Surveillance survey of family history in children with neural tube defects

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OBJECTIVE Although there are known risk factors for the development of neural tube defects (NTDs), little is known regarding the role of family history. The authors' goal in this study is to describe the family history in their population of patients with NTDs.

METHODS Surveys were completed for 254 patients who were accompanied by their biological mother during their annual visit to the multidisciplinary Spina Bifida Clinic at Children's of Alabama. An NTD has been diagnosed in all patients who are seen in this clinic (myelomeningocele, lipomeningocele, split cord malformation, and congenital dermal sinus tract). Each mother answered questions regarding known NTD risk factors and their pregnancy, as well as the family history of NTDs, other CNS disorders, and birth defects.

RESULTS The overall prevalence of family history of NTDs in children with an NTD was 16.9% (n = 43), of which 3.1% (n = 8) were in first-degree relatives. In patients with myelomeningocele, 17.7% (n = 37) had a positive family history for NTDs, with 3.8% in first-degree relatives. Family history in the paternal lineage for all NTDs was 8.7% versus 10.6% in the maternal lineage. Twenty-two patients (8.7%) had a family history of other congenital CNS disorders. Fifteen (5.9%) had a family history of Down syndrome, 12 (4.7%) had a family history of cerebral palsy, and 13 (5.1%) patients had a family history of clubfoot. Fourteen (5.5%) had a family history of cardiac defect, and 13 (5.1%) had a family history of cleft lip or palate.

CONCLUSIONS The family history of NTDs was 16.9% in children with NTD without a difference between maternal and paternal lineage. This high rate of positive family history suggests that genetics and epigenetics may play a larger role in the pathogenesis of NTD in the modern era of widespread folate supplementation.

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KEY WORDS spina bifida; neural tube defect; family history; genetics; congenital

EACH year approximately 1500 babies are born in the United States with myelomeningocele, the most common form of neural tube defect (NTD).⁷ According to the Centers for Disease Control and Prevention NTD data and statistics, the prevalence of NTD by ethnicity is as follows: 4.17 per 10,000 in Hispanics, 2.64 per 10,000 in non-Hispanic African Americans, and 3.22 per 10,000 in non-Hispanic whites.²⁷ Although the incidence of NTD has decreased during the last 20 years, possibly

due to folic acid supplementation, it remains the most common permanently disabling congenital defect.²⁰

Known risk factors include maternal obesity, poor diet, folate deficiency, pregestational diabetes, gestational diabetes, and anticonvulsant drug use.^{11,15,21} Understanding the role that family history plays in the development of NTDs may be particularly important in an era in which folate supplementation is now sufficiently widespread. The purpose of the present study is to characterize the family

ABBREVIATIONS NTD = neural tube defect.

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history in patients with NTDs seen at a multidisciplinary, comprehensive outpatient clinic within a large medical center.

Methods

Our study population consisted of patients attending the multidisciplinary Spina Bifida Clinic at Children's of Alabama from June 2012 to December 2013. The patients in this clinic are between 0 and 21 years of age with a diagnosis of an NTD (e.g., spina bifida aperta, lipomeningocele, split cord, and congenital dermal sinus). The institutional review board of the University of Alabama at Birmingham provided approval prior to performing this study.

We conducted a cross-sectional survey of biological mothers of all patients attending the multidisciplinary clinic at Children's of Alabama to participate in the study on behalf of their children. We approached the qualifying families during their clinic visit, provided a letter describing the purpose and procedures of this project, and consecutively distributed a total of 254 surveys. The research staff completed the surveys while interviewing the patients' mothers in the privacy of the examination room. Data were only collected from patients who were seen in clinic with their biological mother to ensure the accuracy and reliability of the data.

During the study period, 419 patients were examined during 576 appointments in our multidisciplinary Spina Bifida Clinic. Of these patients, 254 were accompanied by their biological mother and consequently met our criteria for inclusion in our study. For the 254 eligible patients with NTDs, surveys were distributed and completed for all 254 eligible patients prior to data analysis, representing a 100% response rate. Of these, 209 patients had a diagnosis of myelomeningocele while 45 patients had a diagnosis of closed spinal dysraphism. Basic patient demographics are presented in Table 1.

Each participating patient's mother answered questions on family history. The nonmodifiable family factors included the family history of NTDs and family history of other relevant disorders, such as other congenital CNS problems, Down syndrome, cerebral palsy, clubfoot, congenital heart defect, cleft palate, kidney malformation, cystic fibrosis, and sickle cell disease. All of the family history questions included information regarding lineage (maternal, paternal, or both) and the degree of the identified relative. Degrees of relationship were defined as previously described: first degree (parents, siblings, and children), second degree (grandparents, grandchildren, aunts, uncles, nieces, nephews, and half-siblings), or third degree (great grandparents, great grandchildren, great aunts/uncles, and first cousins).¹³ All other relationships were categorized as beyond third degree. A sample patient survey is available for reference (Appendix A).

Descriptive statistics were calculated for the family history in all patients with NTDs. We then compared patients with myelomeningocele to those with closed spinal dysraphism (lipomyelomeningocele, dermal sinus tract, and split cord malformation) using the chi-square test. The chi-square statistic was used to test for statistical differ-

TABLE 1. Characteristics in 254 patients with NTDs

Variable	% of Patients
Race	
White	74.0
White, Hispanic	5.1
Black or African American	18.5
Asian	0.4
Other	2.0
Primary diagnosis	
MMC	82.3
Closed spinal dysraphism	17.7
Maternal age at delivery, yrs	
<18	4.7
18–25	38.6
26–34	49.6
>35	7.1

MMC = myelomeningocele.

ence between the degrees of relatives in the family history of the NTD. The results were tabulated and analyzed using commercially available software (SPSS version 22, IBM).

Results

A total of 254 patient surveys were included in the analysis, of which 209 were from patients with myelomeningocele and 45 were from patients with closed spinal dysraphism. The overall prevalence of family history of NTDs was 16.9% (n = 43). Approximately 3.1% (n = 8) of the patients had first-degree relatives with NTD, 2.4% (n = 6) had second-degree relatives with NTD, 3.1% (n = 8) had third-degree relatives with NTD, and 8.3% (n = 21) had beyond third-degree relatives with NTD (Table 2). In the myelomeningocele population (n = 209), the prevalence of a positive family history was 17.7% (n = 37) versus 13.3% (n = 6) in the closed dysraphism group (p = 0.642). Of the myelomeningocele patients, 3.8% (n = 8), 2.4% (n = 5), 3.3% (n = 7), and 8.1% (n = 17) had first-, second-, third-,

TABLE 2. Family history of NTDs for all NTD patients

Variable	No. of Patients (%)			p Value*
	All NTDs (n = 254)	MMC (n = 209)	Closed Dysraphism (n = 45)	
Positive FH	43 (16.9)	37 (17.7)	6 (13.3)	0.642
Positive paternal FH	22 (8.7)	19 (9.1)	3 (6.7)	0.787
Positive maternal FH	27 (10.6)	23 (11.0)	4 (8.9)	0.575
Relative				
1st degree	8 (3.1)	8 (3.8)	0 (0)	0.183
2nd degree	6 (2.4)	5 (2.4)	1 (2.2)	0.879
3rd degree	8 (3.1)	7 (3.3)	1 (2.2)	0.696
>3rd degree	21 (8.3)	17 (8.1)	4 (8.9)	0.575

FH = family history.

* Chi-square test comparing myelomeningocele and closed dysraphism.

TABLE 3. Prevalence estimates of disorders in the US population: frequency of a positive family history in surveyed myelomeningocele and closed dysraphism patients

Disorder	US Prevalence Estimates/ 10,000 Live Births ^{1,5,6,10–13}	MMC (% w/ positive FH)	Closed Dysraphism (% w/ positive FH)	p Value*
Spina bifida	6.67	37 (17.7)	6 (13.3)	0.642
Congenital CNS disorder	0.8–3.5	20 (9.6)	2 (4.4)	0.267
Down syndrome	13.6	13 (6.2)	2 (4.4)	0.645
Cardiac defect†	0.7–4.7	12 (5.7)	2 (4.4)	0.726
Clubfoot	10	13 (6.2)	0 (0)	0.085
Cleft lip/palate	10.6	12 (5.7)	1 (2.2)	0.332
Cerebral palsy	40	12 (5.7)	0 (0)	0.098
Kidney malformation	32.6	3 (1.4)	2 (4.4)	0.186
Cystic fibrosis	4	2 (1.0)	0 (0)	0.509
Sickle cell anemia‡	27.4	1 (0.5)	0 (0)	0.645

* Chi-square test comparing myelomeningocele and closed dysraphism.

† Cardiac defects include common truncus, transposition of the great vessels, tetralogy of Fallot, septal defects, and hypoplastic left heart syndrome.

‡ Sickle cell anemia prevalence is in African Americans.

and beyond third-degree relatives with NTDs, respectively (Table 2).

Family history in the paternal lineage was 8.7% (n = 22) versus 10.6% (n = 27) maternal lineage in all patients. In the myelomeningocele group, 9.1% (n = 19) had a positive family history in their paternal lineage versus 11.0% (n = 23) maternal (Table 2). The trend toward maternal lineage was not significant for all patients or the myelomeningocele subgroup (p = 0.751 and p = 0.453, respectively).

The overall prevalence of family history of other congenital CNS disorders was 8.7% (n = 22). For the 2 subgroups, myelomeningocele and closed spinal dysraphism, the prevalence was 9.6% (n = 20) and 4.4% (n = 2), respectively. Other congenital anomalies found in family members of myelomeningocele and closed spinal dysraphism patients, respectively, are as follows: 6.2% (n = 13) and 0% (n = 0) of patients had a family history of clubfoot; 5.7% (n = 12) and 0% (n = 0) of patients, cerebral palsy; 6.2% (n = 13) and 4.4% (n = 2) of patients, Down syndrome; 5.7% (n = 12) and 4.4% (n = 2) of patients, cardiac defect; 5.7% (n = 12) and 2.2% (n = 1) of patients, cleft lip or palate; 1.4% (n = 3) and 4.4% (n = 2) of patients, kidney malformation; 1.0% (n = 2) and 0% of patients, cystic fibrosis; and 0.5% (n = 1) and 0% of patients had a family history of sickle cell anemia (Table 3). There was no statistically significant difference between the subgroups (i.e., myelomeningocele and closed spinal dysraphism) for a family history of any of these conditions (Table 3).

Patients were also surveyed on other known risk factors for the development of NTDs. The prevalence of selected risk factors is reported in Table 4.

Discussion

While the prevalence of NTDs has declined since the advent of widespread folic acid fortification in the 1990s, NTD remains the most common and devastating congenital abnormality.³ There are multiple known risk factors for NTDs, but genetic factors such as inheritance patterns remain largely unexplored. A few of the known risk factors

include obesity, folate status, diabetes, and anticonvulsant drug use.^{11,15,21} Previous literature regarding the family history of NTDs is reviewed in Table 5.^{1,4,8,14,16,21,23,28–30}

Family History of Spina Bifida, Central Nervous System Disorders, and Lineage

The important finding of our study is the overall high prevalence of family history of NTDs (16.9%) and other congenital CNS disorders (8.7%) in children with NTDs. Subgroup analysis of myelomeningocele and closed dysraphisms did not show a significant difference between these groups. These findings support a complex role of genetics in the development of NTDs.

Previous reports have suggested that once a mother has a child with an NTD, the risks of NTD in subsequent pregnancies are significantly higher than the reported population risks.²³ Furthermore, the risk of NTD in a subsequent pregnancy quadruples after a second NTD child is born in a given family.³⁰ Several other authors have described the familial aggregation of congenital CNS malformations

TABLE 4. Prevalence of other known risk factors

Variable	No (%)	Yes (%)
Maternal age at delivery, yrs		
<18		12 (4.7)
18–25		98 (38.6)
26–34		126 (49.6)
>34		18 (7.1)
Fertility treatment	241 (94.9)	13 (5.1)
Hypertension	232 (91.3)	21 (8.3); during pregnancy: 1 (0.4)
Diabetes mellitus	239 (94.1)	15 (5.9)
History of DVT or PTE	254 (100)	0
SLE	254 (100)	0

DVT = deep vein thrombosis; PTE = pulmonary thromboembolism; SLE = systemic lupus erythematosus.

TABLE 5. Previous studies focusing on family history of patients with spina bifida

Authors & Year	Design	Patients	Main Findings	Other Relevant Findings
Richards et al., 1972	Retrospective review	172 cases of SB & 146 cases of anencephaly reviewed	An NTD was present in 6.5% of siblings born subsequent to an anencephalic propositus & in 4.4% of siblings born subsequent to a patient w/ SB	Strong tendency for affected children w/in a sibship to have the same defect
Partington & McLone, 1995	Population survey	Surveys received from 363 patients (35.5% of the clinic population) & analyzed	The MMC recurrence rate was 4.3%	A family history of SB was found to be evenly distributed btwn maternal & paternal relatives, rather than tending to follow through the maternal side
Chatkupt et al., 1992	Genetic analysis	50 families (491 individuals in 137 sibships) w/ >1 living case of isolated, nonsyndromic SB analyzed genetically	Twice as many gene-carrier females (56) as gene-carrier males (28) ($p < 0.005$), suggesting a possible role of imprinting in SB	Penetrance was higher for offspring of female parents than of male parents, but the difference was not statistically significant; both male & female gene-carriers were frequently found in the same pedigree
Angerpointner et al., 1990	Case-control study	257 children w/ SB compared w/ 537 healthy controls	Risk of recurrence was 0.5% if 1 parent was affected & 4% if a sibling was affected	In 22.9% of children w/ SB, "malformed" relatives were found, whereas this was the case in only 6.4% of the children of the "non-malformed" control group
Myrianthopoulos & Melnick, 1987	Prospective study	71 children w/ nonsyndromal NTDs compared w/ a group of 400 randomly selected healthy control infants	71 single-born children (13.33/10,000) found to have a nonsyndromal NTD; FH present in only 1 case	There was no increased risk for NTDs among siblings of children w/ major malformations such as tracheoesophageal "dysraphism," cleft lip/palate, or renal agenesis; NTDs are apparently etiologically heterogeneous
Khoury et al., 1982	Retrospective review	223 single NTD & 66 NTD w/ other defects (multiples) analyzed	Siblings of single NTD had a higher recurrence rate for NTDs (2.0% vs 0.0%)	Compared w/ siblings of multiples, siblings of singles had a higher recurrence rate for birth defects in general (10.9% vs 3.0%)
Seller, 1981	Retrospective review	958 consecutive patients who consulted a genetic advice center reviewed	Overall recurrence was 3.44% (1/29)	If the index case was the 1st affected child in the family, the recurrence in the next sibling was 3.15% (1/32), & if it was the 2nd affected child, the recurrence was 11.76% (1/9)
Nightingale et al., 1975	Population survey	107 SB patients surveyed	9 had >1 affected child, 9 had a positive FH for NTDs, & 9 of the patients & 7 of an estimated total of 220 siblings had an unrelated major birth defect	There was no deficiency of twinning among the sibships, or of males among the Spina Bifida Service patients
Carter et al., 1968	Retrospective review	551 patients in South Wales reviewed	Overall incidence of the CNS malformation was 4.61% in relatives w/ SB, anencephaly, & congenital hydrocephalus	Overall incidence of the 3 malformations was 8–12/1,000 total births & the individual incidences 4.13, 3.54, & 0.45%, respectively
Lorber, 1965	Retrospective review	722 infants who were born w/ SB cystica reviewed	Of 1,256 siblings, 85 (6.8%) had gross malformation of the CNS	In 118 families cases of gross malformation of the CNS were known to have occurred among members of the family other than siblings; cases occurred in 3 generations

SB = spina bifida.

and NTDs in patients with NTD. Carter et al. documented a high incidence of CNS malformations in relatives of NTD children.⁴ Richards et al. and Lorber reported that approximately 6% of the siblings of children with NTDs had NTDs and a similar percentage had CNS malformations.^{16,29} Partington and McLone documented a family history of myelomeningocele in 5.9% of NTD patients in their population survey,²⁸ while Nightingale et al. reported a rate of 8.4% of positive family history of NTDs in 107 patients with NTDs.²³

Although our percentages of family history of NTDs and CNS abnormalities in spina bifida children are higher, the aforementioned authors' estimations primarily reflect

pre-folate fortification era. The associated risk from folate deficiency may have been minimized in the postfortification era, which may emphasize the role of other risk factors such as genetics and epigenetics and may explain the higher prevalence of positive history in our sample. This phenomenon could also apply to other risk factors (e.g., poverty, environmental toxins, or drug use) in the postfortification era. Additionally, it is possible that regional and geographic differences play a role in the increased prevalence observed in our sample.

In our study, there was no statistically significant difference in maternal or paternal lineages for the family history of NTDs in both myelomeningocele and closed

dysraphism groups. This is consistent with prior findings²⁸ and argues against female-dependent inheritance (X-linked recessive or mitochondrial inheritance) and an excess of female carriers, which has been proposed.⁸ Our results do not suggest simple mode of genetic transference involved in NTD development.

Family History of Other Associated Diseases

Our study demonstrated prevalence of a family history of Down syndrome in 5.9% of NTD patients compared with 1 in 691 babies born each year in the US.²² This increased prevalence in our population suggests a common causative mechanism for both pathologies. There is some evidence that mothers of infants with Down syndrome have mutation of the methylenetetrahydrofolate reductase (*MTHFR*) gene involved in folic acid and methionine metabolism, which is also well established in NTDs.¹² Barkai et al. also provide support for this link between Down syndrome and NTDs.²

Our results show a high prevalence of a family history of nonneural midline defects in our myelomeningocele population. Approximately 5.7% have a family history of cardiac or conotruncal defects, and 5.7% show a family history of cleft lip or palate. Each of these are higher than the reported US prevalence, which is less than 1% for both.^{5,6,27} These results are consistent with the theory that birth defects resulting from fusion failure of the embryo's midline have a common etiology.^{9,24,25} Previous studies support this theory, with the finding that infants with a midline defect often have more than 1 defect.^{9,24} Additionally, familial clustering of midline defects has been reported,^{17,18,26} which also supports a role of genetics in NTDs.

Overall Findings

Epigenetics has been identified in regulating gene expression, which may play a role in the susceptibility to developing an NTD.^{10,19} The findings in our study suggest a complex genetic relationship with the development of NTDs that may reflect the role of epigenetics in this phenomenon. Our study supports previous claims that defining epigenetic mechanisms and gene profiling will help identify parents at increased risk.

Limitations

Our study has several limitations. First, we collected the data for the study through a retrospective survey, which introduces selection and recall bias into the results. The selection bias inherent in our study design is referral bias. Participants who volunteered to complete our survey may differ from the general population with NTDs, in particular, those with milder forms of NTDs, those who do not have shunt-treated hydrocephalus, and parents who chose elective termination of pregnancy.

There is also an informational or recall bias inherent in survey-based research. Consequently, the family history of NTDs may have been under- or overreported. We attempted to minimize this by ensuring only the biological mother completed the survey and by having medically trained personnel available to define terms in the survey

and answer questions; however, this remains an important source of potential bias. Despite these limitations, surveys are useful because the phenomena of NTDs and its risk factors are not directly observed.

We did not survey for all possible risk factors, including socioeconomic status, environmental exposures, hot tub use, drug abuse, and excess vitamin A or tea use. We chose not to collect these data, as this is a descriptive study and is not designed to account for potential confounders; however, it is possible these factors played a role. It was not feasible with our study design to evaluate corresponding incidences of positive family history in pregnancies with a normal outcome. Including a comparison group of unaffected pregnancies would allow for these additional analyses, and this additional knowledge may be valuable and should be considered when designing future studies.

Conclusions

NTDs remain one of the most frequent and devastating congenital anomalies, and the etiology is complex. The results of our study show a high prevalence (16.9%) of a family history among NTD patients. In an environment in which optimal folic acid intake is common, our results suggest that genetics and epigenetics may play a larger role in the pathogenesis of NTD.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Rocque, Patel, Blount. Acquisition of data: Hopson, Arynchyna, Bishop. Analysis and interpretation of data: Rocque, Dupépe, Patel. Drafting the article: Patel. Critically revising the article: Rocque, Dupépe. Reviewed submitted version of manuscript: Rocque, Dupépe, Blount. Approved the final version of the manuscript on behalf of all authors: Rocque. Statistical analysis: Patel, Hopson, Arynchyna. Administrative/technical/material support: Hopson, Arynchyna, Bishop. Study supervision: Rocque, Blount.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Appendix A. <https://thejns.org/doi/suppl/10.3171/2016.12.PEDS1668>.

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