Risk factors for recurrent respiratory tract infections or acute respiratory failure in children with spinal muscular atrophy

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Abstract

Introduction: Assessment of and intervention for sleep-disordered breathing and malnutrition are related to respiratory management for preventing recurrent respiratory tract infections (RRTIs) and acute respiratory failure (ARF) in children with spinal muscular atrophy (SMA). However, the specific standard has not been clarified. **Purpose:** The study aimed to obtain the risk factors and the predictive index for RRTIs and/or ARF in children with SMA. **Methods:** In this retrospective study, the differences in clinical characteristics in patients with or without RRTIs and ARF were compared, and binary logistic regression analysis was carried out. The best cutoff points of the positive predictive index were obtained. **Results:** Type 1 (OR = 4.12, 95% CI 1.30-13.07, P =.016) and apnea hypopnea index (AHI) (OR = 1.14, 95% CI 1.05-1.24, P =.001) were risk factors, while body mass index z score (BMIz) (OR = 0.68, 95% CI 0.49-0.94, P =.018) and mean pulse oxygen saturation ($MSpO_2$) (OR = 0.67, 95% CI 0.50-0.91, P =.010) were protective factors. The sensitivity and specificity of the standard of $MSpO_2 < 96\%$ and AHI > 10 events/h or BMIz < -1 with the occurrence of RRTIs and/or ARF were 0.513 and 0.957, respectively. **Conclusion:** SMA Type 1, BMIz, AHI and $MSpO_2$ should be used to estimate the risk for RRTI or ARF in children with SMA. $MSpO_2 < 96\%$, and AHI > 10 events/h or BMIz < -1 should be used as the intervention standard.

Title

Risk factors for recurrent respiratory tract infections or acute respiratory failure in children with spinal muscular atrophy

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Keywords

Spinal muscular atrophy in children; Respiratory tract infection; Acute respiratory failure; Polysomnography; Risk factors.

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Conclusion: SMA Type 1, BMIz, AHI and $MSpO_2$should be used to estimate the risk for RRTI or ARF in children with SMA. $MSpO_2$< 96%, and AHI > 10 events/h or BMIz < -1 should be used as the intervention standard.

1 INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by deletion or mutation of the survival motor neuron 1 (SMN1) gene with progressive muscle atrophy, weakness and paralysis. The incidence rate of live births is approximately 1/11000. SMA in children is classified into types 1-3 depending on the age of onset and maximal motor milestone achieved.[1] SMA is the primary genetic disease leading to the death of children under two years old, and respiratory failure is the most common cause of death.[2] Nocturnal hypopnea is the first respiratory problem in SMA, subsequently developing into daytime hypopnea. Early pulmonary function can still be compensated. However, patients are very prone to acute respiratory failure (ARF) once pulmonary infection occurs. The more severe the case, the more likely children are to have various respiratory complications, including sleep-disordered breathing, recurrent pneumonia and ARF.[2,3] Appropriate and effective strategies of respiratory management are crucial to stabilize lung function and reduce the incidence of respiratory complications and mortality in children with SMA. The literature and expert opinion support using a sleep study to confirm when a patient has sleep-disordered breathing and needs to use noninvasive ventilation to prevent recurrent respiratory tract infections (RRTIs) and ARF. In addition, nutritional assessment and intervention are also related to respiratory management.[2,4] However, there is still no specific standard to evaluate and intervene in these respiratory problems. Therefore, the aim of the present study was to obtain the risk factors for RRTI and/or ARF and the specific values in children with SMA. This is the largest study of polysomnography (PSG) in children with SMA reported thus far.

2 MATERIALS AND METHODS

2.1 Setting and patients

The clinical data of SMA children in the division of respiratory and sleep disorders of the Children's Hospital Affiliated with the Capital Institute of Pediatrics in Beijing, China, from March 2016 to December 2021 were analyzed retrospectively. RRTIs and ARF were considered severe conditions requiring intervention, and clinical characteristics were analyzed to determine the risk factors for RRTIs and/or ARF in children with SMA who had not started treatment with disease-modifying medications or mechanical ventilation. This study was reviewed and approved by the ethics committee of the Capital Institute of Pediatrics (Identifier, SHERLL2019014). The study was exempt from informed consent.

2.2 Diagnostic criteria

SMA was diagnosed by a defect in the SMN1 gene localized to 5q11.2-q13.3 and classified into clinical groups on the basis of age of onset and maximum motor function achieved: very weak infants unable to sit unsupported (type 1), non-ambulatory patients able to sit independently (type 2), and ambulant pediatric patients (type 3).[1]

RRTIs were diagnosed by the following criteria: for children under two, upper respiratory infection [?] 7 episodes/year, bronchitis [?] 3 episodes/year, or pneumonia [?] 2 episodes/year; two to five years old, upper respiratory infection [?] 6 episodes/year, bronchitis [?] 2 episodes/year, or pneumonia [?] 2 episodes/year; over five years old, upper respiratory infection [?] 5 episodes/year, bronchitis [?] 2 episodes/year, or pneumonia [?] 2 episodes/year. The number of lower respiratory infections could replace the number of upper respiratory infections, but not vice versa. The interval between onsets of respiratory infection was at least seven days.[5]

The diagnostic criterion of ARF caused by infectious pneumonia was severe dysfunction of ventilation with arterial partial pressure of oxygen < 8.0 kPa (60 mmHg) while breathing room air, with/without arterial partial pressure of carbon dioxide (PCO_2) > 6.7 kPa (50 mmHg).[6]

2.3 Inclusion and exclusion criteria

At enrollment, children were under eighteen years old and genetically confirmed to have homozygous SMN1 gene alterations; all completed PSG without signs of respiratory tract infection. Exclusion criteria included the initiation of treatment with disease-modifying medications or mechanical ventilation, alone or combined with the presence of other congenital diseases or other neuromuscular disorders. All children were divided into a disease group and a control group according to whether RRTIs and/or ARF occurred within one year.

2.4 Data collection

The electronic and handwritten medical records created by doctors in the division of respiratory and sleep disorders were reviewed to collect the clinical data, including sex, age, height, weight, type of SMA, genetic results, regular use of mechanical insufflation-exsufflation (MI-E), number of occurrences of respiratory tract infection and ARF in one year, past history and medication history. Spirometry was performed in children over five years old who could complete the flow-volume loop test using MasterScreen (Jaeger, Germany) equipment. The percent predicted scores of spirometry were reported. PSG was attended by trained pediatric sleep nurse using Alice 6 LDx (Philips, USA) equipment and was scored using the American Academy of Sleep Medicine Version 2.3 pediatric criteria[7] (see further details in E-appendice 1). The age-specific body mass index z score (BMIz) was obtained according to the WHO child growth standard and the 2000 American CDC growth curve standard.[8,9]

2.5 Statistical analysis

Continuous data conforming to a normal distribution are represented by ($x \pm s$), and the differences between two groups were evaluated by the t test. Data not conforming to a normal distribution are represented by M (Q1, Q3), and the differences between two groups were evaluated by the Mann–Whitney U test. Categorical variables are expressed as cases (%), and comparisons between groups were performed with the chi-square test and Fisher's exact test. The differences in clinical indices between the two groups were compared, and the variables with statistically significant differences were included in the binary multivariate logistic regression. The results showed the risk of each covariate in the model and 95% confidence interval to obtain the independent risk factors for RRTIs and/or ARF in children with SMA. Receiver operating characteristic (ROC) curves were constructed to determine the best cutoff point for positive indicators that could best predict the occurrence of RRTIs and/or ARF. The statistical significance of all verifications was based on a bilateral P value < 0.05. SPSS 25.0 software was used for statistical processing, and GraphPad Prism 9.3.1 was used to draw ROC curves.

The clinical data were screened before logistic regression on the basis of the clinical characteristics. The parameters of the spirometry were not included because the test was not performed in children under five. Because sleep stages vary greatly among children of different ages, for instance, the sleep structure of infants is

very different from that of older children, such indicators with age differences were not considered. In addition, in order to minimize the possible effects of multicollinearity, the representative apnea hypopnea index (AHI) was chosen because there is overlap among the parameters of respiratory events in PSG; moreover, the AHI is the sum of apneas and hypopneas occurring per hour. In addition, the mean pulse oxygen saturation ($MSpO_2$) with small individual differences was selected because the standard deviation of $MSpO_2$ was less than the lowest pulse oxygen saturation ($LSpO_2$).

3 RESULTS

3.1 Clinical characteristics

During the study period, 115 patients were screened, and 109 patients were enrolled, excluding 4 patients who had been using noninvasive ventilators and 2 patients treated with nusinersen. The age of the 109 patients were 4.2 (2.1, 7.6) years, ranged (0.2-15.8) years. Fifty-two patients were males. Twenty-three cases were type 1, 74 cases were type 2, and 12 cases were type 3. Thirty-four cases (31.2%) had RRTIs, 20 cases (18.3%) had ARF within one year, and 31 cases (28.4%) used MI-E regularly. The general characteristics, survival motor neuron 2 (SMN2) copies, MI-E usage, main parameters of PSG and lung function of different types of SMA are shown in Table 1.

3.2 Differences in sex, age, type, BMI and MI-E between the two groups

According to the group criteria, 109 patients were divided into the disease group with 39 cases and the control group with 70 cases. The proportion of type 1 was higher and the BMIz was lower in the disease group than in the control group ($P < 0.05$). There was no significant difference in sex, age or MI-E usage between the two groups. (Table 2)

3.3 Differences in lung function between the two groups

Spirometry was performed in 21 of the 39 patients in the disease group and 57 of the 70 patients in the control group. The percent predicted scores representing restrictive ventilation dysfunction, including forced vital capacity (FVC), inspiratory vital capacity (VC IN), expiratory vital capacity (VC EX), forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), maximum expiratory flow at 75% vital capacity (MEF_{75}), maximum expiratory flow at 50% vital capacity (MEF_{50}) and maximum midexpiratory flow at 25% to 75% vital capacity ($MMEF_{75/25}$) in the disease group were all lower than those in the control group ($P < 0.05$). There was no significant difference in the FEV1 to FVC ratio % predicted to represent obstructive ventilation dysfunction between the two groups (Table 2).

3.4 Differences in PSG between the two groups

End-tidal carbon dioxide ($EtCO_2$) was measured in 9 patients in the disease group and 18 patients in the control group while PSG was performed. Nonrapid eye movement stage 2 (N2) was higher and N3 was lower in the disease group. In addition, the respiratory arousal index, AHI, [?] 3% oxygen desaturation events and index were higher, and the average oxygen desaturation, $MSpO_2$ and $LSpO_2$ were lower ($P < 0.05$). Hypopnea was the main respiratory event in children with SMA. The events, index, mean time and longest time of hypopnea in the disease group were all higher than those in the control group ($P < 0.05$). There was no significant difference in apnea events between the two groups (Table 3).

3.5 Logistic regression analysis of risk factors for RRTIs and/or ARF in children with SMA

Type 1, BMI, AHI and $MSpO_2$ with statistically significant differences between the two groups were entered as covariates into binary logistic regression, and all had statistical significance ($P < 0.05$), as shown in Table 4. The risk for the occurrence of RRTIs and/or ARF in SMA type 1 was approximately four times higher than that in types 2 and 3. Meanwhile, the risks were approximately 1.5, 1.1 and 1.5 times higher for every 1 decrease in BMIz, 1 events/h increase in AHI and 1% decrease in $MSpO_2$, respectively.

3.6 ROC curve analysis of BMIz, AHI and $MSpO_2$

ROC curves were drawn to analyze the prediction efficiency of BMI, AHI and $MSpO_2$ for RRTIs and/or ARF. The best cutoff points of these three continuous variables were obtained by taking the maximum Jordan index, and the sensitivity and specificity are shown in Figure 1 and Table 5. The diagnostic value of $MSpO_2$ was the best, with the highest area under the receiver operating characteristic curve (AUC). The sensitivity, specificity and accuracy of $MSpO_2 < 95.5\%$ with the occurrence of RRTIs and/or ARF were 0.539, 0.886, and 0.761, respectively. To improve the specificity and accuracy, the indicators were used in combination. With the standard of $MSpO_2 < 96\%$ and AHI > 10 events/h or BMI < -1, the specificity and accuracy were increased to 0.957 and 0.798, respectively, and the sensitivity was 0.513.

4 DISCUSSION

SMA of type 1 is more severe, and both the age at death and the number of people using ventilators are respectively earlier and more than those in other SMA types.[1,10] Most children with SMA type 1 over two years of age need tracheotomy or all-day noninvasive ventilation for survival.[11] Children with type 2 have a progressive decline in overall function and need noninvasive ventilation from five to thirteen years old.[12]Similarly, our study showed that the risk for RRTIs and/or ARF in type 1 is approximately four times higher than that in types 2 and 3. The average age of type 1 patients in our study was over two years, but none of them had received disease-modifying medications or long-term mechanical ventilation therapies. Among the 14 cases of type 1 with SMN2 copy number detected, five cases had 2 copies, and nine cases had 3 copies, which indicated the milder SMA types 1b and 1c.[1] This was because most of the patients who could come to Beijing for treatment from other areas of China would have had mild symptoms, and the type 1 population in China might carry more copies of SMN2.[13] Therefore, if all patients were considered, the risk of type 1 RRTIs and/or ARF should be higher.

Malnutrition is common in children with SMA. Our study showed that age-specific BMIz decreased in all three types and was lowest in type 1, which was consistent with other studies.[14]Malnutrition in SMA is always related to the severity of pulmonary complications. For example, children with dysphagia often have aspiration pneumonia and respiratory distress and rely on mechanical ventilation earlier.[15] The age at gastrostomy is related to the first appearance of ARF and initiation of continuous mechanical ventilation.[11] Similarly, our study showed that BMIz is an independent risk factor for RRTIs and/or ARF in children with SMA, and the risk increases by approximately one and a half times for every one unit decrease in BMIz. In terms of mechanism, masticatory muscle weakness, dysphagia and respiratory problems will reduce the intake of calories, while the work of breathing will increase energy consumption. As a result, the more severe the children are, the higher their risk of malnutrition.[1] Therefore, it is crucial to pay attention to the BMIz level to prevent the occurrence of RRTIs and/or ARF. The appropriate intervention includes adequate nutritional supplementation, treatment with disease-modifying medications and treatment with hypopnea.

PSG is the gold standard for the diagnosis of sleep-disordered breathing, which can be used to monitor the problem of nocturnal hypopnea in children with SMA. Although expert opinion supports using PSG for diagnosing and noninvasive ventilation to prevent recurrent RRTIs and ARF, there is still no specific standard.[2]The diagnostic criteria for obstructive sleep apnea are only suitable for patients with obstructive problems in the airway, not for patients with neuromuscular disorders mainly caused by hypopnea.[16] The Duchenne muscular dystrophy guidelines[17] have proposed the following indication for nocturnal noninvasive ventilation: PCO_2> 6.7 kPa (50 mmHg) or > 1.3 kPa (10 mmHg) of the awake baseline at least 2% of the total sleep time, oxygen saturation < 88% for at least five minutes, or AHI > 5 events/h. This standard may be used as a reference for SMA, but the data were not obtained from SMA patients themselves. The questionnaires could be used to assess sleep disorders in SMA.[18] but have limitations of subjectivity because nocturnal hypopnea can also be found in pediatric SMA patients without clinical symptoms.[19,20] Sleep-disordered breathing is associated with RRTIs in children with SMA, and long-term noninvasive ventilation can improve PSG scores and reduce the incidence of respiratory tract infection.[21] Our study used SMA children as samples and analyzed the association between PSG scores and the occurrence of RRTIs and ARF, which ensured the objectivity of the results and applicability to SMA disease. Our study showed that AHI > 10.2 events/h and $MSpO_2 < 95.5\%$ suggested a high risk for RRTIs and/or ARF in children with

SMA.

Lung function declines with age, and the severity is also related to the type of SMA.[22,23] Our study also showed that the FVC and PEF % predicted in type 2 were lower than those in type 3 and were lower in the disease group than in the control group. The raw scores of FVC and PEF in type 2 were approximately 60% of the predicted scores, which were approximately 90% in type 3, approximately 40% - 50% in the disease group, and approximately 60% - 70% in the control group. Spirometry can only be performed with the cooperation of children over five years old, so the lung function test could only be used for the evaluation of older children with types 2 and 3. However, for SMA patients, type 1 with younger age is more severe and requires closer observation and proactive intervention. Therefore, for children under five years old, especially those with type 1, it is more important to pay attention to BMIz and PSG scores.

Our study showed that age, MI-E usage and $EtCO_2$ were not associated with RRTIs and/or ARF. The reasons for these inconsistencies with conventional thinking may be as follows. First, the patient's condition should degenerate with age and progression of the disease. The factor of age should be based on the type and severity of individual cases. Therefore, there was no correlation in our study because the subjects included all three types of SMA. The cutoff points of age to assess the risk for RRTIs and/or ARF for each SMA type might be obtained if the sample size was sufficient. Second, MI-E usage had a positive effect on the intervention against respiratory problems in SMA patients with types 1 and 2.[2] However, our study did not show a correlation, indicating that the effect of MI-E usage should be shown only in patients who have a weak cough and need airway clearance techniques. Finally, the diagnostic criterion for sleep-related hypoventilation diseases is $PCO_2 > 6.7$ kPa (50 mmHg), which accounts for more than 25% of the total sleep time according to the international classification of sleep diseases.[24] However, our study showed that in 27 cases, only one child of type 2 with severe adenoidal hypertrophy complied with the criteria mentioned above. The OAI of this patient was 29.3 events/h, which was much higher than the HI representing hypopnea of 5.0 events/h. Our study also did not show a correlation between PCO_2 and hypoventilation in children with SMA. This might be because the tested value of $EtCO_2$ in patients with neuromuscular disorders was lower than the realistic value.[25] On the other hand, this might be consistent with the finding from another study that higher values of PCO_2 were not measured in type 1 than in types 2 and 3, and PCO_2 levels during sleep might not be used to accurately evaluate hypopnea in children with SMA.[3,26]

Over the last decade, the approach to treating the respiratory manifestations of SMA has shifted from a reactive approach only when there is a clear indication to a proactive approach of applying therapies earlier in the disease process.[2] The use of disease-modifying medications such as nusinersen may delay the decline in lung function, but the effect on long-term improvement is unknown.[27-29] Proactive respiratory management and nutrition support still play important roles in the improvement of living conditions in SMA.[30,31] Therefore, the assessment of BMIz and PSG should be performed. Furthermore, malnutrition and hypoventilation should be treated to prevent RRTIs and ARF. Our study showed that the accuracy, sensitivity and specificity of the standard of $MSpO_2 < 96\%$ and AHI > 10 events/h or BMIz < -1 with the occurrence of RRTIs and/or ARF in SMA were 0.798, 0.513 and 0.957, respectively. The high specificity meant that children with SMA who reached this standard would almost certainly develop RRTIs or ARF and should receive intervention.

5 CONCLUSION

Type of SMA, BMI, AHI and $MSpO_2$ are independent risk factors and should be used to estimate the risk for RRTI or ARF in children with SMA. $MSpO_2 < 96\%$, and AHI > 10 events/h or BMIz < -1 should be used as the intervention standard with high specificity.

AUTHOR CONTRIBUTIONS

Wenhui Guo, Ling Cao contributed to the study concept, data analysis and interpretation, and writing of the manuscript. Wenhui Guo and Linghui Meng contributed to statistical analysis.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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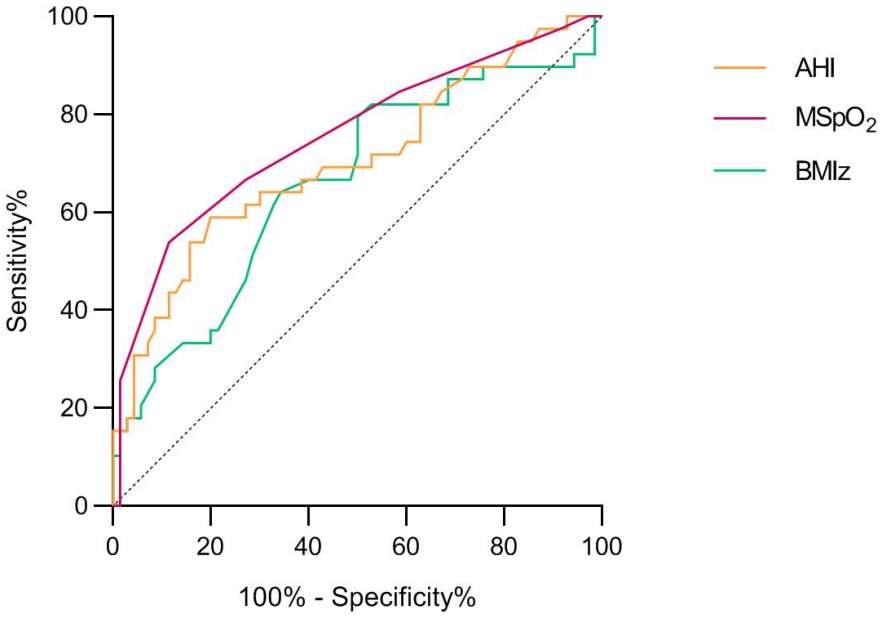

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