

Risk factors of sudden death in young adult patients with myelomeningocele

Clinical article

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Object. Although survival for patients with myelomeningocele has dramatically improved in recent decades, the occasional occurrence of sudden, unexplained death in young adult patients with myelomeningocele has been noted by the authors. This study was undertaken to determine risk factors for sudden death in this population.

Methods. The authors performed a retrospective chart review of patients born between 1978 and 1990 who received care at Children's Hospital Boston. The relationship between sudden death and patient demographics, presence of CSF shunt and history of shunt revisions, midbrain length as a marker for severity of hindbrain malformation, seizures, pulmonary and ventilatory dysfunction, body mass index, scoliosis, renal dysfunction, and cardiac disease was evaluated using the t-test, Fisher exact test, and logistic regression analysis.

Results. The age range for 106 patients in the study cohort was 19–30 years, with 58 (54.7%) women and 48 (45.3%) men. Six patients, all of whom were young women, experienced sudden death. In multivariate analysis, female sex, sleep apnea, and midbrain elongation ≥ 15 mm on MR imaging remained significantly associated with a higher risk of sudden death. These risk factors were cumulative, and female patients with sleep apnea and midbrain length ≥ 15 mm had the greatest risk (adjusted risk ratio 24.0, 95% CI 7.3–79.0; $p < 0.05$). No other comorbidities were found to significantly increase the risk of sudden death.

Conclusions. Young adult women with myelomeningocele are at significantly increased risk of sudden death in the setting of midbrain elongation and sleep apnea. Further investigation is needed to determine the benefit of routine screening to identify at-risk patients for closer cardiopulmonary monitoring and treatment.
(<http://thejns.org/doi/abs/10.3171/2011.11.PEDS11269>)

KEY WORDS • risk factor • sudden death • myelomeningocele •
spina bifida • Chiari malformation • sleep apnea • spine

ALTHOUGH there has been a steady decline in the prevalence and severity of myelomeningocele over the past 25 years, it remains the most common CNS birth defect in the US and causes significant disability.⁶ This decline in prevalence is related to maternal folic acid supplementation, as well as advances in prenatal diagnosis that have created the option for termination of the pregnancy.^{9,24} There has been a concomitant increase in the survival of these children into adulthood related to advances in medical treatment and

decreased complications, as well as improved functional outcomes.^{3,4,12,14,16,18,26} The likelihood of survival into adulthood increased from 60% in 1960 to 90% in 1985.¹⁷

Nevertheless, we have been disturbed to note the occasional occurrence of sudden, unexplained death in our young adult patients with myelomeningocele. We undertook this study to investigate what factors might contribute to this phenomenon, in the hope of identifying adolescent and young adult patients at risk for sudden death and reducing its incidence. Herein we describe a specific patient profile that appears related to significantly increased risk of sudden death in this population, and we suggest strategies to prevent its occurrence.

Abbreviations used in this paper: BMI = body mass index; CM = Chiari malformation; RR = relative risk.

Methods

Study Cohort

After obtaining appropriate institutional approval from Children's Hospital Boston, we reviewed the records of young adult patients born between 1978 and 1990 with a primary diagnosis of myelomeningocele who received care at our institution. Patients were identified in the neurosurgery myelomeningocele clinic database, and their prospectively collected data from clinic visits and hospital admissions were reviewed. Surviving patients without a recent clinic visit (within the past 2 years) were excluded. In 106 patients identified as meeting the criteria for the study, we examined a number of clinical variables that might be related to death, including patient demographics, presence of shunts and history of shunt revisions, anatomical level of the myelomeningocele, presence and severity of the hindbrain malformation, indicators of pulmonary and ventilatory dysfunction, BMI, presence and degree of scoliosis, indicators of renal dysfunction, and any history of cardiac disease or seizures (Fig. 1).

Outcome Measure

The single outcome measure was sudden death, defined as unanticipated death with no associated acute illness or defined cause. All patients included in the sudden death group had been found unresponsive in bed with no history of antecedent illness. Patients with a known cause of death and those who died under the circumstances of a recent surgery or a suspected shunt malfunction were excluded from the sudden death group and were included in the group of all other patients.

Severity of Hindbrain Malformation

The CM Type II was considered a potential risk factor for sudden death arising from brainstem dysfunction and respiratory arrest. We sought an objective, imaging-based measure of severity that might correlate with possible

brainstem dysfunction. Brainstem length was chosen as a reflection of hindbrain elongation and distortion. Although level of descent of the cerebellar vermis or fourth ventricle has been previously used as a clinical indicator of the severity of the CM, we believed a more direct assessment of the degree of intrinsic brainstem distortion was important. After considering a number of options, the parameter chosen for this study was the length of the midbrain as measured from the mammillary bodies to the pontomesencephalic junction (Fig. 2). This distance provided discrete anatomical boundaries and allowed reproducible measurements. We postulated that this simple measurement might be a reflection of the degree of overall brainstem distortion. The distance from the mammillary body to the pontomesencephalic junction was measured on brain MR images using the Synapse radiographic imaging software (Fujifilm USA) by 3 authors (S.C.J., R.M.S., and B.C.W.) who were blinded to patient identity, sex, age, and clinical outcome. For each patient, the mean of the 3 independent measurements was taken as the midbrain length. We determined that the interrater reliability for this measurement was very high (0.95).

Other Clinical Variables

Sex and age of the patients were determined from the medical record. A number of clinical characteristics and comorbidities that might increase mortality risk were investigated: the presence of a ventriculoperitoneal shunt and the number of prior shunt revisions documented since January 1, 2001; presence of a thoracic-level myelomeningocele lesion; indicators of pulmonary or ventilatory comorbidity (diagnosis of sleep apnea, use of nighttime continued positive airway pressure, diagnosis of restrictive lung disease, presence of tracheostomy, home ventilator use); indicators of cardiac comorbidity (hypertension, arrhythmias, congenital cardiac disease); BMI; diagnosis of seizures; indicators of renal dysfunction or disease (baseline creatinine ≥ 1.4 mg/dl or charted diagnosis of

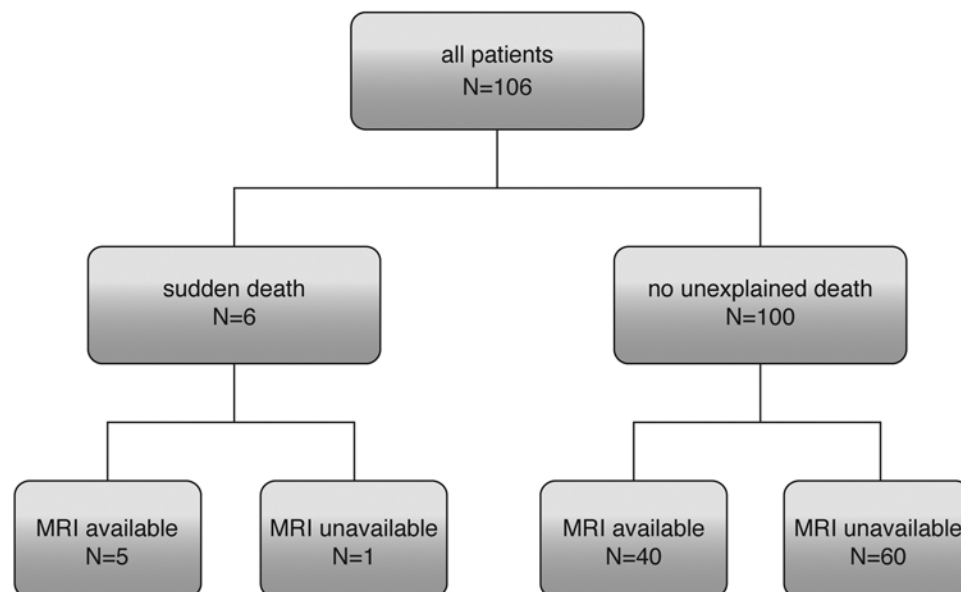


Fig. 1. Flowchart diagramming patient selection.

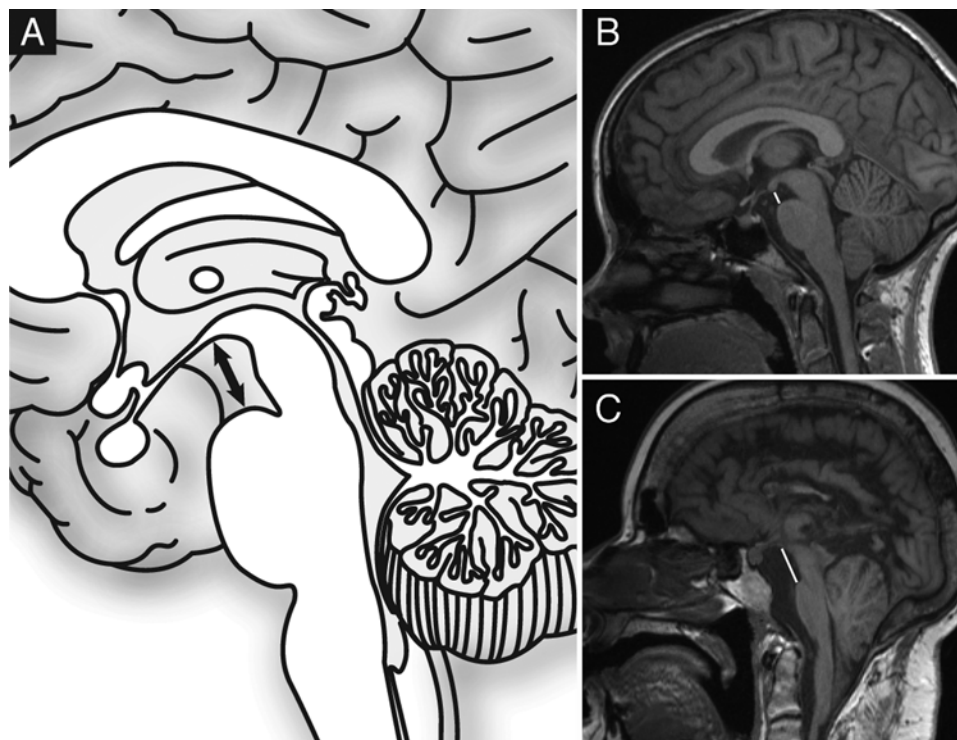


Fig. 2. Images depicting measurement of the midbrain length. **A:** Illustration of the measurement of midbrain length (arrows). **B:** Sagittal T1-weighted MR image of a surviving patient with myelomeningocele with a midbrain length of 6.6 mm (white bar). **C:** Sagittal T1-weighted MR image of a patient with myelomeningocele who suffered a sudden death, with a midbrain length of 21.0 mm (white bar).

chronic renal insufficiency, history of urological procedures; and presence and degree of severity of scoliosis.

Statistical Analysis

We used a 2-tailed t-test or Fisher exact test to examine the relationship between continuous and categorical patient attributes, respectively, with the prevalence of sudden death. Attributes found to be significant ($p \leq 0.05$) in bivariate analysis were entered into a logistic regression model. Bonferroni adjustment was performed for all multivariate analyses. All probability values reported in the results are the adjusted values, with statistical significance set at $p < 0.05$. The statistical software SPSS and GraphPad Prism software were used for all analyses.

Results

We identified 106 (67.9%) of the 156 patients undergoing myelomeningocele closures at Children's Hospital Boston during the study period who were older than 18 years of age at the time of the study (age range 19–30 years) and met the follow-up criteria. Fifty (32.1%) of the 156 patients were lost to follow-up. Of the study cohort, 58 patients (54.7%) were women and 48 (45.3%) were men, which is a female-to-male ratio of 1.2. Of the 106 patients, 45 (42.5%) had brain MR images available for review (Fig. 1). Eleven patients (10.4%) had died. Of these 11 patients, 6 had sudden unexplained death at a mean age of 24.1 ± 3.7 years. The causes of death in the remaining 5 patients were acute respiratory distress syndrome (2 patients), acute shunt malfunction (2 patients), and house

fire (1 patient). Mean age of death in this group was 24.2 ± 2.0 years ($p = 0.9$). The mean age of the surviving patients was 23.5 ± 3.3 years ($p = 0.6$). The mean age of all patients in the study was 23.6 ± 2.9 years, and the mean age of all patients not affected by sudden death was 23.5 ± 1.6 years ($p = 0.7$; Table 1).

Sex

All 6 patients who suffered a sudden death were female, in comparison with 54.7% of the entire study group and 52% of patients not affected by sudden death (RR 1.9, 95% CI 1.6–2.3; $p = 0.03$; Table 1).

Lesion Level

Among the sudden death group, 33% had a thoracic-level myelomeningocele, compared with 13% of the remainder and 14.1% of the entire group. However, this difference was not statistically significant (RR 0.8, 95% CI 0.4–1.4; $p = 0.2$; Table 1).

Shunt Dependence

The prevalence of a ventriculoperitoneal shunt did not vary between the group of patients experiencing sudden death and the group that did not (100% vs 91.0%, respectively; RR 1.10, 95% CI 1.03–1.17; $p = 1.0$; Table 1). Also, the average number of shunt revisions for malfunction did not vary significantly between groups, with sudden death patients undergoing a mean of 1.5 revisions in the previous 10 years, and all other patients undergoing a mean of 1.3 revisions in the same time period ($p = 0.9$).

TABLE 1: Demographics and comorbid conditions of the study cohort (106 patients)

Characteristic	All Patients	Sudden Death		p Value
		Yes	No	
female	54.7%	100%	52%	0.03*
mean age (yrs) \pm SD	23.6 \pm 2.9	24.1 \pm 3.7	23.5 \pm 1.6	0.7
thoracic myelodysplasia	14.1%	33%	13%	0.2
thoracolumbar, lumbar, or lumbosacral myelodysplasia	85.8%	66%	87%	0.2
ventriculoperitoneal shunt	91.5%	100%	91%	1.0
sleep apnea	16.3%	66.7%	12.2%	0.005*
positive airway pressure use	15.1%	66.7%	7%	0.0009*
tracheostomy	3.8%	16.7%	3%	0.2
cardiac comorbidity	11.3%	0%	12%	0.6
epilepsy	17.9%	33%	17%	0.6

* Statistically significant.

Sleep Apnea and Other Indicators of Pulmonary or Ventilatory Dysfunction

A diagnosis of sleep apnea was present in 16.3% of patients and was more prevalent in patients with sudden death (66.7% vs 12.2%, respectively; RR 5.4, 95% CI 2.5–11.8; $p = 0.005$; Table 1). There was no sex difference in the diagnosis of sleep apnea, with the diagnosis present in 19.0% of female and 13.0% of male patients (RR 1.5, 95% CI 0.6–3.6; $p = 0.4$). Likewise, continued positive airway pressure use was more prevalent among patients with sudden death (66.7% vs 7%) and was associated with an increased risk of sudden death (RR 9.5, 95% CI 3.8–23.7; $p = 0.0009$). However, none of the patients with a clinical diagnosis of sleep apnea had the results of a formal sleep study in their medical records. Thus, it was not possible to distinguish between obstructive and central sleep apnea in this retrospective study. Among patients with a clinical diagnosis of sleep apnea, 1 of 4 sudden death patients and 3 of 12 other patients had formal pulmonary function tests, all of which demonstrated restrictive lung disease with no element of obstructive disease. Eight remaining survivors without sleep apnea had undergone pulmonary function tests, 5 of which demonstrated restrictive disease, and 3 of which showed normal lung function. There was no significant difference between groups in the prevalence of tracheostomy use ($p = 0.2$; Table 1).

Body Mass Index

The mean BMI of patients experiencing sudden death was 28.2 ± 6.8 while for all other patients it was 27.6 ± 6.9 . This was not a significant difference ($p = 0.8$).

Renal Dysfunction

Comparing the sudden death group with the other patients, the prevalence of chronic renal insufficiency (16.7%

vs 8.2%, respectively; $p = 1.0$), history of Mitrofanoff continent catheterizable stoma (16.7% vs 19.6%, respectively; $p = 1.0$), and history of bladder augmentation (16.7% vs 18.6%, respectively; $p = 1.0$) did not differ between patients in these 2 populations.

Epilepsy

A diagnosis of epilepsy was recorded in 17.9% of all patients, 33% of the sudden death group, and 17% in the remainder; this difference was not significant (RR 0.8, 95% CI 0.5–1.4; $p = 0.6$; Table 1).

Cardiac Dysfunction

None of the patients with sudden death were identified as having any baseline cardiac diagnosis or dysfunction.

Scoliosis

There was not a significant difference in the prevalence of scoliosis requiring posterior spinal fusion between the groups (16.7% in the sudden death group vs 12.2% in the remainder; RR 1.5, 95% CI 0.2–9.9; $p = 0.5$). We found no significant difference in the degree of average scoliosis or kyphosis between the patients who experienced sudden death and those who died of acute respiratory distress syndrome, with an average scoliotic curve of 83° (normal $< 15^\circ$) and thoracic kyphosis of 8.3° (normal $20^\circ - 40^\circ$), and a slightly higher than normal average diaphragm level at rib 7 (normal at rib 9).

Midbrain Elongation

Magnetic resonance imaging studies were available in 5 of 6 sudden death patients and in 40 of 100 patients who did not experience sudden death. For the entire study group, mean midbrain length from the mammillary bodies to the pontomesencephalic junction was 14.9 mm in males and 13.9 mm in females, but this was not statistically significant ($p = 0.4$). The patients who experienced sudden death, all female, had a mean midbrain length of 16.4 mm compared with 13.7 mm for unaffected females ($p < 0.05$) and 14.9 mm for unaffected males ($p < 0.05$; Fig. 3).

The midbrain length of those with and without sudden death was compared by subgroups of patients with or without different comorbidities (Table 2). Midbrain length was significantly greater for those experiencing sudden death among patients with any pulmonary comorbidity.

Multivariate Analysis

In multivariate analysis, female sex, sleep apnea, and increased midbrain length on MR imaging remained significantly associated with a higher risk of sudden death in adult patients with myelomeningocele. The RR of sudden death in sleep apnea patients was 4.6 (95% CI 2.9–7.3; $p < 0.05$). The RR of sudden death in patients with a midbrain length ≥ 15 mm was 1.7 (95% CI 1.2–2.3; $p < 0.05$). The risk of sudden death increased with the number of risk factors present. Patients with both sleep apnea and midbrain length ≥ 15 mm had an RR of sudden death of 8.0 (95% CI 3.8–17.0; $p < 0.05$). The RR of sudden death

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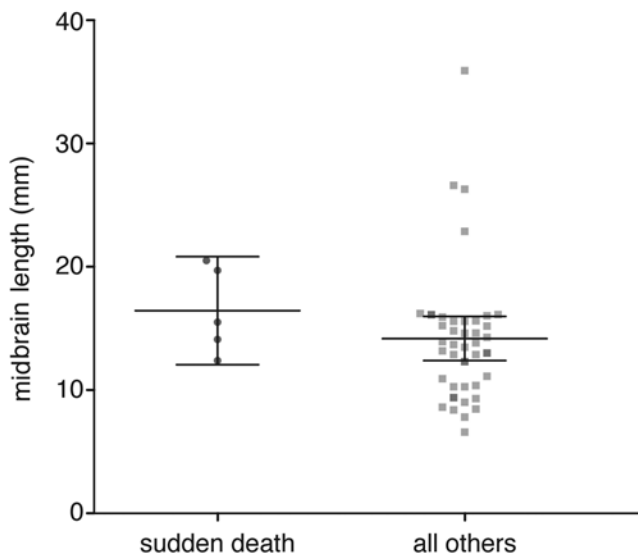


FIG. 3. Scatter plot graph demonstrating the midbrain lengths for both the sudden death patients and all other patients. Bars represent the group mean with 95% CIs.

for female patients with this combination was 24.0 (95% CI 7.3–79.0; $p < 0.05$).

Discussion

In this study, we observed important risk factors for sudden death among a small cohort of young adult patients with myelomeningocele. Female sex, sleep apnea, and midbrain elongation were independently associated with an increased risk of unexplained, sudden death. Patients possessing all 3 of these factors had the greatest risk for sudden death, which was 24 times that of male patients without sleep apnea or midbrain elongation.

We were unable to determine the reasons why female patients were at higher risk for sudden death. Sex-related survival differences among patients with congenital health conditions are unusual. Higher mortality in women undergoing congenital heart disease surgery has been reported, which was not explained by a higher prevalence of comorbid conditions or hormonal differences, and increased morbidity is also observed in critically ill women undergoing tracheostomy.^{2,5,7,20} We observed no statistically significant sex differences in midbrain length or comorbid conditions. However, sleep apnea tended to be more commonly diagnosed in our female patients (19% vs 13%). This finding contrasts with the sleep apnea sex prevalence in the general population, where it is diagnosed up to 5 times more often in men.^{15,28}

Autopsy had not been performed in any of the sudden death patients, so the actual cause of death was not confirmed. It is possible that the unexplained sudden death experienced by our patients was the result of acute-onset apnea and cardiorespiratory failure during sleep. Several observations support this. Although chronic tonsillar herniation and hydrocephalus have been associated with sudden death in adult patients with myelomeningocele,^{8,13,22,27} we observed no relationship between shunted hydro-

TABLE 2: Comparison of midbrain lengths by selected comorbidities*

Characteristic	All Patients	Sudden Death		p Value
		Yes	No	
sex				
female	13.9	16.4	13.7	0.003
male	14.9	NA	14.9	0.2
ventriculoperitoneal shunt				
present		16.4	14.6	0.03†
absent		NA	7.5	NA
sleep apnea				
present		17.1	12.9	0.01†
absent		14.1	14.5	0.07
positive airway pressure use				
present		16.3	13.6	0.04†
absent		16.9	14.2	0.007†
tracheostomy				
present		15.5	15.3	0.1
absent		16.7	14.1	0.03†
any pulmonary comorbidity				
present		17.0	12.8	0.05†
absent		14.1	14.6	0.7
cardiac comorbidity				
present		NA	15.4	NA
absent		16.4	14.0	0.006†
epilepsy				
present		17.3	15.3	0.3
absent		15.9	13.8	0.05†

* Midbrain lengths given in millimeters. Abbreviation: NA = not applicable.

† Statistically significant.

cephalus and sudden death. Likewise, seizures, cardiac arrhythmia or other dysfunction, scoliosis, and renal and urological dysfunction were not associated with sudden death. In contrast, we did observe a higher prevalence of chronic sleep apnea in patients experiencing sudden death. These patients might have experienced noncompliance or dysfunction with their noninvasive ventilation support, but this was not known.

Chiari malformation Type II in patients with myelomeningocele is characterized by downward displacement of the medulla, fourth ventricle, and cerebellum into the cervical spinal canal, as well as midbrain and pons elongation. These may be related to the relatively small posterior fossa resulting from loss of CSF through the neural tube defect with consequent deflation of the cerebral vesicles during fetal brain development.¹⁹ In addition, patients with myelomeningocele have been found to possess significant brainstem anomalies beyond those generally included in the CM Type II continuum, including a decrease in the number of neurons of the pontine cranial nerve nuclei, olivary nuclei, and tegmentum, as well as in the hypoglossal and dorsal vagal nuclei.¹⁰

Midbrain elongation was a consistent attribute among

patients experiencing unexpected sudden death, and this may have reflected a clinically meaningful degree of midbrain dysfunction that predisposed these patients to sudden death. Alternatively, it may be a marker for the degree of overall brainstem distortion and dysfunction. We postulate that midbrain elongation might reflect an impaired ability of the mesencephalic reticular activating system to regulate arousal and modulate respiratory and cardiovascular rhythms. The reticular activating system cardiovascular and respiratory centers overlap, and immaturity of these centers is believed to be involved in sudden infant death syndrome.²¹ Midbrain serotonergic neurons are also central chemoreceptors that, when fully developed and functional, are very sensitive to small changes in carbon dioxide and pH.²³ Some patients with myelomeningocele have a slower hyperventilation response to hypercarbia, suggesting intrinsic dysregulation of reticular activating system-mediated ventilatory control.²⁵ Our finding that the relative severity of CM Type II is a risk factor for sudden death may lend support to in utero myelomeningocele repair, given reports that this approach mitigates development of the CM.^{1,11}

This study has several limitations. It is a retrospective study with a small sample size and is limited to 1 clinical site of care. Formal sleep studies were not available, and no distinction could be made between obstructive and central apnea. Although 5 of 6 sudden death patients had MR images available for review, these were only available in 40% of the other group. No autopsies were performed, and we were unable to obtain additional information surrounding the circumstances of death for our patients, including the use of alcohol or drugs that could have had an acute influence on the patients' respiratory drive and control. However, all the patients in the study had undergone recent clinical follow-up and consistent care. All of those experiencing sudden death either lived with family support or in a group home environment. Thus, these did not appear to be situations in which medical neglect had been a factor.

Conclusions

Our findings suggest that young adult women with myelomeningocele are at significantly greater risk (RR 24) of sudden death in the context of sleep apnea and midbrain elongation relative to other adult patients with myelomeningocele. Further investigation is needed to determine the benefit of routine sleep apnea testing and midbrain length measurement with brain imaging by the time of adolescence to identify those who are at the highest risk for sudden death. Certainly, routine screening for sleep apnea symptoms by medical history is warranted. For patients diagnosed with sleep apnea, we recommend consistent management with maximized treatment compliance. For those with the clinical profile described in this study (women with sleep apnea and a midbrain length ≥ 15 mm), routine cardiac, apnea, and oxygen saturation monitoring during sleep along with appropriate counseling of the patient and family members may prompt effective intervention to arouse the patient or initiate cardiopulmonary resuscitation in time to avoid prolonged apnea and sudden death.

Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Warf, Jernigan, Scott. Acquisition of data: Warf, Jernigan, Karlin, Hobbs, Scott. Analysis and interpretation of data: Warf, Jernigan, Berry, Bauer, Karlin. Drafting the article: Warf, Jernigan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Warf. Statistical analysis: Jernigan, Graham. Administrative/technical/material support: Warf. Study supervision: Warf.

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Manuscript submitted July 1, 2011.

Accepted November 11, 2011.

Please include this information when citing this paper: DOI: 10.3171/2011.11.PEDS11269.

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