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Wheezing, asthma, and atopy in premature infants at 2 years of age

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Background/aim: We aimed to evaluate wheezing, bronchial asthma (BA), and atopy in premature infants at 2 years of age via a cross-sectional study.

Materials and methods: Premature infants at <37 weeks of gestational age (GA) were assessed for atopy by skin-prick test and serum immunoglobulin E level at 2 years of age. The family's and infant's histories of allergy, BA, atopy, and wheezing were obtained by questionnaire and from hospital records.

Results: There were 98 infants, with mean birth weight (BW) 1517.4 ± 486.5 g and GA 30.8 ± 2.9 weeks. The frequencies of wheezing, asthma, and bronchopulmonary dysplasia (BPD) were 32.7%, 16.3%, and 14.3%, respectively. Skin-prick tests were positive for 11 subjects, with allergy to cereals for 7 infants, egg for 3, and peanut for 1.
Wheezing was related to GA, BW, respiratory distress syndrome, mechanical ventilation, sepsis, asphyxia, smoking, antenatal steroid, BA, palivizumab prophylaxis, number of people in the household, and duration of hospitalization ($P < 0.05$). Wheezing was negatively correlated to GA. Family history of BA, smoking, and number of people in the household were linked to BA ($P < 0.05$).

Conclusion: Wheezing was related to degree of premature birth, but BA was linked to BA in the family and smoking. Increased gestation should improve the infant's respiratory health up to 2 years of age.

Key words: Atopy, premature, wheezing

1. Introduction

Respiratory morbidity is a major health problem among premature infants in early childhood (1–3). Premature infants, particularly those with bronchopulmonary dysplasia (BPD), have increased risk of chronic respiratory morbidities (4,5). Recurrent respiratory symptoms requiring treatment and lung function abnormalities at follow-up are common for subjects born even late preterm (6,7). It is suggested that preterm birth increases the risk of asthma and wheezing disorders during childhood and the risk of asthma/wheezing disorders increases as the degree of prematurity increases in a systematic review and meta-analysis (8). Premature infants, especially BPD patients, experience more hospital readmissions and outpatient and emergency rooms visits, and are more likely to suffer from respiratory illnesses and to need bronchodilator therapy (9,10).

Previous studies related to the effect of prematurity on atopy in early childhood have been inconclusive. While atopy has not been related to high lifelong prevalence of respiratory symptoms, persistence of wheezing has been associated with allergen sensitization in premature infants (11). Antigen exposure in early life has been supposed to be associated with long-lasting effects on atopic sensitization. Thus, allergen sensitization of children born premature can be assumed to differ from that of children born at term (1,2). Prematurity at birth was linked with a decreased long-term risk of allergen sensitization (12). Pregnancy length and very early childhood were reported to be important in the development of atopy, and timing of the environmental exposure was of importance for the immune system (13). The first months of life are supposed to be an enclosed period of particular vulnerability towards environmental risk factors, especially exposure to aero-allergens (14).

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In the present study, we aimed to evaluate the effect of gestational age, birth weight, and perinatal risk factors on wheezing, bronchial asthma (BA), and atopy in premature infants at 2 years of age. Atopy was assessed by skin-prick test and serum IgE level. Respiratory morbidities, especially wheezing, atopy, and BA, were determined by a questionnaire and from hospital records.

2. Materials and methods

A cross-sectional study including premature infants born before 37 weeks and followed up at our neonatology outpatient clinic regularly was designed. Information about the infant's respiratory morbidity, care, and evolution during the first two years of life was obtained in a single interview with the parents at a routine hospital visit for the child. The information specifically related to significant illnesses, medications, and intervention services from the parent was obtained. Hospital admissions of the infant due to wheezing at any time and requirements of bronchodilator therapy were also determined from hospital records.

A questionnaire was implemented to identify the family's and infant's data related to respiratory and atopic symptoms at the visit. The questionnaire included the subject's birth weight (BW), gestational age (GA), postnatal age, perinatal disorders, parental and family characteristics, smoking of parents, attendance at school or daycare for the subject and siblings, breast-feeding, formula and/or complementary feeding for the first months, vaccination, palivizumab prophylaxis, history of allergy and/or atopy for the family and subjects (asthma, eczema, food or drug allergy, allergic rhinitis, other allergies), medical history for respiratory disorders, admission to hospital secondary to respiratory complaints, and therapy for these complaints and its duration (Appendix).

GA was defined by last menstrual date, ultrasound examination (in the absence of a menstrual date or when a difference of 2 or more weeks existed between menstrual age and that derived sonographically), or the New Ballard Score (in the absence of obstetrical indexes) (15). Small for gestational age was defined as a birth weight below the 10th percentile of Fenton's fetal growth charts (16). Bronchopulmonary dysplasia was defined according to the National Institute of Child Health and Human Development consensus criteria (17). Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture.

Detailed perinatal, natal, early postnatal, and clinical data of the infants were recorded. The infants were examined regularly for physical growth, neurodevelopment, and retinopathy of prematurity at the outpatient clinic of neonatology. The infants had routine vaccinations and respiratory syncytial virus (RSV) immunoprophylaxis with palivizumab according to the guideline of the Turkish Neonatal Society. The Turkish Neonatal Society suggests palivizumab prophylaxis for premature infants born before 29 weeks of gestation for the first year and for those diagnosed with BPD for 2 years (18). The infants were supported by vitamin D until 2 years old and iron prophylaxis for the first year.

The premature infants at 2 years of age were examined for possible hypersensitivity or allergic sensitization at the allergy department. Atopy was verified by skin-prick test and by measuring serum total IgE level. Total IgE level was measured by nephelometry (Siemens Healthcare Diagnostics Products; Marburg, Germany). The infants with recurrent respiratory symptoms, such as lower airway obstruction or recurrent wheezing, followed up at the neonatology outpatient clinic were referred to the allergy department regardless of age. The children were diagnosed with BA if they had wheezing, shortness of breath, or cough attacks exceeding 24 h at least 2–3 times per year.

The skin-prick test was carried out on the back and read after 15 min. A commercial extract of inhalant allergens (*Dermatophagoides pteronyssinus*, *D. farinea*, *Alternaria*, *Cladosporium*, aspergillus, cockroach, cat and dog dander) and food allergens (milk, egg, peanut, fish, soy, wheat) (Stallergenes, Antony, France) were used. Histamine HCL (Stallergenes) and allergenic extract sterile diluent (Stallergenes) were used as positive and negative controls, respectively. Results were assessed as positive if the wheal mean diameter was 3 mm or more than the reaction of the negative control.

The ethical committee of our hospital approved the study and all parents of the participants provided written informed consent.

2.1. Statistical analysis

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis of the obtained data. The definitions were provided as number and percentage for discrete variables and mean and standard deviation for continuous variables**.** Multivariate analysis was used to analyze potential independent effects of several risk factors on wheezing, atopy, and BA. Pearson's correlation coefficient was used to investigate the relationship between two quantitative, continuous variables. P values less than 0.05 were defined as statistically significant.

3. Results

There were 98 premature infants evaluated by a questionnaire, skin-prick test, and measurement of serum total IgE level at 2 years of age in this study. The mean BW of the premature infants was 1517.4 ± 486.5 g and mean GA was 30.8 ± 2.9 weeks. The results of sociodemographic factors and postnatal data of the subjects are shown in Tables 1 and 2.

Table 1. The socio-demographic factors related to infants.

Factor	Result
Birth weight (g) *	1517.4 ± 486.5 (550–3100)
Gestational age (weeks) *	30.8 ± 2.9 (26–36.5)
Postnatal age (months) *	25 ± 1 (24–28)
Mother's age *	30.7 ± 5.4 (19–43)
Father's age *	34.4 ± 5.7 (23–51)
Sex ** Female Male	 46 (46.9%) 52 (53.1%)
Delivery route ** Spontaneous vaginal Cesarean section	 17 (17.3%) 81 (82.7%)
Consanguinity **	8 (8.2%)
Number of siblings **	1.2 ± 1 (0–4)
Attendance at daycare **	24 (24.5%)
Sibling at school or daycare **	47 (47.5%)
Breast-feeding **	85 (86.7%)
Breastfeeding duration (months) *	8.6 ± 8.2 (0–30)
Duration of hospitalization * (months)	35.4 ± 28 (2–118)
Number of people in the household *	4.6 ± 1.3 (3–8)

* Mean ± standard deviation (minimum–maximum), ** n (%)

The frequencies of wheezing, BA, and BPD were 32.7% (n = 32), 16.3% (n = 16), and 14.3% (n = 14), respectively. Skin-prick tests were negative for 87 subjects (positive test ratio 11.1%). We determined allergy to cereals for 7 subjects, egg for 3, and peanut for 1. The mean serum IgE level of the subjects was 58.2 ± 108.2 (5–639) IU/mL. Serum IgE level was high for 27 subjects (27.6%). There were 3 infants that could not achieve catch-up growth at 2 years old. The results of infants related to respiratory outcome, atopy, and BA are shown in Table 3.

We found that wheezing was related to BW, GA, respiratory distress syndrome (RDS), surfactant therapy, BPD, invasive ventilation, noninvasive ventilation, BA, gastroesophageal reflux (GER), smoking at home, maternal smoking, antenatal steroid therapy for fetal lung maturation, palivizumab prophylaxis, sepsis, asphyxia, the number of people in the household, and duration of hospitalization ($P < 0.05$) (Table 4). Palivizumab prophylaxis was applied to 28% of the infants. The relation between wheezing and palivizumab prophylaxis was significant ($P < 0.001$). There was a weak correlation between wheezing and GA ($r = –0.261$, $P = 0.009$), BW ($r = –0.206$, $P = 0.042$), duration of hospitalization ($r = 0.228$, $P = 0.024$), BA ($r = 0.634$, $P < 0.001$), and the number of people in the household ($r = 0.208$, $P = 0.04$).

Table 2. The postnatal data of the infants related to prematurity.

Data	Result, n (%)
Respiratory distress syndrome	53 (54.1%)
Surfactant therapy	45 (45.9%)
Invasive ventilation	47 (48%)
Noninvasive ventilation	61 (62.2%)
Bronchopulmonary dysplasia	14 (14.3%)
Antenatal steroid therapy	48 (49%)
Steroid therapy for BPD*	8 (8.2%)
Small for gestational age	7 (7.1%)
Patent ductus arteriosus	22 (22.4%)
Air leak syndrome	1 (1%)
Proven sepsis	48 (49%)
Palivizumab prophylaxis	28 (28.6%)
Intraventricular hemorrhage Grade 1–2 Grade 3–4	 26 (25.6%) -
ROP ** Grade 3–4 and/or laser	7 (7.2%)

* BPD: Bronchopulmonary dysplasia, ** ROP: Retinopathy of prematurity

Table 3. The results of infants related to wheezing, atopy, and asthma.

Data	n (%)
Formula feeding at any time	82 (83.7%)
Maternal smoking	15 (15.3%)
Smoking at pregnancy Active Passive	31 (31.6%) 12 (12.2%) 19 (19.4%)
Smoking at home	49 (50%)
Family history of BA*	29 (29.6%)
Pet ownership	2 (2%)
Family history of allergic rhinitis	15 (15.3%)
Family history of eczema	5 (5.1%)
Wheezing (at any time)	32 (32.7%)
Allergic rhinitis	2 (2%)
Eczema	4 (4.1%)
Gastroesophageal reflux	8 (8.2%)
Bronchial asthma	16 (16.3%)
Skin prick test positive (atopy)	11 (11.1%)

* BA: Bronchial asthma

BA was related to wheezing, family history of BA, smoking at home, maternal smoking, and the number of people in the household ($P < 0.05$) (Table 4). There was a weak correlation between BA and palivizumab cumulative dose ($r = 0.217$, $P = 0.032$) and the number of people in the household ($r = 0.209$, $P = 0.039$). Premature infants with BPD had more wheezing attacks (Table 5).

4. Discussion

It is well described that premature infants are at high risk for respiratory morbidity, i.e. wheezing, childhood allergy, and BA, later in life (1–4). In this cross-sectional study, we aimed to evaluate the effects of BW, GA, and perinatal risk factors on respiratory outcomes, particularly wheezing, atopy, and BA in premature infants. The frequencies of wheezing, BA, and atopy were 32.7%, 16.3%, and 11.1%, respectively. We found that wheezing was related to BW, GA, RDS, surfactant therapy, BPD, invasive ventilation, noninvasive ventilation, BA, smoking at home, maternal smoking, antenatal steroid therapy, palivizumab prophylaxis, sepsis, asphyxia, the number of people in the household, and duration of hospitalization. Notably, there was a weak correlation between wheezing and GA ($r = –0.261$, $P = 0.009$) and BA ($r = 0.634$, $P < 0.001$). We proposed that increasing the length of gestation should improve the infant's respiratory health up to 2 years of age.

Preterm birth increases the risk of BA and wheezing disorders during childhood and the risk of asthma/wheezing disorders increases as the degree of prematurity increases (19). We determined the lesser the gestation, the higher rate of wheezing attacks ($r = –0.261$, $P = 0.009$). There was no such association between BA and GA. Although respiratory system infections were not examined in this study, we proposed that wheezing might be related to nonatopic mechanisms and the result of perinatal and postnatal events, because we determined significant relations between wheezing and BW, GA, antenatal steroid therapy, RDS, surfactant therapy, invasive ventilation, noninvasive ventilation, sepsis, asphyxia, BPD, BA, smoking at home, maternal smoking, palivizumab prophylaxis, the number of people in the household, and duration of hospitalization.

In premature infants, viral agents, especially RSV, most commonly cause respiratory system infections in early childhood, and RSV-induced bronchiolitis has been associated with wheezing and BA (20–22). Palivizumab reduces the severity of RSV infection in premature infants. Prais reported that palivizumab prophylaxis was associated with reduced wheezing episodes and hospitalizations during the first 2 years of life in children born extremely prematurely, but it did not affect pulmonary outcome at school age (23). Yoshihara stated that palivizumab prophylaxis administered to preterm infants 33 to 35 weeks' GA is associated with a significantly lower incidence of recurrent wheezing during the first 3 years of life (24). We determined a significant relation between wheezing and palivizumab prophylaxis ($P < 0.001$, Table 4). This should be related to immaturity of the subjects and possibly having more risk factors for wheezing.

There were studies describing atopy with increased BW (25). A recent analysis by Rzehak et al. observed an increased incidence of asthma until the age of 6 years with a high gain of body mass index in the first 2 years in 8 European cohort studies with 12,050 participants (26). Sonnenschein-van der Voort described increased risk for wheezing and asthma in children with an increased infant weight gain (27). Cesarean section has been associated with the development of asthma and recurrent wheezing (28). Maternal asthma has been associated with increased risk of childhood BA (29). We found that BW, delivery route, gestation, and maternal BA were not related to BA. As there were a small number of infants, the results were unsatisfactory.

Premature infants, especially BPD patients, experience more hospital readmissions and outpatient and emergency rooms visits, and are more likely to suffer from respiratory illnesses and to use respiratory drugs (9,10). Vogt determined increased risk of inhaled corticosteroid therapy in premature infants at 6–19 years of age (30). We

Table 4. The factors affecting wheezing and asthma in the premature infants.

Factor	Wheezing (P)	BA* (P)
Birth weight	0.042	>0.05
Gestational age	0.009	>0.05
Respiratory distress syndrome	0.003	>0.05
Surfactant therapy	0.006	>0.05
Invasive ventilation	0.009	>0.05
Noninvasive ventilation	0.001	>0.05
Bronchopulmonary dysplasia	0.035	>0.05
BA*	<0.001	>0.05
Family history of BA*	0.01	0.01
Smoking at home	0.002	0.006
Maternal smoking	0.014	0.007
Antenatal steroid therapy	0.022	>0.05
Palivizumab prophylaxis	<0.001	>0.05
Sepsis	0.001	>0.05
Asphyxia	0.002	>0.05
Number of people in the household	0.04	0.039
Duration of hospitalization	0.024	>0.05

* BA: Bronchial asthma

found no difference in wheezing, atopy, or BA between premature infants with and without BPD. However, as the number of infants with BPD was low, it is impossible to make any comment related to the influence of BPD on wheezing, BA, and atopy.

There is controversy related to the mechanism of the association between prematurity and allergy, BA, and atopy indicated by different studies (7,8,11,12,20,31–35). The results of various studies and proposed mechanisms of atopy and allergic disease in premature infants involved genetic, perinatal origins, and environmental factors (36). There is evidence that maternal BA increases the risk of BA in children (29). The relation between childhood atopy in premature infants and the histories of atopy, allergic diseases, and BA in the families is not well defined. Most of the studies revealed no such association (37). We determined that family history of BA, smoking, and crowded living environment increased the risk of BA in premature infants at 2 years of age. Genetic and environmental factors, such as smoking, together might increase the risk of BA and allergic sensitization.

The first limitation of our study is the small number of participants and this might explain the lack of significant associations between respiratory morbidity and several factors we analyzed. Future studies with larger samples are needed to clarify the significance. Second, the majority of the respiratory outcomes were reported by parents, a method frequently used in other studies; however, it creates a potential information bias (38). Third, we had no control group including term infants. Moreover, we reported short-term allergic diseases and asthma in premature infants. It would be better to define the long-term results of allergy and BA. The factors affecting wheezing, such as viral infections, were not clear in our study. A higher ratio of wheezing might be related to viral infections in premature infants. The effects of GER, BPD, and viral infections should be investigated by well-designed randomized controlled trials.

In conclusion, wheezing was significantly related to gestation and perinatal risk factors (BW, RDS, surfactant

Table 5. The relation between bronchopulmonary dysplasia and wheezing, atopy, and asthma in the premature infants.

Factor	BPD* +	BPD* –	P
Wheezing	8	60	0.035
Bronchial asthma	3	71	>0.05
Atopy	2	75	>0.05

*BPD: bronchopulmonary dysplasia

therapy, invasive ventilation, noninvasive ventilation, sepsis, asphyxia, BPD, smoking, antenatal steroid therapy, palivizumab prophylaxis, number of people in the household, and duration of hospitalization) in premature infants at 2 years of age. Wheezing attacks were inversely related to GA. We suggested that increasing the length of gestation should improve the infant's respiratory health up to 2 years of age.

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Appendix. The questionnaire filled out for every infant.

PREMATURE INFANTS WHEEZING-ATOPY FORM

Name		**Age**:…..….	**Address:**
Date of birth:		**Sex** □ **F** □ **M**	**City** **Phone:**

PRENATAL	
Maternal prenatal smoking: Active Passive None	
Chronic Disorder:	***Vitamin:*** No Yes
Vaccination:	***Celestone:*** No Yes Dose

NATAL		
Gestational age: ……week	***Route:*** Vaginal: C/S:	***Birth weight***:……..g
Multiple pregnancy: No Twins Triplet		

POSTNATAL			
Resuscitation: Yes No	***RDS:*** Yes No	***Surfactant:*** Yes No: … .dose	
Product: Survanta Curosurf	***PDA:*** No Yes ***Therapy***: Ibuprofen Indomethacin Surgery		
IMV: Yes No	***CPAP:*** Yes No		***MV duration:***
IHB: Yes No	**Phototherapy:** Yes No		**Exchange:** Yes No
BPD: Yes No Type:	***NEC:*** Yes No		***IVH:*** No Yes Grade
Asphyxia:	***AGA:*** ***SGA:*** ***LGA:***		
Duration of hospitalization:	***GER:*** Yes No Therapy:		***Sepsis:*** Yes No
ROP: Grade: Zone: Therapy	***Steroid for BPD:*** Yes No Dose:		
PALIVIZUMAB: Age of first dose: ***Duration:*** ***Total dose:***			

Breast milk: Yes No: Duration:	***D vitamin:*** Yes No:……. Duration:
Multivitamin: Yes No …. Duration:	***Formula:*** Yes No …… beginning age:
Supplemental food:	***Vaccines:*** Yes-whole No Missing
Kindergarten: No Yes Beginning age	***Sibling at kindergarten:*** Yes No
Sibling at school: Yes No	***Recurrent wheezing:*** Yes No
Asthma: No Yes	***Eczema:*** No Yes ***Allergic rhinitis:*** No Yes
Food allergy: No Yes	***Drug allergy:*** No Yes

FAMILY		
Mother age: year	***Father age:*** ……year	***Consanguinity***: No Yes
Number of sibling:	***Number of living at home:***	***Pet:*** No Yes
Mother Smoking: No Yes	***Smoking at home:*** No Yes	

FAMILY HISTORY OF ALLERGY:							
		Asthma	**Eczema**	**Food allergy**	**Allergic rhinitis**	**Drug allergy**	**Allergy other**
Mother	No						
Father	No						
Siblings	No						

PHYSICAL EXAMINATION:			
Weight: (P)	***Length:*** (P)	***Head circumference:*** (P)	***BMI:***
Respiratory:	***CVS:***	***GIS:***	
General:	***Neurologic:***	***Extremity:***	

WHEEZING		
Wheezing at any time: No Yes	***How many:***	***Age at first wheezing:*** month
Hospitalization: No Yes	***How many:***	***Therapy:***
BA diagnosed by MD: No Yes	***Therapy:*** No Yes Steroid LTRA	

ATTACKS OF WHEEZING:			
Age:	***Duration:***	***Therapy:***	***Hospitalization:***
Age:	***Duration:***	***Therapy:***	***Hospitalization:***
Age:	***Duration:***	***Therapy:***	***Hospitalization:***
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