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Investigation of the frequency of wheezing and airway resistance using the interrupter technique in children born premature and over 3 years old

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ABSTRACT

Aims: The term wheezy child is a complex condition that includes different phenotypes, differences in duration and course, and a group of diseases with distinct pathophysiology. Prematurity is a risk factor for early transient wheezing. However, its restrictive effect on respiratory function tests may also predispose to persistent wheezing. This study aimed to investigate the frequency of wheezing phenotypes and their effect on airway resistance in children born prematurely and over the age of 3.

Methods: Prematurely born children over the age of 3 who were followed up in our hospital were included in our study. The effect of neonatal risk factors, especially prematurity, on persistent wheezing and increased airway resistance has been investigated. The presence of persistent wheezing and asthma in patients was investigated with the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. To evaluate respiratory functions, airway resistance was measured with the interrupter technique.

Results: There was no significant correlation between Rint values indicating airway resistance and week of gestation, birth weight, gender, mechanical ventilation, oxygen therapy, presence of BPD, and smoking exposure at home ($p>0.05$).

Conclusion: Although there are studies in the literature showing a relationship between recurrent preschool wheezing and prematurity. Airway resistance was successfully measured and interpreted with Rint in preschool children who could not comply with the respiratory function test. Although prematurity is expected to increase airway resistance, it is interesting that we did not detect this effect in our patients, which may be due to the limited number of extremely premature patients.

Keywords: Prematurity, persistent wheezing, airway resistance

INTRODUCTION

Prematurely-born children (<37 weeks) experience many problems, especially respiratory problems, in the later stages of their life. Normal lung development begins on the 26th day of the embryological period. After the 36th week, the alveolar developmental stage begins. In preterm babies younger than 28 weeks, respiratory problems occur due to the incompleteness of the canalicular and saccular stages, and therefore the lack of surfactant production. In addition to these issues, exposure of preterm babies to oxygen during their postnatal follow-up, other environmental factors, and intensive care follow-up also increase the effects of the increased bronchial muscles and collagen tissue in their lungs.[1]

Due to such risk factors in children born prematurely, it causes an increase in wheezing and coughing attacks and airway resistance in the later stages of their lives.

Wheezing is a high vibration polyphonic musical sound produced by rapid air vibration due to narrowing of the lower airways. The definition of 'wheezing child' is a complex condition that includes heterogeneous phenotypes, differs in duration and course, and includes a group of diseases with separate pathophysiology. Prematurity, nursery care at an early age, cigarette smoking of the mother during pregnancy, and low maternal age are the most important risk factors associated with the development of 'transient early wheezing' fenotype. On the other hand, persistent wheezing phenotype may also be seen due to the restrictive effect of premature delivery on pulmonary function tests. Perinatal characteristics such as low birth weight (<2500 g) and premature history (<33 weeks of gestation) are among the important factors that facilitate wheezing in childhood. Many studies have found a relationship

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between prematurity and wheezing.[2] In this study, it was aimed to investigate the frequency of wheezing infants and wheezing phenotypes and their effects on airway resistance in children born prematurely and completed 3 years of age.

METHODS

The study was carried out with the permission of İzmir Dr Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.10.2015, Decision No: 2015/14-06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 54 patients were included, who were followed up in our hospital, born in <37 weeks, completed the age of 3. Detailed histories of the patients were obtained at the outpatient clinic control. Gestational week, birth weight, length of stay on mechanical ventilator, duration of oxygen intake, length of hospital stay, surfactant use, bronchopulmonary dysplasia treatment information were recorded in the case report form from patient files. Detailed physical examination of the patients was performed at the outpatient clinic control; patients with pathological findings in the upper and lower respiratory tract examination were not included in the study. Those with structural anomalies, especially in the upper and lower respiratory tract, and those with underlying genetic diseases such as primary ciliary dyskinesia or cystic fibrosis were not included in the study. For these reasons, 8 patients were not included in the study.

Definition of Wheezy Child or Asthma

Questions about smoking at home and the questions in the International Study of Asthma and Allergies in Childhood (ISAAC) research protocol questions were asked to the relatives of the patients the answers were recorded in the case report form.

Detailed physical examination of the patients was performed under the control of the outpatient clinic, and patients with pathological findings in the upper and lower respiratory tract examinations were not included in the study.

Pulmonary Function Test

Airway resistance kit (Rocc, Rint kit) was attached to the Cosmed Pony FX portable spirometry device. Since the patients were under the age of 5, an "airway resistance kit" was used to evaluate respiratory functions. Children under 4 years of age were studied using a face mask, and those over 4 years old using a mouthpiece (nostrils were closed). By adjusting the parameters of the device, Rint was measured in the expiratory phase during the tidal breathing of the patients [Rint (e)]. At least 5 measurements were made on the patients. If there was crying or talking during the measurement, that measurement was excluded from the evaluation. The median value of the 5 correct measurements was accepted as the child's Rint value.[3]

In the evaluation the findings, SPSS (statistical package for social sciences) for Windows 20.0 software was used for statistical analysis.

RESULTS

Of the 54 subjects included in the study, 30 (55.6%) were female and 24 (44.4%) were male. The age distribution range of all patients ranged from 3 to 4 years. Birth weights were found to be 1777±550 gr, minimum 770 gr, maximum 3400 gr. Considering the distribution of the cases according to their gestational weeks, it was found that 8 patients were at the 28th week or less (14.8%), 20 patients were between the 28th-32nd weeks (37%), 26 patients were at the 32nd-36th weeks (48.2%).

In the first 1-year period of the cases whose nutritional histories were questioned, it was found that 8 (14.8%) cases were fed only with breast milk, 42 (77.8%) cases were fed with formula in addition to breast milk, and 4 (7.4%) cases were fed only with formula.

Neonatal histories of the patients were investigated, 43 (79.6%) of the cases included in the study needed oxygen and 12 (27.9%) of these patients were followed up with only nasal continous positive airway pressure (CPAP), 23 (53.4%) were followed up with mechanical ventilation and then n-CPAP.

21 (38.9%) patients needed surfactant during their follow-up, 33 (61.1%) patients did not need surfactant. Bronchopulmonary dysplasia (BPD) developed in 4 (19%) of 21 patients who were administered surfactant. It was determined that patients who were not given surfactant treatment did not have BPD.

The presence of wheezy child and asthma was investigated by ISAAC. The results of the ISAAC asthma research questionnaire administered to the patients in our study are given in Table 1.

Table 1. ISAAC asthma research survey findings

ISAAC asthma research questions	Yes n/%	No n/%
Having a wheezing or whistling sound in the chest since birth	34/63	20/37
Wheezing attacks in the past 12 months	12/22.2	42/77.8
Dry cough at night since birth (non-infectious)	14/25.9	40/74.1
Dry cough at night in the last 12 months (non-infectious)	10/18.1	44/81.5
History of hay fever or eczema	5/9.3	49/90.7
Receiving more than 3 courses of antibiotics for upper and lower respiratory tract infections since birth	17/31.5	37/68.5
Receiving more than 3 courses of antibiotics for upper and lower respiratory tract infections respiratory tract infections since birth	7/13	47/87
Wheezing during or after exercise since birth	13/24.1	41/75.9
Wheezing during or after exercise in the past 12 months	5/9.3	49/90.7
Waking up with wheezing since birth	14/25.9	40/74.1
Awakening from sleep with wheezing in the past 12 months	7/13	47/87
Consulting a physician for wheezing since birth	34/63	20/37
Consulting a doctor for wheezing in the past 12 months	14/25.9	40/74.1
Coughing severe enough to limit speech since birth	4/7.4	50/92.6
Coughing severe enough to limit speech in the past 12 months	1/1.9	53/98.1

ISAAC: International Study of Asthma and Allergies in Childhood

According to ISAAC results, 34 (63%) of 54 patients described wheezing attack at least once. Wheezing persisted in 22% of these. In the comparison of the patient group with wheezing according to the week of gestation, no statistically significant difference was found (p=0.326).

No statistically significant difference was found when the birth weights of the patients were compared with the findings of non-infectious dry cough (p=0.808). When the gestational week and non-infectious dry cough findings were compared, no statistically significant difference was found (p=0.824). When gender and non-infectious dry cough findings were compared, no statistically significant difference was found (p=0.627).

Awakening from sleep with wheezing was detected in 14 of 54 cases included in the study, and the mean gestational week was found to be 31.5 (±3.15) weeks. There was no statistically significant difference between the two groups (p=0.480). The mean birth weight of the cases with wheezing and waking from sleep was 1807 (±570) g; no statistically significant difference was observed (p=0.512). No statistically significant difference was observed when wheezing and waking up from sleep were compared with gender (p=0.627).

When the oxygen intake of the patients, wheezing, non-infectious dry cough, eczema, use of three consecutive courses of antibiotics, wheezing after exercise, waking up from sleep with wheezing and coughing severe enough to restrict speech are evaluated; no statistically significant difference was found (p>0.05) (Table 2).

Table 2. Correlation between ISAAC questions and oxgygen receiving

Oxgygen receiving (n)	Yes	No	p
Wheezing	5	29	0.178
Dry cough	3	11	0.909
Eczema	2	6	0.659
Receiving more than 3 courses of antibiotics	8	9	0.394
Wheezing during or after exercise	3	1	1.0
Awakening from sleep with wheezing	1	13	0.153
Coughing severe enough to limit speech	0	4	0.571

ISAAC: International Study of Asthma and Allergies in Childhood

When the parameters of wheezing, non-infectious dry cough, eczema, use of three consecutive courses of antibiotics, wheezing after exercise, waking up from sleep with wheezing and coughing severe enough to restrict speech are evaluated with the mechanical ventilator monitoring of the patients; no statistically significant difference was found (p>0.05).

Of a total of 54 patients, 34 (63%) had wheezing since birth and 20 (37%) did not. No statistically significant difference was found when the patient group with wheezing was compared according to gestational week (Table 3).

Table 3. Relationship between wheezing and week of gestation

	Wheezing		p
Gestation week	Yes	No	
26	4	0	
27	3	0	
28	1	1	
29	2	0	
30	1	4	
31	4	3	0.326
32	3	1	
33	0	3	
34	6	3	
35	5	1	
36	5	4	
Total	34	20	

When the family history of the cases was questioned, there was a history of asthma in the 1st degree relatives of 5 (9.3%) cases, and in the 2nd degree relatives of 13 (24.1%) cases, while 36 (66.7%) had no family history of asthma.

The mean Rint value of all patients in our study was 0.53 kPa.L-1.s. It was found to be higher than the mean Rint value of children in the same age group. The median Rint value of 23 patients with mechanical ventilation was 0.618, and the median Rint value of 31 patients without mechanical ventilation was 0.420, and there was no significant difference in Rint values between the two groups (p=0.055). The median Rint value of 43 patients who received oxygen therapy was 0.552, and the median Rint value of 11 patients who did not receive oxygen therapy was 0.394, and there was no significant difference in Rint values between the two groups (p=0.114). The mean Rint value of 21 patients who received surfactant treatment was 0.576 (±0.208), and the mean Rint value of 33 patients who did not receive surfactant treatment was 0.506 (±0.214), and there was no significant difference in Rint values between the two groups (p=0.242). No significant correlation was found between Rint value and week of gestation (p=0.15, r=-0.19), mechanical ventilation time (p=0.33, r=0.21), oxygen uptake time (p=0.42, r=0.12) (Figure).

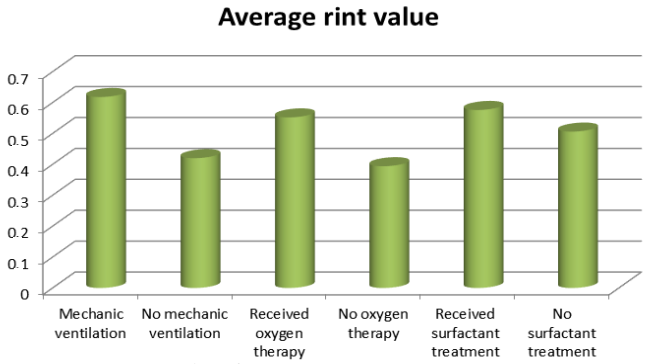

Figure. AvaregeRint value of patients

DISCUSSION

In our study, variables that create a predisposition for persistent wheezing risk in children born prematurely were questioned, and contrary to some views in the literature, no significant relationship with prematurity was found.

Recurrent respiratory diseases are a common cause of hospital admissions, and are more common in children born prematurely (<37 weeks) in the first year of life. It is difficult to distinguish which of the children who experience wheezing attacks in the first years of life will become asthmatic in the future. For this reason, the relationship between wheezing in infancy and later development of asthma has been investigated for many years. Since the mid-1990s, applications to hospitals with the complaint of wheezing have increased considerably, especially in industrialized countries. In international study of ISAAC conducted in 56 countries and 155 centers, the prevalence of wheezing was found to be 4-32% in different countries.[4]

Three different wheezing phenotypes were determined according to the age of wheezing, the atopic background in the child, the change in respiratory functions and the risk factors carried by the patient. These are transient early wheezing, non-atopic persistent wheezing, and atopic wheezing.[5] Prematurity, nursery care at an early age, cigarette smoking of the mother during pregnancy, and low maternal age are the most important risk factors associated with the development of temporary early wheezing.[6] In the study of Elder et al.,[7] recurrent wheezing attacks occurred in the first year of life in 14.5% of

525 premature babies born before the 33rd gestational week, while this rate was found to be only 3% in term newborns. In the cohort study conducted by Harju et al.[1] with 44173 patients between 1989 and 2008, it was found that the prevalence of asthma increased significantly in children born under 32 weeks. In a study by Leps et al.,[8] which included the follow-up of 18118 cases at the age of 3, 5, 7 and 11 years, a significant relationship was found between the week of miscarriage and the frequency of wheezing, and it was stated that there was also the use of drugs related to this. In our study, unlike the literature, no significant difference was observed when the patient group with wheezing was compared according to the week of gestation.

Gender also has an important role in wheezing phenotypes. In the study of Guilbert et al.,[9] wheezing was found more frequently in all three phenotypes in males, and while wheezing was more severe in males, a more rapid deterioration was also detected in pulmonary function test. Possible reasons for this may be relative airway stenosis, delay in immune maturation, low lung volume, high airway resistance, hormonal differences, or vascular/bronchial tone difference. In the study of Hennessy et al.[10] performed on 197 prematurely born 30-month-old children, no significant difference was found between the presence of wheezing, waking up with wheezing at night, and gender. Similar to the literature, no significant difference was found in our study between waking up with wheezing at night and gender.

In the study conducted by Elder et al.[7] in children born under 33 weeks of age and followed up in the neonatal intensive care unit of King Edward Memorial Hospital between 1990 and 1991, it was found that the frequency of recurrent wheezing in preterm infants was 14.5%. The relationship between the history of having oxygen therapy in the neonatal period and the frequency of wheezing was found in the children in this group, and in our study, the relationship between having oxygen therapy and future wheezing attacks was evaluated, but no significant difference was found.

In a study by Useman et al.[8] in which term and preterm early infants were included, the mean Rint value was found to be higher in term infants. It was thought that the reason for this was due to the incompleteness of fetal lung developmental stages. In our study, although the mean Rint value of preterm patients was found to be lower than that of term-born healthy children, no statistically significant difference was found. Although we think that the small number of our patients affected this data, our finding of a significant difference also supports the transient wheezing phenotype.

Measurement of lung volumes by spirometry and bronchial hypersensitivity tests have taken their place as diagnostic criteria in asthma in children older than 6 years and adults. However, the application of these techniques in pre-school children is limited due to the difficulty of breathing. Some techniques that can be applied in clinical practice continue to be developed for the diagnosis of asthma in the pre-school age group. Measuring airflow resistance with the interrupter technique is one of them. This technique can be easily used in the infant age group because it requires minimal patient compliance. The working principle of the interrupter technique is based on the assumption that the alveolar pressure equals the mouth pressure with an interruption made by the device during passive breathing. Thus, the pressure measured from the mouth shows us the resistance of the airways.[11] This technique can be easily applied to the portable pulmonary function test device by attaching the apparatus containing the flow meter and pressure transmitter parts. Although it is sufficient for the patients to be calm and preferably asleep for the technique to be applied, many studies have been conducted regarding the applicability of the test in clinical practice.[12] The airway resistance value (Rint) measured with this technique varies depending on its measurement in expiration or inspiration. In a study, it was observed that while an increase was detected in Rint [Rint (e)] measured during expiration in healthy children with mild respiratory tract infection compared to the control group, there was no change in Rint [Rint (i)] measured during inspirium. Likewise, many studies have shown that there is a more significant increase in Rint (e) than Rint (i) when airway obstruction develops, therefore it has been found that Rint (e) value better reflects airway resistance.[3] In our study, Rint values were measured in the expiratory phase of tidal respiration by adjusting the parameters of the device. In the study of Özek et al.,[13] consisting of term born, healthy 28 males (56%), 22 females (44%) a total of 50 patients with a mean age of 3.2±1.8 years, the mean Rint value was found to be 0.489 kPa. L-1.s and the mean Rint value was found to be 0.53 kPa.L-1.s in our study. The data we obtained does not meet the expectation of increased airway resistance in prematurity.

In the study conducted by VR Kairamkonda et al.[14] in children born prematurely between the ages of 2-4 years, Rint values of patients with chronic lung disease (n: 28) and healthy patients (n: 18) were compared, and the Rint value in the preterm control group was found to be 1.16 (1.03-1.32) kPa. .L-1.s in the group with chronic lung disease, and 1.33 (1.21-1.42) kPa.L-1.s was found to be in the group with chronic lung disease. In the study conducted by Vrijlandt ET et al.[15] with patients born premature, aged 3-5 years, with and without BPD, no significant difference was found in Rint values between the two groups. In our study, no significant difference was found between the group with and without BPD.

Limitations

There are also some limiting features in our study. One of the most important limiting factors is the low number of patients who were born premature (<37 weeks), completed the age of three, and included in the study. Therefore, the parameters found to be related to each other in similar studies were not found significant in our study. Although the Rint value indicating airway resistance increased as the gestational week decreased, statistically significant data could not be obtained. There is a need for studies with larger patient groups in order to detect airway resistance in pre-school children born prematurely with the interrupter technique.

CONCLUSION

In conclusion, although transient wheezing is an expected condition in preschool children, we wanted to determine whether premature birth and subsequent intensive care follow-up contribute to this condition. Although there are reports with similar results in the literature, studies with a larger patient population are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İzmir Dr Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.10.2015, Decision No: 2015/14-06).

Informed Consent

All relatives of the patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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