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Factors Associated With Strabismus in Spina Bifida Myelomeningocele

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Abstract

Purpose—Higher prevalence of strabismus in individuals with spina bifida myelomeningocele (SBM) has previously been attributed to hydrocephalus; however, SBM is associated with many other complications. This study investigates the relation between strabismus and other factors in SBM.

Methods—Children aged 3 to 18 years with SBM (n = 112) received an eye examination including assessment of ocular alignment by cover or Hirschberg test. Gestational age, respiratory distress at birth, birth weight, maternal age at birth, number of shunt revisions, and spinal lesion level were also obtained. The relation between these factors and strabismus was analyzed.

Results—Forty-two participants had strabismus. Maternal age ($P = .4$) and respiratory distress ($P = .6$) were not significantly related to strabismus. Lower birth weight was suggestive of a relation with strabismus (logistic regression, $P = .05$) and younger gestational age was related to strabismus (logistic regression, $P = .01$). Participants who had at least one shunt revision were more likely to have strabismus (Fisher's exact test, $P = .038$). Spinal lesion level was significantly related to strabismus with increased likelihood of strabismus for spinal lesions closer to the brain (Wald chi-square, 1,100 = 4.29, $P = .038$).

Conclusion—These findings indicate that several factors are associated with strabismus in SBM. Some of these factors (lower birth weight and younger gestational age) are associated with strabismus in the general population, whereas the association of strabismus and level of spinal lesion may be unique to SBM and may be related to the more severe brain dysmorphology associated with upper level spinal lesions.

INTRODUCTION

Spina bifida myelomeningocele (SBM) is a developmental disorder in which the spinal cord and meninges protrude through a defect in the vertebral column. The spinal lesion can occur anywhere along the vertebral column, resulting in various manifestations of lower limb motor paralysis, sensory deficits, and bladder or bowel difficulties below the lesion. SBM is commonly associated with hydrocephalus, which is observed in approximately 80% of

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patients.[1] A recent imaging study demonstrated a link between the location of the spinal lesion and the severity of anomalous brain development, with higher lesions being associated with more severe brain dysmorphology.[2]

In addition to these functional deficits, numerous studies have reported an increased prevalence of ocular conditions in children with SBM, most notably strabismus.[3–8] These studies report a prevalence of strabismus as great as 34% to 61% in children with SBM,[3,4,6,8] which is in contrast to the 2% to 3% prevalence observed in the general population.[9,10] In these studies, investigators observed that most people with strabismus also had hydrocephalus.[3–7] Given that hydrocephalus itself is known to be associated with an increased prevalence of strabismus,[11–13] many investigators concluded that the increased prevalence of strabismus observed in people with SBM is due to the presence of hydrocephalus rather than being linked directly to SBM itself.[3–5] However, previous studies have also observed people with SBM who manifest strabismus even with normal intracranial pressure.[7,14] In addition, a large percentage of people with SBM and hydrocephalus did not manifest strabismus in these studies, and the cause of the hydrocephalus in SBM is different from other affected populations in that it often results from a congenital malformation of the hindbrain and cerebellum known as the Chiari II malformation. Thus, it is not clear that the increased prevalence of strabismus observed in SBM is linked solely to the presence of hydrocephalus.

The purpose of this study was to investigate whether other notable factors observed in individuals with SBM, such as lesion level, are linked to the presence of strabismus. The identification of additional related factors to ocular alignment in these individuals may aid medical practitioners in the treatment of children with SBM by helping them to determine which individuals could be at greater risk for strabismus.

PATIENTS AND METHODS

All participants in this study were children who had been enrolled in the Spina Bifida Assessment of Neurobehavioral Development International (SANDI) study, which was conducted in both Houston, Texas, and Toronto, Ontario, Canada.[15] Houston participants were enrolled at either the Spina Bifida Clinic at Texas Children's Hospital or the Shriner's Hospital for Children. Participants from Toronto and the surrounding areas were enrolled at The Hospital for Sick Children. This study was approved by the institutional review boards at both The University of Texas Health Science Center in Houston, Texas, and The Hospital for Sick Children in Toronto, Ontario, Canada. After parents and children agreed to participate, written consent was obtained from parents and assent obtained from each child.

From the larger sample enrolled for the parent study,[15] 112 of 347 participants volunteered for an ophthalmologic examination with an age range from 3 to 18 years (mean age = 10 ± 4 years) and a gender distribution of 40% male and 60% female. All participants had previously been diagnosed as having SBM. Chiari malformations were present in 95% and 94% had associated hydrocephalus that had also previously been diagnosed and documented in medical records separate from the study eye examinations. A comprehensive eye examination was performed for all participants by one of two pediatric ophthalmologists. The examination protocol was standardized between examiners and included testing to evaluate ocular health, oculomotor ability, binocular vision, and refractive error (summary of testing procedures listed in the Appendix). The primary measurements of interest for the current study were ocular alignment testing with Hirschberg or unilateral cover test, observational evaluation for nystagmus, and cycloplegic retinoscopy.

Additional information regarding each participant's birth and health history was obtained through parental survey and medical record reviews conducted at a separate visit as part of the SANDI study protocol before the opportunity to receive a vision examination. In an interview, parents were asked to report the maternal age at birth, gestational age, birth weight, presence or absence of respiratory distress at birth, and the number of shunt revisions performed for the management of hydrocephalus. These responses were verified with medical record reviews whenever possible. Spinal lesion level was determined from the original hospital discharge summaries, the neurosurgical operative reports, or the medical records from the time of birth.[2] In cases in which the lesion was large or asymmetric, the level of the spinal lesion was defined as the highest level at which a lesion was present. The relation between these factors and the presence of strabismus was analyzed using Fisher's exact test, logistic regression, and the Wald chi-square test.

RESULTS

Birth history, presence of hydrocephalus, number of shunt revisions, spinal lesion level, and the presence of Chiari II malformation were compared for those who volunteered for the ophthalmologic examination and those who did not. There were no significant differences between the groups with the exception of maternal age, which was older in the group that participated in the ophthalmologic examination (mean age = 28 vs 26 years; $P = .002$, *t* test).

Ocular alignment findings were obtained for 107 of the 112 participants. Forty-two participants (39% of those evaluated) had strabismus. Esotropia was the most common type of deviation (n = 26), followed by exotropia (n = 14). There were also 6 participants with hypertropia in combination with their horizontal deviation. Two participants were identified as having strabismus, but the type was inadvertently not listed on the standardized, scannable examination form submitted to the centralized data center. Of the participants with strabismus, 10 were documented as having an A-pattern deviation and 1 a V-pattern deviation. The presence or absence of nystagmus was documented for all 112 participants and 29 (26%) had nystagmus. Of the 29 participants with nystagmus, 23 also had strabismus. Cycloplegic retinoscopy was obtained for 108 participants. The mean refractive error was similar between eyes and was close to zero, although the overall range of refractive errors for the group was large. The mean sphere power was +0.27 ± 2.38 diopters (D) for the right eye (range: −13.50 to +6.50 D) and +0.36 ± 2.05 D for the left eye (range: −6.75 to +6.75 D). The mean cylinder power was +0.54 ± 0.73 diopters cylinder (DC) for the right eye (range: 0 to +3.50 DC) and +0.67 ± 0.80 DC for the left eye (range: 0 to +3.50 DC). Spherical refractive error was significantly related to participant age and became more myopic with increasing age as tested by linear regression analysis (right eye: $R^2 = 0.10$, $P < .001$; left eye: $R^2 = 0.13$, $P < .001$). Cylinder power was not significantly related to age (right and left eyes: $R^2 = 0.03$, $P > .05$).

Data regarding maternal age at birth, gestational age, birth weight, respiratory distress at birth, and number of shunt revisions were obtained for at least 91% of participants and are listed in Table 1. Parent interviews were not obtained from 6 subjects (5%), usually because the parent did not accompany the child and also declined a telephone interview. The other small percentage of missing information was due to parents not knowing or not remembering the information. Spinal lesion level was obtained for 102 of the 112 participants (91%) and was grouped into three categories: thoracic (n = 25), lumbar (n = 70), and sacral (n = 7). The data from the parental interview and the spinal lesion level were then used to identify any significant associations between the presence of strabismus and these other factors as shown in Table 2. Shorter gestational age was significantly related to the presence of strabismus (logistic regression, $P = .01$) and lower birth weight was suggestive of a relationship to the presence of strabismus (logistic regression, $P = .05$). Participants who had undergone at least one shunt revision procedure were significantly more likely to have strabismus than those who had not undergone a shunt revision for their hydrocephalus ($P = .038$, Fisher's exact test). Factors that were not significantly associated with strabismus were maternal age ($P = .39$, logistic regression) and respiratory distress at birth ($P = .62$, Fisher's exact test).

A Wald chi-square test was used to analyze the association between spinal lesion level and the presence of strabismus as shown in Table 3. There was a significant association between strabismus and lesion level with an increasing percentage of participants manifesting strabismus for lesion levels closer to the brain (Wald chi-square, 1,100 = 4.29, $P = .038$). This same association was observed for nystagmus (Table 3) with an increasing percentage of participants manifesting nystagmus for lesion levels closer to the brain (Wald chi-square, 1,100 = 3.94, $P = .047$). The relationship between A-pattern strabismus and spinal lesion level was not formally analyzed due to the small number of participants with A-pattern; however, of the 10 patients with A-patterns, 5 had thoracic lesions, 4 had lumbar lesions, and 1 had a sacral lesion. This distribution may be suggestive of a trend but cannot be determined from this sample.

Examination of other aspects of oculomotility, such as the accuracy of smooth pursuits and voluntary saccades (Appendix), was performed in 96% of the participants. These measurements were conducted using common clinical observation techniques because eye movement recording devices were unavailable in the practices in which the participants were seen. It was observed that 20% of participants had deficits in smooth pursuit; however, all but 3 were participants with nystagmus. Additionally, 6% of participants had saccadic inaccuracies, but all of these also had nystagmus. Thus, a separate analysis of the relation between inaccuracies in smooth pursuit and saccades with other variables in SBM was not conducted due to the relation of these oculomotor abnormalities with the presence of nystagmus. More robust evaluations of oculomotility with the use of eye tracking devices in this population may reveal inaccuracies that are not observed clinically.

DISCUSSION

The participants in this study were individuals from a larger cohort of children with SBM who volunteered for an optional ophthalmological examination portion of the study. Because the ophthalmological examination was added at a later date from initiation of the original SANDI study protocol, many of the participants' parents were offered the ophthalmological examination through letter distribution after they had already completed other SANDI study visits. This required the parent to take initiative to participate in this additional study appointment, and may have contributed to the smaller percentage who ultimately participated in the examinations. Our analysis of medical history variables for the entire cohort demonstrated that the participants who did participate in the ophthalmological examination were similar to those who opted out. However, these variables did not include ocular specific information and thus it is possible that parents who had more concerns about ocular and visual problems in their children were the ones who were more likely to have their children participate in the ophthalmological examination. This recruitment aspect represents a limitation to our study in terms of the generalizability of the overall percentage of individuals with SBM who had strabismus or other ocular abnormalities. However, it should be noted that the percentage of individuals with strabismus in our cohort is consistent with other studies of populations with SBM as discussed below. Thus, we do not believe our cohort was unnecessarily biased toward individuals with the most severe ocular abnormalities.

Thirty-nine percent of the participants in this study had strabismus, which is similar to the prevalence reported in other studies of children with SBM.[3,4,6,8] Two-thirds of the participants with strabismus had esotropia compared to one-third with exotropia, which is similar to the ratio reported by Rothstein et al.[3] and Biglan.[8] As expected, most of our participants had hydrocephalus (94%), and thus it is difficult to determine whether hydrocephalus by itself is linked to the observation of strabismus in this group of participants. Of the 6% without hydrocephalus, one participant was noted to have strabismus, although the type was not specified.

A new finding reported in this study is that the prevalence of strabismus was greater for participants who had undergone at least one additional surgical procedure for shunt failure than for those who had never required a shunt revision. In these patients, a possible explanation could be that increases in intracranial pressure that necessitated shunt revision led to additional clinical signs, such as strabismus. The relation between additional revision surgeries and strabismus has also been studied in people with hydrocephalus who do not have SBM, but the findings among those studies are not in agreement. Altintas et al. found a significantly larger percentage of people who had undergone shunt revisions manifested strabismus than those who had not had revisions.[12] Aring et al. included participants both with and without SBM, but found no relation between shunt revisions and the prevalence of strabismus for either etiology.[16] One possible explanation given by Aring et al. for the difference in findings between these two studies was the large difference in mean age of the participants.[16] The mean age was 24 months in the Altintas et al. study[12] and 9.7 years in the Aring et al. study.[16] The mean age of our participants was closer to that of the Aring et al. study; however, our finding regarding the relation between strabismus and shunt revisions is in agreement with the Altintas et al. study. It is unclear whether our finding of a positive relation between strabismus and shunt revisions is unique to children with SBM or simply related to hydrocephalus in general.

Another significant finding from this study that is specific to SBM is the relation between lesion location and strabismus. This result is of particular interest given the findings reported by Fletcher et al. in a study that linked lesion level and brain structure in SBM.[2] They used magnetic resonance imaging to quantify the volume of cerebral and cerebellar structures, as well as identify structural abnormalities in the brains of individuals with SBM, and tested many of the same participants included in the current study, although the numbers were too small to perform meaningful statistical analysis on our study subset.[2] The study by Fletcher et al. found that children with upper level spinal lesions had more severe anomalous brain development, as well as smaller overall size of cerebellar and cerebral structures.[2] Given this relation, it is possible that these more severe brain dysmorphologies could significantly affect oculomotor control, resulting in an increased prevalence of strabismus in individuals with upper level spinal lesions.

In our study, the same relation between lesion level and nystagmus was observed, with a greater percentage of participants with upper level spinal lesions manifesting nystagmus. Although most participants with nystagmus also had strabismus, there were 6 cases of nystagmus without strabismus, of which 2 had thoracic, 4 had lumbar, and zero had sacral lesions. Given these findings, individuals with upper level spinal lesions may be at an increased likelihood of oculomotor problems in general.

Other significant factors related to strabismus in this study were lower birth weight and shorter gestational age. This finding in and of itself may not be specifically related to SBM because it has been shown that low birth weight and prematurity are associated with a greater prevalence of strabismus in the general population without developmental disabilities.[17–19] The mean birth weight of our participants with strabismus was well above the 2,500 g cut-off for classification of low birth weight and the mean gestational age of our participants with strabismus was greater than the 37 week cut-off for classification as "full term"; however, there were 8 participants in our cohort with both low gestational age and birth weight, 6 of whom had strabismus. In particular, two individuals with birth weight less than 1,500 g both had strabismus, but the relation between gestational age and strabismus remained without these two lowest birth weight subjects. This supports our interpretation that given the presence of SBM, low birth weight and gestational age are additional risk factors for strabismus.

CONCLUSION

This study identifies additional factors aside from hydrocephalus that are associated with strabismus in children with SBM. Some of these factors (lower birth weight and younger gestational age) are also associated with strabismus in the general population, whereas the association of strabismus and spinal lesion level is likely unique to SBM and may be related to the more severe brain dysmorphology associated with upper level spinal lesions in these children.

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APPENDIX. Summary of Examination Procedures

1	Observation of head position (eg: normal, face turn, head tilt, etc.)
2	Gross observation of globe and ocular adnexae
3	Binocular vision assessment with Worth 4-dot & Titmus tests
4	Visual fixation pattern
5	Fixation preference with the 10 prism diopters BU test
6	Visual acuity – most advanced test possible (Teller, Cardiff, HOTV, or Linear)
7	Confrontation fields
8	Color vision
9	Ocular alignment at distance and near (Hirschberg or cover test)
10	Extraocular motilities to determine muscle underaction/overaction
11	Ocular muscle paresis
12	Ductions
13	Evaluation of pursuits (smoothness, accuracy)
14	Evaluation of saccades (smoothness, accuracy)
15	Near point of convergence
16	Optokinetic response
17	Vestibulo-ocular reflex
18	Observation for nystagmus in primary and eccentric gaze
19	External measurements (inner canthal distance, outer canthal distance, interpupillary distance)
20	Lacrimal system assessment (gross observation)
21	Corneal sensitivity
22	Slit-lamp biomicroscopy
23	Intraocular pressure (tactile or tonometry)
24	Pupils
25	Cycloplegic retinoscopy
26	Dilated fundus examination

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TABLE 1

Total Responses to Parental Survey Questions

Survey Question and No. of Respondents	Mean	Minimum	Maximum
Maternal age at birth, y (n = 105)	28 ± 5	15	43
Gestational age, wk (n = 103)	39 ± 2.7	27	44
Birth weight, g (n = 102)	3,322 ± 634	930	4,536
Respiratory distress at birth (n = 105)	19% = yes	–	–
No. of shunt revisions (n = 98/99 with shunts)	1.76 ± 1.97	0	9

TABLE 2

Associations Between Strabismus and Other Factors

Category	Strabismus	No.[a]	Without Strabismus	No.[a]	Test	*P*
Mean birth weight (g)	3,154 ± 778	39	3,409 ± 511	58	LR	.05[b]
Mean gestational age (wk)	38 ± 3	40	39 ± 2	58	LR	.01[b]
Mean maternal age (y)	28.6 ± 5	41	27.7 ± 5	59	LR	.39
% with respiratory distress at birth	22.5%	40	18%	60	FET	.62
% with shunt revisions for hydrocephalus	84%	38	64%	58	FET	.038[b]

LR = logistic regression; FET = Fisher's exact test.

[a] Indicates the number of participants who were included in the analysis for each comparison.

[b] Significant associations.

TABLE 3

Relation Between Strabismus[a] and Nystagmus[b] and Spinal Lesion Level

Category	Thoracic Lesion (n = 25)	Lumbar Lesion (n = 70)	Sacral Lesion (n = 7)
Participants with strabismus	14	27	1
Participants without strabismus	11	43	6
Total percentage with strabismus	56%	39%	14%
Participants with nystagmus	11	17	1
Participants without nystagmus	14	53	6
Total percentage with nystagmus	44%	24%	14%

[a]There was a significantly increased likelihood of strabismus for participants with spinal lesions closer to the brain (Wald chi-square, 1,100 = 4.29, $P = .038$).

[b]There was a significantly increased likelihood of nystagmus for participants with spinal lesions closer to the brain (Wald chi-square, 1,100 = 3.94, $P = .047$).