiologies of CH cause ventriculomegaly in utero. Improved understanding of the risk factors associated with CH can augment available screening methods. In contrast with an earlier smaller study that analysed several common prenatal risk factors and their association with CH,[27] our study has found that a number of these factors were statistically significant. Family history of CH, as demonstrated previously,[28] was also an important component of the risk spectrum for CH.

Earlier studies have documented a higher percentage of male CH cases among live born and stillborn neonates,[29] as well as the majority CH patients at autopsy[30]; no significant racial differences were found. The absence of an increased prevalence of males among our CH population and the significantly higher percentage of African Americans could reflect several unique characteristics of our study population. The population of Mississippi is 61.2% Caucasian (non-Hispanic), 36.9% African American and less than 2% other ethnicities and races, which differs markedly from the country as a whole. Infant mortality among African Americans in Mississippi is also much higher (14.4, Mississippi Department of Health, 2006) than in Caucasians (6.9, Mississippi Department of Health, 2006) or in the country as a whole (6.4 in 2007). Worthy of further investigation is whether or not the predominance of African Americans in our patient cohort stems from similar healthcare disparities that may also contribute to the racial difference in infant mortality.

Secondly, CH patient populations have demonstrated significant epidemiological changes over time,[6] and the distinct demographic makeup of our patients with CH could reflect their more recent birth dates. If consistent nationwide, this trend could provide a reason for the higher mortality rate of African American infants attributed to CH compared with Caucasian infants.[31] Although we cannot rule out the possible impact of environmental factors specific to our population (especially access to prenatal care and nutrition), the statistically even distribution of CH pregnancies across the state suggests that environmental factors that do play a role in the pathogenesis of CH are not unique to the relatively poor or sparsely populated counties of Mississippi but rather to the state as a whole. The increased risk of developing congenital hydrocephalus due to the absence of prenatal care found in our study has been demonstrated previously in studies utilising solely ICD-9 codes.[32]

Our study found that advanced maternal age did not increase the risk of having a child with CH. This finding contradicts a much larger study conducted in the Czech Republic, examining 3650 patients with CH born between 1961 and 2000, which found that maternal age of 37 years or greater was significantly ($p<0.001$) associated with the incidence of CH.[33] However, during the study period the incidence of CH decreased from 8.93 to 3.92 per 10 000 live births, a dramatic trend which creates some uncertainty as to whether the association between advanced maternal age and CH would still exist in the more recently born population.

The significantly greater use of alcohol during pregnancy by CH mothers is consistent with our understanding of its teratogenic potential in human and animal models. Alcohol related neurodevelopmental disorder encompasses a number of different neurological pathologies, of which hydrocephalus has been included.[34] Ethanol disrupts the function of L1CAM, leading to disordered neurite outgrowth.[7] This mechanistic similarity to X linked hydrocephalus is manifested in a similar phenotypical outcome.

The association between pregnancy induced hypertension or pre-eclampsia and CH is not well documented. Although the pathogenesis of pre-eclampsia is not entirely understood, fetal and placental hypoxia appear to be a necessary component of the initiation of the maternal syndrome.[35] The amalgamation of fetal hypoxia and iatrogenic prematurity would seem to place these fetuses at higher risk of developing hydrocephalus because of the malformed vasculature that would increase the risk of intraventricular haemorrhage. However, empirical evidence has demonstrated that fetuses of pre-eclamptic women[36] and of mothers with pregnancy induced hypertension[37] are less likely to develop an intraventricular haemorrhage, thus indicating that the aetiology of hydrocephalus lies in another aspect of pre-eclamptic pathology.

Maternal diabetes mellitus is a significant risk factor for congenital malformations, particularly in the cases of cardiovascular and neural tube defects.[38 39] The moderate association we found between maternal diabetes and hydrocephalus is likely attributable to the pathological subset of CH cases associated with spina bifida. Alterations in gene expression of important signalling pathways during embryogenesis, secondary to hyperglycaemia during pregnancy,[40] could have profound effects on neural migration and differentiation, leading to other aetiological causes of CH, but little research has been conducted to demonstrate the precise mechanisms by which this could occur.

The prevalence of familial cases (12.1%) within our CH cohort is much higher than that of reported X linked CH (2–7%).[14] The nearly identical risk factor profiles of familial and sporadic CH patients suggest that familial cases do not develop because of unique environmental exposure. The increased probability of familial CH mothers receiving prenatal care early in the pregnancy confirms the less prominent role of nutritional deficiencies in the pathogenesis of familial cases. The increased risk of multiparous pregnancies among familial congenital hydrocephalics is also consistent with a genetic aetiology of CH, although the unique physiology of twin gestation cannot be entirely ruled out as a pathogenic factor. Considered as a whole, these data indicate the increased incidence of CH within individual families is more likely attributable to genetic inheritance than to environmental exposure. The higher percentage of familial cases beyond those statistically attributable to X linked CH can most likely be attributed to non-X linked patterns of inheritance, confirming our previous belief based on animal models.[26]

Animal models have established autosomal dominant and recessive patterns[26] of inheritance for CH, and case studies in humans have added support to the existence of these patterns.[18–25] Our results indicate that autosomal patterns of inheritance for CH are not rarities, but should be considered in familial cases of hydrocephalus in which X linked inheritance is unlikely. If the genetic principles of animal models of CH are applicable in humans,[26] then we can expect hydrocephalic genes to exist at multiple loci. This multi-loci model would be consistent with the diversity of pathological findings independently associated with the ultimate outcome of CH.

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