Risk Factors for Early Wheezing in Preterm Infants: A Retrospective Cohort Study

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Abstract

Background: The related factors that cause recurrent wheezing in children are complex, and premature delivery may be one of the reasons. Little is known about early wheezing in preterm infants.

Methods: Data sourced from 1616 children born between 2007 and 2013 from 8 hospitals of Guangxi in China. All children were followed by telephone or questionnaire through the sixth year of life. Children were grouped by characters of age: Group A: gestational age (GA) $\leq$ 32 weeks, Group B: 32 weeks < GA < 37 weeks, Group C: 37 weeks $\leq$ GA < 42 weeks.

Results: The incidence and the risk factors of early wheezing in preterm infants were analyzed. The incidence of early wheezing: Group A > Group B > Group C. In Group A, the proportion of small-for-gestational-age (SGA) infant was higher in early wheezing group than in normal group ($P = 0.005$). Male (95% *CI*: 1.611 to 4.601) and family history of allergy (95% *CI*: 1.222 to 3.411) were the risk factors for early wheezing in Group B.

Conclusions: Newborns with younger GA had a higher risk of early wheezing. SGA was a possible factor influencing early wheezing in preterm infants with $GA \leq 32$ weeks. Male and family history of allergy were the risk factors for early wheezing in preterm infants with 32 weeks < GA < 37 weeks.

Background

Asthma is the most common chronic respiratory disease in children. Wheezing is the most typical clinical manifestation of asthma in children. About 57% of children had at least one attack of wheezing at the age of three years [1]. Recurring wheezing or asthma affects the growth of children, increases medical costs, and also imposes a larger burden on the family and society [2]. According to the progress of the disease, children's wheezing is divided into two types: early wheezing (transient early wheezing and persistent early wheezing) and delayed wheezing (Asthma) [3–5]. The related factors that cause recurrent wheezing and even asthma in children are complex, and premature delivery may be one of the reasons. The researches showed that the incidences of wheezing and abnormal lung function were greater in preterm infants than those in full-term infants and premature caused lung damage, lasted for a long time [6]. In addition, preterm infants may be related to small airway disease and chronic obstructive pulmonary disease [7–10]. Therefore, it is extremely important to identify and prevent early wheezing in preterm infants. This study used stratified analysis and comparison with full-term infants to find out the risk factors that caused early wheezing in preterm infants, with the aim to provide some guidance and help for early identification and effective avoidance of potential risk factors.

Methods

2.1 | The sample population

A retrospective cohort study examined 1616 children (premature and full-term infants) born between 2007 and 2013 from 8 provincial and municipal hospitals in Guangxi of China. All children were followed through the sixth year of life. Children were grouped by characters of age: Group A: gestational age (GA) ≤ 32 weeks, Group B: $32 \text{ weeks} < \text{GA} < 37 \text{ weeks}$, Group C: $37 \text{ weeks} \leq \text{GA} < 42 \text{ weeks}$.

2.2 | Data collection

The clinical data were collected by telephone or questionnaire (Appendix 1). Early wheezing is characterized by the onset of wheezing symptom at or before the age of 3. Transient early wheezing is a type of early wheezing, which gradually disappears before the age of 3, while persistent early wheezing continues to the age of 6. These diseases that cause early wheezing include bronchiolitis, asthmatic bronchitis, asthmatic bronchopneumonia, bronchopulmonary dysplasia, and excluding tracheobronchial foreign bodies and other congenital diseases, such as congenital heart disease, tracheoesophageal fistula, laryngeal chondroplasia and mediastinal space occupying. The incidences of early wheezing, transient early wheezing, and persistent early wheezing in each group were compared, and the possible factors for early wheezing in preterm infants were analyzed by stratified analysis. These possible factors include gender, mode of delivery, birth weight (BW), relationship between BW and GA, breast feeding, personal history of allergy, family history of allergy, invasive mechanical ventilation and passive smoking.

2.3 | Data analysis

Enumeration data was expressed by the number of cases or incidence. Each variable was assigned a value: dichotomous variables were used (0 = no, 1 = yes), and unordered multi-categorical variables were assigned by definition. SPSS version 23.0 used to analyze the data of each group by analysis of variance, chi-square test, *Bonferroni* method for multiple comparisons, univariate analysis and multivariate analysis.

Results

3.1 | Comparison of the incidence of early wheezing in each group

There was a significant difference in the incidence of early wheezing among each group ($P = 0.000$) (Table 1). The incidence of early wheezing in group A was significantly greater than that in group B ($P = 0.005$) and group C ($P = 0.000$), and that in group B was significantly greater than that in group C ($P = 0.005$) (Additional file 1, 2).

Table 1
Comparison of the incidence of early wheezing among each group.

Groups	Early wheezing	Normal	Total	Incidence of early wheezing (%)
Group A	37	100	137	27.0
Group B	92	460	552	16.7
Group C	60	867	927	6.5
Total	189	1427	1616	11.7
χ^2				68.795
P				0.000*
“*” indicate significant results with P value < 0.05.				
Grouped by characters of age. Group A: gestational age (GA): ≤ 32 weeks, Group B: $32 \text{ weeks} < \text{GA} < 37$ weeks, Group C: $37 \text{ weeks} < \text{GA} < 42$ weeks.				

3.2 | The incidences of persistent and transient early wheezing in each group

There were significant differences in the incidence of early persistent wheezing ($P = 0.000$) and early transient wheezing ($P = 0.000$) among the groups (Table 2). The incidence of early persistent wheezing in group A ($P = 0.000$) and group B ($P = 0.000$) was significantly greater than that in group C; and the incidence of early transient wheezing in group A was significantly higher than that in group B ($P = 0.001$) and group C ($P = 0.000$) by pairwise comparison (Additional file 3, 4).

Table 2

Comparison of the incidence of persistent early wheezing and transient early wheezing among each group.

Groups	Persistent early wheezing		Transient early wheezing		Total
	number	%	number	%	
Group A	17	12.4	19	13.8	137
Group B	62	11.2	30	5.4	552
Group C	10	1.1	50	5.4	927
Total	87	5.4	96	6.0	1597
χ^2	82.234		15.604		
P	0.000*		0.000*		
“*” indicate significant results with P value < 0.05.					
Grouped by characters of age. Group A: gestational age (GA): ≤ 32 weeks, Group B: $32 \text{ weeks} < \text{GA} < 37$ weeks, Group C: $37 \text{ weeks} < \text{GA} < 42$ weeks.					

3.3 | Univariate analysis of early wheezing in each group

3.3.1 | Premature group of $\text{GA} \leq 32$ weeks

Since the birth weight of preterm infants with a gestational age of less than 32 weeks is usually less than 2500 g. In this group, we used the relationship between BW and GA ((small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA)) instead of BW for evaluation. The results showed the proportion of SGA infants in early wheezing group was significantly higher than that in normal group ($\chi^2 = 8.154$, $P = 0.005$) (Table 3).

Table 3

Univariate analysis for risk associated with early wheezing in preterm infants (GA $\leq$ 32 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	<i>P</i>
Gender			0.169	0.681
Male	20(54.1)	58(58.0)		
Female	17(45.9)	42(42.0)		
Mode of delivery			1.861	0.175
Natural labor	17(45.9)	59(59.0)		
Cesarean section	20(54.1)	41(41.0)		
BW-GA			8.154	0.005*
SGA	12(32.4)	12(12.0)		
AGA	25(67.6)	88(88.0)		
Breast feeding (< 3 months)			0.078	0.781
Yes	25(67.6)	65(65.0)		
No	12(32.4)	35(35.0)		
Personal history of allergy			2.897	0.091
Yes	16(43.2)	28(28.0)		
No	21(56.8)	72(72.0)		
Family history of allergy			1.248	0.266
Yes	8(21.6)	16(16.0)		
No	29(78.4)	84(84.0)		
Invasive mechanical ventilation			3.399	0.067
Yes	25(67.6)	50(50.0)		
No	12(32.4)	50(50.0)		
Passive smoking			0.200	0.656
Yes	21(56.8)	61(61.0)		
No	16(43.2)	39(39.0)		
“*” indicate significant results with <i>P</i> value < 0.05.				
BW: birth weight, GA: gestational age, BW-GA: the relationship between BW and GA. SGA: small-for-gestational-age, AGA: appropriate-for-gestational age				

3.3.2 | Premature group of 32 weeks < GA < 37 weeks

The proportion of male ($\chi^2 = 17.686$, $P = 0.000$), the positive rate of personal history of allergy ($\chi^2 = 7.350$, $P = 0.007$), the positive rate of family history of allergy ($\chi^2 = 12.797$, $P = 0.000$) in the early wheezing group were significantly higher than those in normal group (Table 4).

Table 4
Univariate analysis for risk associated with early wheezing in preterm infants (32 weeks < GA < 37 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	<i>P</i>
Gender			17.686	0.000*
Male	70(76.1)	242(52.6)		
Female	22(23.9)	218(47.4)		
Mode of delivery			0.254	0.615
Natural labor	35(38.0)	188(40.9)		
Cesarean section	57(62.0)	272(59.1)		
BW (< 2.5 kg)			0.002	0.969
Yes	56(60.9)	279(60.7)		
No	36(39.1)	181(39.3)		
Breast feeding (< 3 months)			0.071	0.790
Yes	46(50.0)	237(51.5)		
No	46(50.0)	223(48.5)		
Personal history of allergy			7.350	0.007*
Yes	47(51.1)	166(36.1)		
No	45(48.9)	294(63.9)		
Family history of allergy			12.797	0.000*
Yes	33(35.9)	88(19.1)		
No	59(64.1)	372(80.9)		
Invasive mechanical ventilation			0.443	0.506
Yes	5(5.4)	18(3.9)		
No	87(94.6)	442(96.1)		
Passive smoking			0.000	1.000
Yes	48(52.2)	240(52.2)		

* indicate significant results with *P* value < 0.05.

GA: gestational age, BW: birth weight

Independent variable	Early wheezing (%)	Normal (%)	χ^2	P
No	44(47.8)	220(47.8)		
* indicate significant results with P value < 0.05.				
GA: gestational age, BW: birth weight				

3.3.3 | Full-term group of 37 weeks $\leq$ GA < 42 weeks

The proportion of male ($\chi^2 = 8.486$, $P = 0.004$), the positive rate of personal history of allergy ($\chi^2 = 3.949$, $P = 0.047$), and the positive rate of family history of allergy ($\chi^2 = 6.126$, $P = 0.014$) in the early wheezing group were significantly higher than those in normal group (Table 5).

Table 5
Univariate analysis for risk associated with early wheezing in preterm infants (37 weeks $\leq$ GA < 42 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	<i>P</i>
Gender			8.486	0.004*
Male	47(78.3)	515(59.4)		
Female	13(21.7)	352(40.6)		
Mode of delivery			0.123	0.726
Natural labor	41(68.3)	611(70.5)		
Cesarean section	19(31.7)	256(29.5)		
BW (< 2.5 kg)			0.304	0.581
Yes	1(1.7)	25(2.9)		
No	59(98.3)	842(97.1)		
Breast feeding (< 3 months)			1.046	0.307
Yes	31(51.7)	389(44.9)		
No	29(48.3)	478(55.1)		
Personal history of allergy			3.949	0.047*
Yes	23(38.3)	230(26.5)		
No	37(61.7)	637(73.5)		
Family history of allergy			6.126	0.014*
Yes	18(30.0)	150(17.3)		
No	42(70.0)	717(82.7)		
Passive smoking			0.477	0.490
Yes	29(48.3)	459(52.9)		
No	31(51.7)	408(47.1)		
“*” indicate significant results with <i>P</i> value < 0.05.				
GA: gestational age, BW: birth weight				

3.4 | Multivariate analysis of early wheezing in each group

Univariate analysis showed that the relationship between BW and GA was the possible factor influencing early wheezing in preterm infants with GA $\leq$ 32 weeks, but further analysis of its effect by the method of

logistic regression showed no significant difference (Additional file 5).

Male ($OR = 2.723$, 95% CI : 1.611 to 4.601), family history of allergy ($OR = 2.042$, 95% CI : 1.222 to 3.411) were risk factors for early wheezing in preterm infants with 32 weeks < GA < 37 weeks (Additional file 6).

Male ($OR = 2.516$, 95% CI : 1.331 to 4.755), family history of allergy ($OR = 1.975$, 95% CI : 1.096 to 3.560) were risk factors for early wheezing in full-term infants with 37 weeks $\leq$ GA < 42 weeks (Additional file 7).

Discussion

It has been confirmed that premature birth can cause immature lung, low lung function, immature immune system function, thereby increasing the risk of wheezing in children [11–14]. Enrico Lombard et al showed that GA and the development of the lung were closely related [15]. In this study, included newborns were grouped and compared by GA, and the results confirmed that newborns with younger GA were at higher risk of early wheezing, which was consistent with the study of Unal et al [16]. However, the incidence of early wheezing in different GA groups in this study was lower than that reported in the previous literature [17, 18], considering that it might be related to the short follow-up and the small sample size.

This study showed that the incidence of early transient wheezing in preterm infants with GA $\leq$ 32 weeks was significantly greater than that of preterm infants with 32 weeks < GA < 37 weeks. However, there was no significant difference in the incidence of early persistent wheezing between the two groups. The reason for this result may be that the respiratory system of preterm infants gradually develops with age, resulting in a decrease in early persistent wheezing [19]. In addition, this study also found that the incidence of early persistent wheezing in preterm infants was significantly higher than that in full-term infants, which was consistent with previous literature reports [17].

Birth weight is a well-established indicator of prenatal growth, intrauterine nutritional status and maternal health. It is a sensitive indicator of fetal respiratory and immune system development [20]. Global Initiative for Asthma (GINA) also added low birth weight as a risk factor for persistent airflow limitation [2]. In this study, we found that the proportion of SGA infants was significantly higher in the early wheezing group than in normal group among preterm infants with GA $\leq$ 32 weeks. However, the relationship between them was analyzed by the binary logitc method, and no significant difference was found. In addition, in preterm infants with 32 weeks < GA < 37 weeks and full-term infants with 37 weeks $\leq$ GA < 42 weeks, SGA was not found to be associated with early wheezing, which was inconsistent with that reported in the literature [21]. Therefore, the results will be further verified with a large sample size in the future.

Some studies have shown that preterm infants with very low birth weight had a high incidence of impaired lung function, and the degree of impaired lung function was more severe in preterm infants with recurrent wheezing attacks [11, 22]. However, because this study was a retrospective study, most of the included neonates lacked lung function data. The relationship between early wheezing and lung function

in preterm infants is expected to be further demonstrated by a large sample of prospective studies in the future.

Gender was another risk factor for early wheezing in infants. In this study, we found that the proportion of males in the early wheezing group was significantly higher than that in normal group in both preterm infants with $32 \text{ weeks} < \text{GA} < 37 \text{ weeks}$ and full-term infants with $37 \text{ weeks} \leq \text{GA} < 42 \text{ weeks}$. Meanwhile, the results of univariate analysis and multivariate analysis showed that male was a possible influencing factor and risk factor for early wheezing, respectively. This was in line with previous studies [17, 23]. However, this study did not find an association between gender and early wheezing in preterm infants with $\text{GA} \leq 32 \text{ weeks}$.

Personal history of allergy was a risk factor for wheezing in children². We also found that newborns with a personal history of allergy had a higher risk of early wheezing whether they were preterm infants with $32 \text{ weeks} < \text{GA} < 37 \text{ weeks}$ or full-term infants with $37 \text{ weeks} \leq \text{GA} < 42 \text{ weeks}$, which was consistent with previous studies [24]. However, personal history of allergy did not show a significant difference in early wheezing in preterm infants with $\text{GA} \leq 32 \text{ weeks}$, suggesting that personal history of allergy might not be associated with early wheezing in preterm infants with $\text{GA} \leq 32 \text{ weeks}$. Family history of allergy was also an important risk factor for wheezing in children [25]. The result of this study showed that family history of allergy was a risk factor for early wheezing in preterm infants with $32 \text{ weeks} < \text{GA} < 37 \text{ weeks}$, which was consistent with previous findings [24]. However, there was no correlation between family history of allergy and early wheezing of preterm infants with $\text{GA} \leq 32 \text{ weeks}$ in this study, which was consistent with previous reports [17]. This suggested that a family history of allergy might not be associated with early wheezing in preterm infants with $\text{GA} \leq 32 \text{ weeks}$. The above results indicated that the main cause of early wheezing in preterm infants with $\text{GA} \leq 32 \text{ weeks}$ might be immature respiratory system, rather than personal history of allergy and family history of allergy.

Previous studies have shown that cesarean section delays and alters the development of intestinal flora in infants, thereby increasing susceptibility to wheezing [26]. However, whether cesarean section increased the risk of wheezing in children was controversial. Some studies have demonstrated that the risk of asthma in preterm infants undergoing cesarean section was higher than that in spontaneous delivery [27]. It has also proposed that although the proportion of cesarean section has increased. There was no correlation between cesarean section and the risk of wheezing [28]. The result of this study showed that there was no significant difference between cesarean section and children's early wheezing. However, this did not indicate that cesarean section must not be a risk factor for early wheezing in children. Because the incidence of cesarean section in each group was greater in early wheezing group than in normal group, the failure to obtain statistically significant results might be related to the small sample size of cases.

Tobacco exposure increased the risk of wheezing by decreasing lung function and increasing airway hyperresponsiveness. A prospective birth cohort study showed that preterm infants whose mothers smoked during pregnancy had an increase in the number of wheezes and recurrent wheezing in early

childhood [29]. Another study found that passive smoking was positively correlated with wheezing of preterm infants [16]. However, this study did not find a correlation between passive smoking and early wheezing in children in each group. Considering that with the continuous popularization of popular science information, more and more parents were aware that smoking was harmful to their children's health, so the amount and frequency of smoking were reduced, as well as avoiding smoking at home. This reduced smoke exposure in children to some extent, thereby weakening the increased risk of early wheezing and its adverse effects by passive smoking.

It has been demonstrated that breast feeding can reduce the risk of wheezing by preventing respiratory tract infection, promoting lung growth and development and supporting the maturation of the immune system. However, this study did not find that feeding pattern was related to early wheezing in each group. It was inconsistent with previous literature [30]. The reason might be related to the improvement of current process of formula milk.

Some studies have shown that the use of invasive mechanical ventilation was associated with wheezing in preterm infants [16]. Preterm infants, especially those with bronchopulmonary dysplasia, required respiratory support due to immature lung development in the early postnatal period. While the use of mechanical ventilation played a role in respiratory support, it might cause lung injury, leading to wheezing in children with bronchopulmonary dysplasia [31].

It has been found that preterm infants with GA < 28 weeks of age are exposed to oxygen during the first 3 days of life or frequent episodes of hypoxemia, which increased the risk of wheezing in children [32]. Although the use rate of invasive mechanical ventilation in preterm infants with GA $\leq$ 32 weeks and 32 weeks < GA < 37 weeks was higher than that in normal group in this study, it was not statistically significant. The reason might be related to the small sample size of cases using invasive mechanical ventilation.

Limitations

It is a retrospective study, most of the included neonates lacked lung function data. And the short follow-up and the small sample size are also its limitations.

Conclusion

1. Newborns with younger GA had a higher risk of early wheezing.
2. The incidence of persistent early wheezing in preterm infants is higher than that in full-term infants.
3. SGA was a possible factor influencing early wheezing in preterm infants with GA $\leq$ 32 weeks. Male, personal history of allergy and family history of allergy were the possible factors influencing early wheezing of preterm infants with 32 weeks < GA < 37 weeks. Among them, male and family history of allergy were the risk factors for early wheezing.

Abbreviations

GA: Gestational age

SGA: Small-for-gestational-age

BW: Birth weight

AGA: Appropriate-for-gestational-age

GINA: Global Initiative for Asthma

Declarations

Ethical approval and consent to participate

This study was ethically approved by the Medical Ethics and Human Subject Committee of First Affiliated Hospital of Guangxi Medical University (ID: 2015(028)). All parents or legal guardians provided written informed consent for infants to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Chen X, Yang MJ and Huang SZ: contributed equally to the study, conceived and designed the study, collected clinical data, prepared an analytical plan, analyzed data, and drafted the initial manuscript. Nong GM: contributed for the conception and design of the study, supervised the study, analysed and interpreted data, drafted the manuscript and critically revised it. Qin XL, Pan ZJ, Zhu ML, Zeng DY, Huang YF, Liang T, Liang CM: collected clinical data and reviewed and revised the manuscript. All authors: commented on the manuscript and approved the final manuscript as submitted.

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