Recurrence risks for neural tube defects in siblings of patients with lipomyelomeningocele

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Purpose: Neural tube defects (NTDs) are a group of widely varying congenital malformations resulting from incomplete or improper fusion of the neural tube during embryonic development. NTDs are traditionally classified by the presence or absence of a layer of skin covering the spinal defect. Although a genetic component has been well established in the etiology of open NTDs, studies examining the genetics of closed NTDs such as lipomyelomeningocele are rare. We and others have previously observed families in which multiple members were affected with a broad spectrum of NTDs, suggesting the possibility of a common genetic etiology. **Methods:** We calculated the sibling recurrence risk in 52 pedigrees in which the proband was diagnosed with lipomyelomeningocele (LMM), defining recurrence broadly to include both closed and open neural tube defects. **Results:** Although no recurrences of LMM were observed among younger siblings, one younger sibling had myelomeningocele, yielding an estimate of recurrence risk of 0.04 (95% CI 0.01–0.20). When all siblings of the proband were included, two additional affected siblings were identified, one with anencephaly and another with fatty filum, yielding an estimate of recurrence risk of 0.043 (95% CI 0.01–0.12). **Conclusions:** Although the sample size is small, these data are not inconsistent with recurrence risks for myelomeningocele, ranging from 2% to 5% in siblings. These data suggest the underlying genetic basis for closed defects may be the same or closely related to that for myelomeningocele in some families, although a larger sample will be necessary before these data are appropriate for use in a clinical setting. Further characterizations, including whether risk for recurrence of NTDs or LMM in families in which the proband is affected with LMM are altered by folate supplementation, may shed light on the underlying genetics.
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Key Words: *neural tube defects, closed NTDs, lipomyelomeningocele, congenital malformations, sibling recurrence*

Neural tube defects (NTDs) are the second most common congenital malformation, occurring once in every 1000 live births. The term "NTD" encompasses a wide range of defects resulting from the abnormal fusion and development of the neural tube during embryonic development. NTDs can be classified according to a number of criteria, including vertebral level and degree of severity. Another commonly accepted method of classifying NTDs is the presence or absence of a layer of skin covering the spinal defect. Open NTDs, those without skin covering, occur when the brain and/or spinal cord is exposed at birth through a defect in the skull or vertebrae. The two most common forms of open NTDs are myelomeningocele and anencephaly.

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In contrast, closed NTDs, also known as occult spinal dysraphisms, have a layer of skin overlying the spinal defect. One common occult lesion is lipomyelomeningocele, characterized by fatty elements infiltrating through a vertebral defect into the spinal column. The prevalence of lipomyelomeningocele has been estimated to be 1 in 4000, with a female:male ratio of 1.5:1.[1–3] However, this figure may underestimate the true prevalence because patients with lipomyelomeningocele are sometimes clinically asymptomatic. Alternatively, they may present with vague symptoms, such as leg pain and weakness or recurrent urinary tract infections and incontinence.[3] Often, the only indication of a lipomyelomeningocele is a small dorsal cutaneous abnormality, such as a midline dimple, skin tag, or hemangioma.[4] In the absence of an obvious dorsal fatty mass, some patients may be overlooked until more serious neurological problems arise. In addition, imaging modalities used before the development of the MRI were less sensitive and more likely to miss smaller defects. Thus, it has only been in recent years that this defect can be reliably diagnosed.

Open NTDs have a complex etiology, involving both genetic and environmental factors. A significant genetic component in the etiology of open NTDs is supported by several lines of

evidence including associations with known genetic syndromes,[5,6] associations with cytogenetic abnormalities,[7,8] and a plethora of animal models.[9,10] In addition, the recurrence risk in families with one member affected with an NTD (2–5%) is 25- to 50-fold higher than the 1 in 1000 incidence of NTDs in the general population.[11]

Although the role of genetic factors in the etiology of open NTDs is unequivocal, it remains unclear whether the genetic basis for closed NTDs such as LMM is due to the same or different causes. Open and closed NTDs are thought to be due to different etiologies because they originate at different times during embryonic development.[3] However, there is evidence that at least some of the underlying etiologic factors are common to both open and closed NTDs. We and others have previously reported families in which closed and open NTDs occur[12–14]; such families suggest an underlying gene(s) with pleiotropic effects. To investigate this hypothesis, we estimated the recurrence risk to siblings of a proband with lipomyelomeningocele and hypothesized that it would not be different than the recurrence risk to siblings of a proband with an open neural tube defect. We conclude that this similarity may suggest a common underlying gene(s) with pleiotropic effect.

MATERIALS AND METHODS

Families in this study included those in which the proband was diagnosed with lipomyelomeningocele. Ascertainment of these families occurred through a variety of resources, including web-based advertising, support groups such as the Lipomyelomeningocele Family Support Network (LFSN) and the Adult Tethered Cord Syndrome Support Group, e-mail listservs, and referrals from collaborating neurosurgeons. Detailed family history[15] and pregnancy history information were collected. Diagnosis in affected family members was confirmed by review of imaging studies, operative reports, and/or medical records. Open neural tube defects included patients with anencephaly or myelomeningocele. Closed neural tube defects included lipomyelomeningocele and other spinal lipomas (myelocystoceles, terminal lipomas, fatty filum, intraspinal lipoma). Families in which nonproband members had lipomyelomeningocele were identified and tracked to document familial aggregation, but are not included in the recurrence risk calculations. This study was approved by the Duke University Medical Center Institutional Review Board and informed consent was obtained from all subjects.

Recurrence risk

Sibling recurrence risks were calculated using data collected from the standardized interviews. All siblings born subsequent to the proband were included in the calculation. The proportion of these siblings affected by a broad spectrum of neural tube defects, both open and closed, represents the sibling recurrence risk. Overall occurrence risk was calculated by including all siblings of the proband, regardless of the birth order. Confidence intervals (95%) for the risk were calculated allowing for a continuity correction.

RESULTS

Study population

The sample used for this study consisted of 52 American Caucasian families in which the proband was diagnosed with lipomyelomeningocele. Of the 52 probands, 23 (44%) were female and 29 (56%) were male; this difference is not statistically significant. Of the cases, 15 (29%) were confirmed by review of preoperative films; for the remaining 37 cases, preoperative films were not available and operative reports and/or medical records were evaluated.

Sibling recurrence risk

Recurrences are shown in Table 1. The sample population included a total of 52 families in which the proband was diagnosed with a lipomyelomeningocele. These families included 25 younger siblings; of these siblings, none were affected with lipomyelomeningocele. However, one sibling was diagnosed with myelomeningocele. The recurrence risk for this broad spectrum of neural tube defects is 4.0% (95% CI 0.01–0.20). When all siblings of the proband with lipomyelomeningocele were considered, there were a total of 69 siblings, three of whom had NTD or related phenotypes (one myelomeningocele, one anencephaly, and one with fatty filum). Thus, the overall occurrence of a broad spectrum of neural tube defects in siblings of probands with lipomyelomeningocele is 4.3% (95% CI 0.01–0.12).

Familial aggregation

Two families (8776 and 8237; Fig. 1) exhibited aggregation with affected individuals outside the nuclear family. In family 8776, a female with lipomyelomeningocele has a brother, a cousin, two second cousins, and 4th degree relative with lumbosacral myelomeningocele. In family 8237, the proband with

Table 1
Phenotypes in siblings of 52 probands with lipomyelomeningocele

Diagnosis in:	Lipomyelomeningocele	Lumbosacral yelomeningocele	Anencephaly	Other spinal lipoma[a]	Unaffected
Younger Siblings	0	1	0	0	25
All Siblings	0	1	1	1[b]	69

[a]OSL, other spinal lipomas (myelocystoceles, terminal lipomas, fatty filum, intraspinal lipomas).
[b]Older sibling had fatty filum.

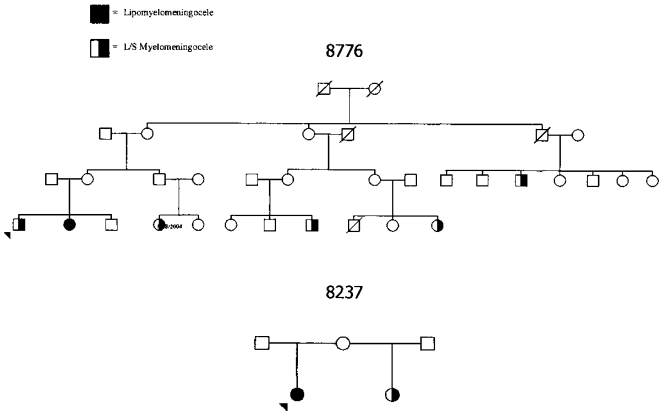

Fig. 1. Two families demonstrating occurrence of lipomyelomeningocele and other NTD outside of the nuclear family.

lipomyelomeningocele has a half-sibling with lumbosacral myelomeningocele.

DISCUSSION

The recurrence risk for a broad spectrum of neural tube defects in the siblings of probands affected with lipomyelomeningocele is consistent with the recurrence risk to siblings of probands with open neural tube defects, within the range of 2% to 5%. These studies indicate open and closed NTDs may share the same or a similar underlying genetic mechanism, and they may represent the pleiotropic effects of a gene or genes segregating within these families. Although a large number of studies have examined the genetics of open NTDs, less attention has been focused on the genetics of closed NTDs. Carter et al.[13] calculated the sibling recurrence risk for NTDs in 207 families in which the proband had a closed NTD, defined as any one of a spectrum of spinal cord abnormalities, including tethered cord, diastematomyelia, dermoid cysts, spina bifida occulta, and signs of neurological damage in conjunction with an identifiable spinal cord anomaly. In these families, the recurrence risk for any type of NTD was 4.12%, similar to the established recurrence risk for open NTDs. However, given the wide phenotypic variation present within the sample, it is difficult to draw any conclusions about specific types of closed NTDs and their relationship to open NTDs. Furthermore, this study was done before the advent of magnetic resonance imaging studies, so its focus was on the most severe of cases as probands.

Other early studies examined the incidence of spina bifida occulta (SBO) in the parents of a child with an open NTD.[16,17] The results of these studies suggested SBO, which is considered a type of closed spinal anomaly, occurred more frequently in these parents than in control parents although there were variations in risk according to a variety of covariates such as offspring gender, type of NTD (rostral or caudal) in the offspring, and complexity of SBO in the parent, all serving to highlight the complexity of the entire scenario. Although the estimates of SBO incidence in this population varied between these studies, they do suggest some degree of a genetic relationship between open and this particular closed defect.

Our data provide two separate but related lines of evidence consistent with a common genetic etiology for open and closed neural tube defects in some families. First, the recurrence risk to siblings for open and/or closed neural tube defects is not statistically different than the recurrence risk to siblings with open neural tube defects. Secondly, the familial aggregation presented in several families is further evidence suggesting a common basis. It is interesting to note that there were no families exhibiting complete concordance for the type of NTD within our series of families. In fact, there has only been one reported case of a familial recurrence of lipomyelomeningocele[18]; in this report, the prenatal identification of a fetus with lipomyelomeningocele was followed by the prenatal diagnosis of lipomyelomeningocele in a subsequent pregnancy. Although our findings are consistent with a common genetic etiology, other explanations such as a common environmental exposure or chance association cannot be ruled out.

There are several limitations inherent to this study. First, the sample size is relatively small. Although efforts were made to ascertain participants from a variety of sources, the comparatively low incidence of lipomyelomeningocele and the diagnostic difficulties associated with this condition makes obtaining a large sample size difficult. Second, it is possible our recurrence risk calculations may underestimate the true recurrence risk because asymptomatic cases of closed NTD may be undetected.

In conclusion, it appears lipomyelomeningocele may share at least some of the same genetic factors as open NTDs in some families. This finding may lead to the conclusion that folate supplementation may reduce risk for LMM in some findings; however, McNeely and Howes[19] recently reported no reduction in LMM prevalence after folate supplementation in Nova Scotia. It is possible that that are mechanisms for LMM that differ between families, some of which are responsive to folate and others not.

Previous studies suggest this relationship extends beyond lipomyelomeningocele to include other forms of closed NTDs, such as SBO and split cord malformation. Families such as these with presumptive variable presentation will be invaluable for identifying and characterizing whether or not such pleiotropic effects exist once genes for open NTDs are found. Larger samples will be necessary before these results can be clinically applied in a counseling setting regarding recurrence risks

APPENDIX

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