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ORIGINAL ARTICLE

Risk factors for recurrent wheezing in preterm infants who received prophylaxis with palivizumab

Mariana Bueno Manini[1], Natasha Yumi Matsunaga[1,2], Lívea Gianfrancesco[1,2], Marina Simões Oliveira[1,2], Maria Rosa Vieira de Carvalho[3], Gisleine Leila Martins Tengler Ribeiro[3], Eliane de Oliveira Morais[3], Maria Angela Gonçalves O. Ribeiro[4], André Moreno Morcillo[5], José Dirceu Ribeiro[2,5], Adyléia Aparecida Dalbo Contrera Toro[2,5]

1. Programa de Pós-Graduação em Saúde da Criança e do Adolescente, Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
2. Laboratório de Fisiologia Pulmonar, Centro de Investigação em Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
3. Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
4. Centro de Investigação em Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.
5. Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.

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ABSTRACT

Objective: To determine the prevalence of recurrent wheezing (RW) in preterm infants who received prophylaxis against severe infection with respiratory syncytial virus (RSV) and to identify genetic susceptibility (atopy or asthma) and risk factors for RW. **Methods:** This was a cross-sectional study involving preterm infants who received prophylaxis with palivizumab at a referral center in Brazil during the first two years of age. A structured questionnaire was administered in a face-to-face interview with parents or legal guardians. **Results:** The study included 410 preterm infants (median age = 9 months [0-24 months]). In the sample as a whole, 111 children (27.1%; [95% CI, 22.9-31.5]) had RW. The univariate analysis between the groups with and without RW showed no differences regarding the following variables: sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding, number of children in the household, day care center attendance, pets in the household, and smoking caregiver. The prevalence of RW was twice as high among children with bronchopulmonary dysplasia (adjusted OR = 2.08; 95% CI, 1.11-3.89; p = 0.022) and almost five times as high among those with a personal/family history of atopy (adjusted OR = 4.96; 95% CI, 2.62-9.39; p < 0.001) as among those without these conditions. **Conclusions:** Preterm infants who received prophylaxis with palivizumab but have a personal/family history of atopy or bronchopulmonary dysplasia are more likely to have RW than do those without these conditions.

Keywords: Infant, premature; Respiratory sounds; Asthma; Palivizumab; respiratory syncytial viruses; Respiratory hypersensitivity.

INTRODUCTION

Children up to three years of age are subject to several diseases that are manifested by wheezing.[1] Approximately 45% of infants have one episode of wheezing in their first year of life, and about 20% have recurrent wheezing (RW).[1] This condition can decrease their quality of life and increase the demand for health care services and consequent hospitalizations due to the high prevalence of severe wheezing episodes.[2]

Preterm newborns, especially extremely premature infants, are more likely to have chronic lung diseases.[3-5] The structural damage to the lungs of infants caused by pregnancy-related events, such as intrauterine growth restriction, chorioamnionitis, and neonatal diseases, leads to impaired lung function.[6] A systematic review published in 2014 showed that prematurity is related to an increased risk of RW, especially in the group of infants born at fewer than 32 weeks of gestational age.[7] A cross-sectional study with 445 children evaluated the risk factors associated with RW in preterm infants.[8] Birth weight < 1,000 g, < 28 weeks of gestational age, personal or family history of atopy, and two or more children living in the same household were considered risk factors for RW.[8]

Up to two years of age, due to the immaturity of the immune system and modulation of innate and adaptive responses, children are more prone to the action of infectious agents.[9] Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in breastfed young children[10-13] and is responsible for approximately 60 million respiratory infections per year worldwide.[14-16] Exposure to RSV occurs in 60-70% of

Corresponding author:
Adyléia Toro. Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Rua Tessália Vieira de Camargo, 126, Cidade Universitária Zeferino Vaz, CEP 13083-887, Campinas, SP, Brasil.
Tel.: 55 19 3521-8958. E-mail: dalbotoro@terra.com.br
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infants during their first year of life.[11] It is estimated that almost all children have already been infected with RSV by the age of two,[17] and approximately 40% will present with LRTI symptoms due to the initial infection. [18] The risk of severe respiratory disease caused by this pathogen is related both to the immunological characteristics of the host and to the viral ability to cause damage.[17,18]

Severe RSV infection in the first two years of life has been associated with long-term respiratory morbidity, decreased pulmonary function, RW, and asthma.[19] Blanken et al.[20] showed that hospitalization caused by viral infection of the lower respiratory tract is a determining factor for RW in healthy preterm children.

Carbonell-Estrany et al.[21] evaluated the impact of hospitalization due to RSV infection on the health of six-year-old children who had been preterm infants (32-35 weeks of gestational age) and confirmed an increased risk of asthma after severe RSV infection in childhood. However, other authors have shown that there is no well-established association between RSV infection and asthma in healthy preterm infants.[22,23] In a study involving preterm children who received prophylaxis with palivizumab and were monitored until they reached six years of age, the authors concluded that immunoprophylaxis had no impact on asthma prevention, but there was a reduction in the RW rate.[24] However, Simões et al.[25] found that the use of passive immunization decreased the risk of RW only in children without a family history of atopy, which suggests that RSV predisposes to RW regardless of atopy.[26] Simões et al.[8] evaluated risk factors associated with RW in preterm children with a high probability of severe RSV infection. In that study, the authors concluded that low gestational age and presence of atopy were the major risk factors associated with RW.[8]

In 2020, a review by experts convened by the World Health Organization showed that a causal association of RSV-related LRTI with RW and asthma was inconclusive.[27] It is not yet clear whether severe RSV infection during the first year of life alters the immune response and triggers the onset of RW or whether it is simply a marker of genetic predisposition to RW.[28] Therefore, the present study is justified, because risk factors associated with RW can be evaluated despite the possible bias of RSV infection in the population of preterm infants who received immunoprophylaxis against RSV.

The aims of the present study were to determine the prevalence of RW in preterm infants who received prophylaxis with palivizumab against severe RSV infection and to identify genetic susceptibility (atopy/asthma) and risk factors for RW.

METHODS

This was a cross-sectional study based on interviews with parents or legal guardians of preterm infants who received passive immunization (palivizumab) against RSV at the *Centro de Referência para Imunobiológicos Especiais* (Referral Center for Special Immunobiologics) at the State University at Campinas, Brazil. Patient selection and interviews took place in two different years (2012 and 2016) in order to increase the convenience cohort size. The same individuals interviewed the participants using the same questionnaire in both years in order to avoid measurement bias. All preterm infants with gestational age < 36 weeks were included. Full-term newborns and infants diagnosed with heart disease, pulmonary malformation, or pulmonary hypertension were excluded.

RW was defined as three or more wheezing attacks during a one-year-period, either in the first year of life or in the year prior to the interview. Asthma is a disease with several phenotypes and can present with respiratory signs and symptoms, including wheezing. Many children have RW, but this is not always indicative of asthma.[27] In our study, children with RW were considered atopic if they had a history of atopic dermatitis, a medical diagnosis of asthma, or a father or mother with a history of asthma.

A structured questionnaire was used, based on a reduced version of the International Study of Wheezing in Infants questionnaire,[29] which was developed to standardize the investigation of RW. That questionnaire is a tool that provides information on the frequency of RW in childhood, as well as on the treatment and risk factors associated with the condition. The questionnaire was administered to the parents or legal guardians at the referral center.

All statistical analyses were performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). We determined the prevalence of RW (95% CI). In order to evaluate the association of RW with selected variables (sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding duration, day care center attendance, maternal smoking during pregnancy, smoking caregiver, pets in the household, number of children in the household, presence of bronchopulmonary dysplasia, and presence of atopy), we used ORs, initially determined by univariate logistic regression and, subsequently, in an adjusted manner, by unconditional multivariate logistic regression using the Wald method (forward stepwise technique). The probability of inclusion in the model was 0.05, and the probability of exclusion from the model was 0.10. All predictor variables with $p \leq 0.05$ in the univariate analysis and those considered as potential confounding factors (i.e., $0.05 < p < 0.20$) were selected for inclusion in the multivariate model.

The present research project was approved by the Research Ethics Committee of the State University at Campinas (#142,928/2012 and #1,030,707/2015). All parents or legal guardians signed the written informed consent form.

RESULTS

We interviewed parents or legal guardians of 745 patients who received palivizumab. Preterm patients

with gestational age < 36 weeks were selected for the study. Of the 745 individuals interviewed, 57 declined to participate. In addition, 265 and 13 of the infants had heart disease and pulmonary malformation or pulmonary hypertension, respectively, and were excluded. Therefore, 410 preterm children who received palivizumab were included in the study (Figure 1).

The children were classified as having RW (three or more episodes of wheezing in 1 year) or as not having RW. Data on the presence of atopy and the gestational age were collected. Table 1 shows the demographic and clinical characteristics of the sample.

The overall prevalence of RW was 27.1% (95% CI, 22.9-31.5). Table 2 shows the prevalence of RW in relation to independent variables. The univariate logistic regression analysis showed no differences regarding the following variables: sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding duration, number of children in the household, day care center attendance, pets in the household, and smoking caregiver.

The chance of developing RW was higher among children whose mothers reported having smoked during pregnancy than among those whose mothers did not (OR = 2.54; 95% CI, 1.06-6.09; p = 0.037; Table 2). Children with a personal history of allergy or whose parents (one or both) had a history of atopy were almost six times more likely to have RW (OR = 5.79; 95% CI, 3.59-9.35; p < 0.001), whereas those diagnosed with bronchopulmonary dysplasia were twice more likely to have RW (OR = 2.10; 95% CI, 1.34-3.29; p = 0.001; Table 2).

For the unconditional multivariate logistic regression analysis, we selected the following variables: atopy, maternal smoking during pregnancy, and bronchopulmonary dysplasia. Sex, number of children in the household, and day care center attendance were considered confounding variables (i.e., 0.05 < p < 0.20). After the analysis, only atopy (p < 0.001) and bronchopulmonary dysplasia (p = 0.022) remained in the model (Table 3). The prevalence of RW was twice as high among children with bronchopulmonary dysplasia (adjusted OR = 2.08; 95% CI, 1.11-3.89; p = 0.022) and almost five times as high among those with a personal/family history of atopy (adjusted OR = 4.96; 95% CI, 2.62-9.39; p < 0.001) as among those without these conditions (Table 3).

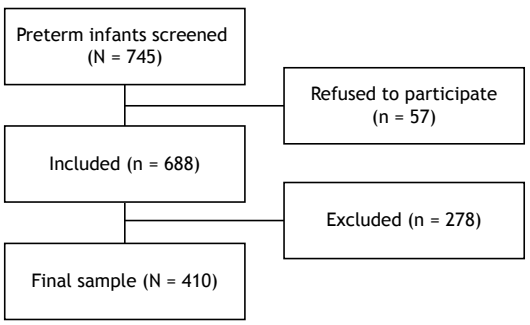

Figure 1. Flow chart of the participant selection process.

DISCUSSION

There are several risk factors reported in the literature associated with RW in the pediatric age group. The prevalence of RW was 27.1% in preterm infants who received palivizumab in the present study. In our sample, the chance of RW was five times higher in the presence of family or personal history of atopy. Although it is well established that there is an association between RSV-related LRTI and RW, it is still unclear whether this association is causal.[30] Several risk factors are related to RW, one of those being atopy.[23]

Simões et al.[25] reported that preventing RSV infection with the use of palivizumab in premature infants without a history of atopy appears to decrease by 80% the relative risk of RW in children from 2 to 5 years of age, an effect that is not seen in those with a history of atopy. In a Brazilian study,[8] atopy and low gestational age were risk factors for RW, and the authors concluded that prophylaxis with palivizumab against RSV significantly reduced the relative risk of subsequent RW in nonatopic premature infants. A systematic review showed that a family history of asthma or atopy is important in the association between severe RSV infection and RW.[23] The authors also suggested that the data in the literature do not support the hypothesis of a causal link between RSV-related LRTI and subsequent wheezing.[23] Another finding of that review was that there was no evidence that immunoprophylaxis protects against subsequent wheezing illness.[23]

Table 1. Demographic and clinical characteristics of the patients studied (N = 410).

Characteristic	n	%
Male	194	47.3
Ethnicity		
Non-White	103	25.1
White	277	67.5
Maternal level of education		
Middle school	65	15.8
High school	146	35.6
Higher education	183	44.6
Recurrent wheezing	111	27.1
Hospitalizations due to wheezing	74	18
Hospitalizations due to pneumonia	60	14.6
Use of inhaled corticosteroid	182	44.4
Atopy	113	27.5
Characteristic	**Median**	**Min-max**
Gestational age, weeks	28	23-36
Birth weight, grams	1.028	505-2.575
Breastfeeding, months	3	0-29
Age at first wheezing attack, months	4	0[a]-17

Min-max: minimum-maximum values. [a]Age < 30 days of life.

Table 2. Risk factors for recurrent wheezing based on the reduced version of the International Study of Wheezing in Infants questionnaire.[29]

Variable	Wheezing				Total	p*	OR	95% CI
	Yes		No					
	n	%	n	%				
Sex								
Male	60	30.9	134	69.1	194	0.097	1.45	0.94-2.24
Female	51	23.6	165	76.4	216		1.00	
Ethnicity								
Non-White	29	28.2	74	71.8	103	0.889	1.04	0.63-1.72
White	76	27.4	201	72.6	277		1.00	
Maternal level of education								
Middle school	13	20.0	52	80.0	65	0.280	0.68	0.34-1.36
High school	44	30.1	102	69.9	146	0.501	1.18	0.73-1.91
Higher education	49	26.8	134	73.2	183		1.00	
Gestational age, weeks								
23-26	33	30.6	75	69.4	108	0.812	1.14	0.38-3.47
27-29	51	25.4	150	74.6	201	0.823	0.88	0.30-2.60
30-32	20	28.6	50	71.4	70	0.947	1.04	0.33-3.30
33-36	5	27.8	13	72.2	18		1.00	
Birth weight, g								
< 1,000	57	29.8	134	70.2	191	0.645	0.71	0.16-3.07
> 1,000-1,500	40	23.5	130	76.5	170	0.375	0.51	0.12-2.24
> 1,500-2,000	8	25.0	24	75.0	32	0.482	0.56	0.11-2.86
> 2,000	3	37.5	5	62.5	8		1.00	
Breastfeeding, months								
Not breastfed	17	27.9	44	72.1	61	0.904	1.06	0.40-2.84
1-3	16	17.6	75	82.4	91	0.283	0.59	0.22-1.55
4-6	12	19.4	50	80.6	62	0.427	0.66	0.24-1.84
≥ 7	8	26.7	22	73.3	30		1.00	
Children in the household								
3-4	14	23	47	77.0	61	0.415	1.42	0.61-3.31
2	12	41.4	17	58.6	29	0.012	3.37	1.30-8.71
1	23	24.7	70	75.3	93	0.247	1.57	0.73-3.36
None	13	17.3	62	82.7	75			
Day care center attendance								
Yes	13	37.1	22	62.9	35	0.104	1.83	0.88-3.80
No	82	24.4	254	75.6	336		1.00	
Pets in the household								
Yes	46	27.2	123	72.8	169	0.533	1.16	0.73-1.85
No	49	24.4	152	75.6	201		1.00	
Maternal smoking during pregnancy								
Yes	10	45.5	12	54.5	22	0.037	2.54	1.06-6.09
No	84	24.7	256	75.3	340		1.00	
Smoking caregiver								
Yes	7	18.4	31	81.6	38	0.289	0.63	0.27-1.48
No	84	26.8	234	73.6	318		1.00	
Atopy								
Yes	61	54.0	52	46.0	113	< 0.001	5.79	3.59-9.35
No	50	16.8	247	83.2	297		1.00	
Bronchopulmonary dysplasia								
Yes	71	34.1	137	65.9	208	= 0.001	2.10	1.34-3.29
No	40	19.8	162	80.2	202		1.00	

*Wald test.

Bronchopulmonary dysplasia is a risk factor for severe RSV infection, but its association with RW in infants is unclear.[31,32] Preterm patients who received immunoprophylaxis and were diagnosed with

Table 3. Multivariate logistic regression for factors associated with recurrent wheezing.

Factor	Wheezing				Total	p	Adjusted OR	95% CI
	Yes		No					
	n	%	n	%				
Bronchopulmonary dysplasia								
Yes	71	34.1	137	65.9	208	0.022	2.08	1.11-3.89
No	40	19.8	162	80.2	202		1.00	
Atopy								
Yes	61	54.0	52	46.0	113	< 0.001	4.96	2.62-9.39
No	50	16.8	247	83.2	297		1.00	

*Wald test.

bronchopulmonary dysplasia were twice more likely to have RW when compared with those who were not. The literature shows that children with severe bronchopulmonary dysplasia at 6 months of age will more commonly present with respiratory symptoms than will those with mild or moderate bronchopulmonary dysplasia.[31,32] However, other risk factors should be investigated as markers of future onset of respiratory symptoms.[31]

We concluded that maternal smoking during pregnancy is a risk factor for RW. However, this factor was eliminated in the unconditional multivariate logistic regression analysis. Our conclusion was corroborated by a meta-analysis that evaluated seven articles, involving a total of 8,579 infant cases of RW, regarding the association between maternal smoking during pregnancy and the risk of RW in childhood.[33] The authors concluded that maternal smoking during pregnancy could increase the risk of RW in childhood.[33] However, that association was found only in the cross-sectional studies evaluated, but not in the cohort studies.[33] In addition, the authors considered that the maintenance of maternal smoking during the postnatal period was a confounding factor and emphasized the need for further studies with a cohort design in order to elucidate this issue better.[33]

On the basis of our study group results, family atopy and bronchopulmonary dysplasia were risk factors for RW. Simões et al.[8] demonstrated an increased chance of RW in preterm infants with a personal history of food allergy or atopic dermatitis. A review article that evaluated the relationship between severe RSV infection and subsequent asthma concluded that there is a high probability that environmental factors, such as RSV infection, act as triggering events.[34] Therefore, we highlight the importance of immunoprophylaxis to prevent preterm infants from having severe RSV infection.

Memory bias can be considered a limitation of the present study, given the importance of the exact number of wheezing episodes for classifying the patient as a recurrent wheezer, and the fact that this information was obtained from parents or legal guardians rather than from medical reports. Another limitation is that there was no control group, because it would be unethical to deprive preterm children of the immunoprophylaxis program in accordance with the criteria defined by health care authorities.[35] Data collected in two nonconsecutive years might have introduced a patient selection bias. However, there were no changes in the palivizumab prophylaxis protocol (gestational age, association with pulmonary disease, and heart disease), and the population treated at our center was the same in terms of socioeconomic characteristics.

In conclusion, RW has different phenotypes, and the risk factors involved are yet to be fully understood. In the present study, the use of immunoprophylaxis against RSV infection did not prevent 27,1% of infants from having RW. Thus, genetic factors related to atopy might play an important role as a predictive factor of RW. Other cohort studies are needed to improve the elucidation of the cause-effect relationship between RSV infection and RW.

AUTHOR CONTRIBUTIONS

MBM and AADCT: conception and design of the study; data acquisition and interpretation; drafting the article; critical review of the relevant intellectual content; and approval of the final version. NYM, LG, MSO, MRVC, GLMTR, EOM, MAGOR, and JDR: data acquisition; critical review of relevant intellectual content; and approval of the final version. AMM: Data acquisition, analysis, and interpretation; critical review of relevant intellectual content; and approval of the final version.

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