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EARLY WHEEZING PHENOTYPES AND COGNITIVE DEVELOPMENT OF 3-YEAR OLDS. COMMUNITY-RECRUITED BIRTH COHORT STUDY

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Abstract

The main purpose of the study was to answer the question whether young children without clinical diagnosis of asthma but experiencing early wheezing disorders and therefore being at high risk of developing asthma may have cognitive deficits. In the ongoing birth cohort study wheezing symptoms were recorded postpartum over two first years of age and subsequently cognitive status of children at the age of 3 years was assessed with the Bayley Mental Development Index (MDI). In the statistical analysis a wide range of modifying and confounding factors (maternal education, gender of children, prenatal exposure to lead and environmental tobacco smoke (ETS) were considered to assess the independent effect of early wheezing phenotypes on cognitive development of children. The MDI score correlated inversely with the number of wheezing days recorded over 24 months ($r = -0.13$, $p=0.007$), lead cord blood concentration ($r = -0.12$, $p = -0.02$), number of siblings ($r = -0.17$, $p = 0.0006$) and the number of cigarettes smoked daily by other household members at home over the pregnancy period ($r = -0.18$, $p = 0.0002$). While the children who experienced wheezing over the first year of age showed deficit of 2 MDI scores (beta coeff. = -2.31 , 95%CI: -4.63 to 0.02), those with persistent wheezing had the score deficit of 4 points (beta coeff. = -4.41 , 95%CI: -8.27 to -0.55).

To our knowledge, it is the first report in the literature showing that early wheezing is associated the cognitive deficit in a community-recruited very young children. Observed cognitive deficit in early wheezers may be caused by RSV infections or can be related to lower lung function attributed to persistent wheezing, which reducing oxygen supply would affect rapidly developing brain.

Keywords

cognitive development; children; wheezing phenotypes; birth cohort study

Introduction

Numerous epidemiologic studies provided a solid evidence that respiratory wheezing and asthma are a major health issue in childhood and are the leading causes of visits to physicians and hospitalization (1 – 8). The International Study of Asthma and Allergies in Childhood (ISAAC) found that the prevalence of wheeze varied greatly between countries and ranged from 4.1 – 32.1% in younger age groups and was particularly high in English speaking countries and Latin America (9 – 10). Wheeze originates in airways which may be narrowed by compression or by intrabronchial or intraluminal obstruction (inflammatory mucosal edema, secretions or spasm), it increases gas velocity within the respiratory tract with the resultant oscillation (11). Early wheezing may be a marker of a subgroup of infants who are prone to early lung damage due to viral infections or environmental factors such as passive smoking or other environmental hazards. Most cases of persistent wheezing and asthma, which begin in early life are frequently associated with reduced infant lung function and increased airway responsiveness (12 – 16).

As it was earlier reported children with medical diagnosis of asthma appear to be at increased risk of behavioral and emotional problems (17), which include anxiety and depression. The results of the National Cooperative Inner-City Asthma Study carried out in US (18) revealed that children with clinically significant behavior problems had significantly more days of wheeze and poorer functional status in the follow-up period. Another cohort study showed that parents of 3-year-olds showing recurrent attacks of severe wheeze and shortness of breath reported significant elevation in children's neurocognitive difficulty (19). In contrast, a large-scale multicenter trial of children with mild to moderate asthma indicated no elevation in neurocognitive difficulty (20).

Most analyses of the association between psychosocial factors have been conducted on clinic-recruited children with asthma, but the few prospective studies focused on healthy children at high risk of developing symptoms (21 – 23). Moreover, some authors suggested that the administration of certain types of corticosteroids in the course of asthma treatment may be associated with hyperactive behaviors (24 – 26).

The main purpose of the study was to answer the question whether community-recruited children without clinical diagnosis of asthma but experiencing early wheezing disorders and therefore being at high risk of developing asthma symptoms later in life may already have cognitive deficits in early childhood. In our birth cohort of infants, wheezing symptoms were recorded postpartum over two first years of age and subsequently cognitive status of children at age of 3 years was assessed with the Bayley Mental Development Index (MDI). In the analysis a wide range of modifying and confounding factors such as maternal education, gender of child, parity, prenatal exposure to lead, prenatal and postnatal exposure to environmental tobacco smoke (ETS) were considered to assess the independent effect of wheezing phenotypes on the cognitive development of children.

Material and Methods

This study uses data from an earlier established birth cohort of children in Krakow being the part of the collaborative study with Columbia University in New York. The design of the study and the detailed selection of the population have been described previously (27). Pregnant women were recruited from ambulatory prenatal clinics in the first and second trimester of pregnancy. Only women 18–35 years of age, who claimed to be non-smokers, with singleton pregnancies, without illicit drug use and HIV infection, free from chronic diseases such as diabetes or hypertension, and residents of Krakow for at least one year prior to pregnancy were eligible for the study. Prior to participation, women read and signed an

informed consent. The Ethical Committee of the Jagiellonian University approved the research.

Upon enrolment, a detailed questionnaire was administered to each woman at the entry to the study to solicit information on demographic data, house characteristics, medical and reproductive history, occupational hazards, and smoking practices of others present in the home. Prenatal ETS was measured by an average number of cigarettes smoked daily in the presence of mother over pregnancy period and postnatal ETS by a number of cigarettes smoked daily at home in the presence of child over two years in postnatal period. Maternal education (years of schooling) was treated as a proxy for the socio-economic status.

A total of 505 pregnant women enrolled to the study gave birth to their children between January 2001 and February 2004. After delivery, newborns were followed-up every three months and trained interviewers carried out detailed standardized interviews on infants' health at each three-month visit. All interviews were performed with the mothers of infants. Data about wheezing or whistling on children chest during each of 8 time points was used to identify three mutually exclusive patterns of wheeze between birth and 2 years: 0. never wheezers (no wheezing at any of the 8 time points); 1. transient early wheeze (wheezed only at any time at 0–12 months or only between 13 and 24 months). 2. persistent wheezing, which developed in the first year of life and continued in the second year of the follow-up. In the final analysis 468 children with complete datasets were included in the study.

Blood sample collection and analysis

A cord blood sample (30–35 ml) was drawn into a vacutainer tube that had been treated with ethylene diamine tetra-acetate (EDTA). The tubes were inverted several times to mix the EDTA and the blood to prevent coagulation. Within 8 hours of blood collection, the blood samples were transported to the clinical biochemistry laboratory at the University Hospital in Krakow for processing and storage. Packed red blood cells and plasma samples were separated and stored in liquid nitrogen in the laboratory prior to shipment to Columbia University. From Columbia University, portions of samples were then sent to the Centers for Disease Control (CDC) for chemical analysis. Blood samples for lead analysis were refrigerated without any processing. Whole blood lead concentrations were determined using inductively coupled plasma mass spectrometry CLIA'88 method "Blood lead cadmium mercury ICPMS_ITB001A". This multi-element analytical technique is based on quadrupole ICP-MS technology (28).

Mental developmental testing

The Bayley Scales of Infant Development – second edition (BSID-II) includes Mental Development Index (MDI) (29). The BSID-II results are based on the assessment of 178 standardized activities. Number and sequence of these activities are chosen for each age group. Mental Scale assesses items such as habituation, problem solving, early number concepts, generalization, classification, memory, vocalization, language and social skills. The BSID-II test was administered to children within 4 weeks of the target age at the Department of Epidemiology and Preventive Medicine by five trained examiners, who were unaware of the child's exposure. Interpretation of the Bayley test was based on the detailed manual of instructions for evaluators (Bayley Scales of Infant Development – Manual). Standardization of mental performance scoring was done within the team in the course of team practice session with the team leader (Dr Ilona Lisowska-Miszczuk) who was trained at the Columbia University with follow-up surveillance of the assessors by Dr J. Jankowski from the Jeshiva University in New York.

Statistical Analysis

The purpose of the statistical analysis was to assess the impact of wheezing phenotypes and cognitive function of 3-year-olds. To identify potential confounders, associations between population characteristics and outcome variables were investigated. In the descriptive analysis, the distribution of various characteristics of women and newborns under study in terms of the cognitive function were considered. Chi-square statistics (nominal variables) and analysis of variance (numerical variables) tested differences between subgroups with different wheezing phenotypes. Association between MDI scores and wheezing phenotypes was adjusted to potential confounders by the multivariable linear regression model. As mentioned we coded wheezing phenotypes from 0 – 2, and the outcome 0 was used as the base reference group. In the multivariable regression models a set of potential confounders or modifiers (maternal education, gender of child, parity, prenatal and postnatal ETS and prenatal lead exposure) were taken into consideration. As distribution of cord blood lead concentrations was markedly skew, in statistical analyses the data were log-transformed. Statistical analyses were performed with STATA 10 version software for Windows (30)

Results

In the total study sample, 126 children (26.9%) had at least one wheezing episode in the first two years of life. The onset of wheezing in the first year of life was recorded in 84 infants (17.9%) and new wheezing beyond the first year of age was observed in 42 children (9.0%). Out of 84 infants for whom onset of wheezing was reported in the first 12 months of age, 30 children (6.4%) had it still through the second year of life. The overall geometric mean lead level in cord blood was 1.29 µg/dL (95% CI: 1.24 – 1.1.34) with the range from 0.44 to 6.90 µg/dL.

Table 1 presents the characteristics of the study sample by the wheezing phenotypes. While there was about the same proportion of boys and girls in the total study sample, there was more boys than girls among children with persistent wheezing (63.3% vs. 36.7%). Mean number of wheezing days over the period of 24 months postpartum was highest in children with persistent wheezing. There was a higher proportion of prenatal and postnatal ETS exposure in children classified as persistent wheezers. Mean MDI score was lower in children with reported wheezing episodes in the first 24 months of life.

Number of wheezing days correlated with the number of siblings (Fig. 1). There was a positive trend of MDI scores with maternal education levels (Fig 2) but negative with the number of siblings (Fig 3). Analysis of MDI score distributions by the wheezing phenotypes showed a clear shift of MDI values toward lower values in the group of children with persistent wheezing (Fig. 4).

The MDI scores inversely correlated with the number of wheezing days recorded over 24 months ($r = -0.13$, $p=0.007$), log transformed lead cord blood concentration ($r = -0.12$, $p = 0.02$), number of siblings ($r = -0.17$, $p = 0.0006$) and the number of cigarettes smoked daily by other household members at home over the pregnancy period ($r = -0.18$, $p = 0.0002$).

The multivariable linear regression model was used to establish the adjusted effect of early wheezing phenotypes on the cognitive function of children measured by the MDI scores (Table 2). While the children who experienced wheezing over the first year of age showed deficit of 2 scores, those with persistent wheezing had the score deficit of 4 points. There was a significant gradient between the wheezing phenotypes and BSIDII scores ($p<0.05$). The observed relationship between MDI scores and wheezing phenotypes was adjusted to a set of potential modifying variables such as maternal education, gender of child, presence of

older siblings, prenatal exposure to lead and presence of prenatal and postnatal exposure to environmental tobacco smoke.

Discussion

Our study provided a new piece of evidence that wheezing in the early postnatal life was associated with a clear cognitive function deficit. The interpretation of the observed association between cognitive function of young children and early wheezing phenotypes is not straightforward and it should consider a complex set of both prenatal and perinatal environmental factors.

Early wheezing usually start before 1 year of age and is typically induced by RSV infection, but seems to be also more common after bronchiolitis caused by less invasive viruses (31 – 37). Viruses may act as triggers for wheezing in early life and probably reveal those infants who have a pre-existing alteration of either airway function or immune system. It may be hypothesized that RSV infections causing wheezing in early childhood may also be responsible for damage of developing brain. In favor of infection hypothesis is the significant inverse correlation of cognitive function with number of wheezing days recorded over the follow-up. The inverse correlation between MDI scores and the number of older siblings may result from the fact that the risk of respiratory infections in the family circle increases with a number of siblings.

Most cases of persistent wheezing and asthma beginning in early childhood are often associated with reduced infant lung function and with increased airway responsiveness (12 – 16). Therefore, cognitive deficit in very young children may be related to lower lung function attributed to persistent wheezing, which reducing oxygen supply would affect rapidly developing brain. Important in this context would be the recent study of Dezateux et al. (14) who reported that the increased plethysmographic airway resistance measured during the first few months of infants' life was associated with wheezing illness in the first year of life. Another study in preschool children in the Manchester Asthma and Allergy Study (16) has also shown that both transient and persistent wheezers have reduced lung function compared with nonwheezing children, but the deficit was considerably greater in persistent wheezers. It is possible that it is not wheezing symptoms per se that lead to lower MDI scores, but that children who have other chronic problems are at particular risk of slower mental development. However, in our study sample no serious chronic ailments were recorded.

To underline strength of our study, we have to mention very careful design, sufficient size of the study sample and the application of the Bayley mental test for measuring early cognitive development of children. The Bayley mental test is a well standardized tool specially designed for measuring intellectual deficits among infants and very young children. Not only are the scales well-standardized, but they offer an early and fairly comprehensive measure of cognitive functioning. The Bayley taps abilities such as attention, memory, and perceptual reasoning are thought to be fundamental components of early as well as later intellectual functioning. Another strong point of our study is very careful monitoring data of respiratory health outcomes in infants performed by trained interviewers over 8 time points household visits over the follow-up. Furthermore, in our study important potential confounders of the relationship between the respiratory health of children and cognitive development of infants such as maternal chronic diseases or active tobacco smoking by mothers in pregnancy have been removed through entry criteria. Other risk factors that are thought to affect the mental development in infancy such as environmental tobacco smoke, parity, maternal education, prenatal lead exposure have been taken into consideration in the

analysis and the estimates of main effects were adjusted in the multivariable linear regression model.

On the side of limitations, our study sample may not be representative for the female urban population in the country because enrollment covered only pregnant nonsmoking women with singleton pregnancies between the ages of 18 and 35 years who were free from such chronic diseases as diabetes and hypertension. However, these inclusion criteria helped us eliminate from the study infants who were at greater risk for neurocognitive disorders because of maternal chronic diseases or active smoking in pregnancy.

Summing up, the results of our study confirmed that the respiratory health in early childhood was associated with cognitive development of children and the effect was independent from prenatal exposure to lead or environmental tobacco smoke. To our knowledge, it is the first report in the literature showing that early wheezing is associated the cognitive deficit in a community-recruited very young children. Observed cognitive deficit in wheezers may be caused by RSV infections in early childhood or eventually be related to lower lung function attributed to persistent wheezing, which reducing oxygen supply would affect rapidly growing brain. Planned further longitudinal observation of the study sample should provide more evidence on the role of respiratory health in the early childhood cognitive development.

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Fig. 1.
Histogram of mean days of wheezing in children over period of 24 months of life grouped by the number of siblings

Fig. 2.
MDI36 score in children by maternal education

Fig. 3.
Histogram of MDI36 scores (with SE) grouped by number of siblings

Figure 4.
Histograms of MDI36 grouped by the wheezing phenotypes

Table 1

Characteristics of the study sample by the wheezing phenotypes in the follow-up period

Variables		Wheezing phenotypes			Total (468)
		0 (N=342)	1 (N=96)	2 (N=30)	
Gender:					
Boys	n (%)	164 (48.1)	52 (54.2)	19 (63.3)	235 (50.2)
Girls	n (%)	178 (52.0)	44 (45.8)	11 (36.7)	233 (49.8)
Birth weight (g):					
	Mean	3413.5	3384.6	3394.3	3406.4
	SD	473.3	478.5	551.9	487.7
Parity:					
1	n (%)	223 (65.2)	56 (58.3)	12 (40.0)	291 (68.2)
2	n (%)	119 (34.8)	40 (41.7)	18 (60.0)	177 (37.8)
Maternal education level (Schooling years)					
	Mean	15.6	15.7	14.8	15.6
	SD	2.7	2.7	2.8	2.7
Prenatal ETS (+)	n (%)	80 (23.4)	29 (30.2)	15 (50.0)	124 (26.5)
Postnatal ETS (+)	n (%)	76 (22.2)	26 (27.1)	11 (36.7)	113 (24.1)
Cord blood lead :					
	Mean	1.41	1.38	1.48	1.41
	SD	0.74	0.63	0.59	0.71
Number of days with wheezing over 24 month					
	Mean	-	11.2	33.1	4.4
	SD	-	14.5	31.7	13.5
Mental Development Index:					
	Mean	104.3	101.6	97.5	103.26
	SD	10.2	9.3	11.0	10.3

Wheezing 0 = no wheezing symptoms at any time

Wheezing 1 = wheezing recorded only in the first 12 months or only in the 13–24 months

Wheezing 2 (persistent) = symptoms recorded both in the first and the second year of the follow-up

Table 2

Estimated effect of wheezing phenotypes on MDI score in 3-year-olds adjusted to potential confounders and modifiers based on the multiple linear regression. (R-squared = 0.18)

Predictors	Coef.	Std. Err.	t	P>t	[95% Conf. Interval]
Maternal education	1.560	0.371	4.21	0.000	0.83 2.29
Parity	-2.235	0.789	-2.83	0.005	-3.79 -0.68
Gender of child	3.976	0.961	4.14	0.000	2.09 5.87
Cord blood lead (µg/dL, log transformed)	-6.613	2.818	-2.35	0.019	-12.16 -1.07
Prenatal ETS	-3.596	1.435	-2.51	0.013	-6.42 -0.77
Postnatal ETS	0.507	0.376	1.35	0.179	-0.23 1.25
Wheezing 0	1.000				
Wheezing 1	-2.309	1.183	-1.95	0.052	-4.63 0.02
Wheezing 2	-4.413	1.963	-2.25	0.025	-8.27 -0.55
Constance	98.802	2.432	40.62	0.000	94.02 103.59

Maternal education: schooling years

Parity: number of siblings

Gender: 0 = boys, 1 = girls

Prenatal ETS: average number of cigarettes smoked daily at home in the presence of mother over pregnancy

Postnatal ETS: average number of cigarettes smoked daily at home in the presence of child

Parity: number of siblings

Wheezing 0: no wheezing at any time

Wheezing 1: transient early wheeze (wheezed only at 0–12 months or only between 13 and 24 months).

Wheezing 2: persistent wheezing