Med Sci Monit, 2001; 7(2): 293-298

Reversibility of asthma-like symptoms and lung function growth over two-year follow-up in preadolescent children

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key words: cohort study, preadolescent children, reversibility of asthma-like symptoms, lung function level and lung function growth

SUMMARY

Background: *The interesting feature of childhood asthma is the great reversibility of symptoms. The main purpose of this study was to assess the effect of persistent and reversed asthma-like symptoms on lung function growth in preadolescent children.*
Material and methods: *The follow-up respiratory health survey has been conducted in the sample of 1129 children aged 9 yrs over two years follow-up. The basic health end-points was the occurrence of asthma-like symptoms and the slower lung function growth (SLFG).*
Results: *Adjusted OR for SLFG(FVC) was significantly higher only in the children having the continued symptoms(OR=3.40; 95%CI: 1.32–8.77). There was a consistent trend of adjusted ORs for SLFG(FEV_1) with the category of symptoms, where OR was 1.46 (95%CI:1.02–2.10) in children with recent new symptoms; 2.06; (95%CI: 0.93–4.58) in those with symptoms remitted, while 3.46; (95% CI: 1.43–8.40) in children who had persistent symptoms. The corresponding ORs for SLFG($FEF_{25-75\%}$) were 2.03; (95%CI: 0.97–4.28), 2.63; (95% CI: 1.38–4.99), and 5.84; (95%CI: 2.53–13.50).*
Conclusions: *The consistent association between reversibility of asthma-like symptoms and lung function gain in preadolescent children confirmed the clinical significance of the symptoms in question. The observed slower lung function gain in preadolescence may have implications for the development of chronic lung disease later in adulthood.*

BACKGROUND

Asthma primarily is a disease in children among whom its prevalence and rate of hospitalisation have increased over the past 20 years [1,2]. About 30 percent of all asthmatics are under the age of 18, and half of all these asthma cases are diagnosed by age 5. The interesting feature of childhood asthma is the great reversibility of symptoms since roughly half of all childhood asthmatics will have their symptoms remit by early adulthood [3].

It is under debate to which extent occasional and recent wheezing may lead to change in lung function in infants and children, although these changes may be within normal values of spirometric reference values. Clinical or cross-sectional studies in children have already indicated that persistent wheeze is associated with reduced pulmonary function [4], but it is not clear whether recent symptoms have also the same impact and whether the symptoms are associated with the lung growth in the preadolescent children. To date the effect of change in wheezing symptoms in terms of lung growth in children has have been explored only in a few studies [5–7]. Interpretation of pulmonary function growth in children in terms of the occurrence of asthmatic symptoms is not an easy task

Received: 2000.11.29
Accepted: 2001.01.10
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because it varies strongly with a child's stage of growth. Cross-sectional analyses have shown that a child's pulmonary function increases linearly with age and height until the adolescent growth spurt, which occurs at approximately 10 years of age in girls and 12 years of age in boys [7–10]. Considerable individual variations in the onset or magnitude of the adolescent height growth spurt and lung function development have been reported in a number of studies [11–15].

The main purpose of this study was to measure the occurrence of asthma-like symptoms over two year period in preadolescent children, and to assess the effect of recent and persistent asthma-like symptoms on lung function growth over two year follow-up. In addition, the effect of symptoms that reversed over two-year period was assessed as well.

MATERIAL AND METHODS

The epidemiologic cohort study was conducted in Krakow, a city with approximately 700,000 inhabitants in Southern Poland. The children from the twelve grammar schools located in the city centre and in the peripheral part of the city have been chosen. The details on the study sample is provided elsewhere [16]. In the chosen schools a full list of students with their residence addresses were prepared, and consequently, parents of all 1165 children attending the second form (9 years of age) of the selected schools were contacted. Out of all 1129 eligible parents, 97% of them agreed to be interviewed on the respiratory health of their children and household characteristics.

The baseline field health survey was performed in 1995 and the annual follow-up has been conducted over subsequent two years (1996–1997). Health assessment has been based on standardized interviews, anthropometry and spirometric measurements. The health questionnaire contained questions on respiratory symptoms recommended by the Epidemiology Standardisation Project and ATS [17].

The basic health end-point for the respiratory symptoms was asthma-like syndrome defined as the occurrence of wheezing and/or attacks of breathlessness. Interviewers instructed the parents that by wheeze sounds we understood whistling in the chest, independent of colds or fever and by attacks of breathlessness the dyspnea attacks accompanied by wheezing or whistling.

Symptoms were assessed separately in each annual survey as present(+) or absent(-), and the subjects were classified in four categories according to the pattern of the symptoms reported. Classification of the children in respect to the occurrence of asthmatic syndrome based on the follow-up was following:

1. Healthy: a syndrome never present; before 1995 and in the period 1995-1997; (– – –)
2. New cases: a syndrome absent in 1995 but present in 1996 or 1997; (– – +) or (– + +) or (– + –),
3. Continued: a syndrome present at least in two surveys; (+ + +) or (+ + –) or (+ – +),
4. Remission: a syndrome present in 1995 but not in 1997; (+ – –).

Spirometric measurements were carried out with computerized Vitalograph Spirotrac III portable spirometer where the measurement of air flow from the subject is made using a Fleisch type pneumotach. The spirometric testing has been done only in the standing position. The spirometer program has chosen the best flow out of three blows executed by each child. The lung function testing included the following indices: FVC, FEV_1 and $FEF_{25-75\%}$. Each day, prior to the lung function examination, the spirometer was checked with one-liter syringe and 3% variablity was acceptable. One trained technician in all health surveys has performed all spirometric testing.

For the purpose of the analysis lung function growth measured over the follow-up has been divided in five categories using quintiles of lung function gain in two years. The main spirometric end point variable of the effects under study was the slower lung function growth (SLFG) over two year period, which was defined whether or not the gain over two years was within the lowest quintile of the distribution of a given spirometric test.

Assessment of body growth (height velocity) was based on the measurements of the standing height of children in cm over two year period. Standing height is assumed to be the single most important determinant of pulmonary function growth and height velocity is a reliable index of the onset of puberty during adolescence. For the purpose of the statistical analysis, the children have been classified in three categories by their growth rate (1. the fast growth rate: 14 cm and more in two years; 2. medium growth rate: 10–13 cm; and 3. slow growth rate: 9 cm or less).

Table 1. Characterics of the study sample by the occurrence of asthma like symptoms over the follow-up (1995-97).

Variable		Asthma-like symptoms			
		No symptoms N=872	New symptoms N=45	Remission symptoms N=54	Continued symptoms N=30
Gender:					
boys		51.1%	48.9%	57.4%	63.3%
girls		48.9%	51.1%	42.6%	36.7%
Parental education:					
low		25.9%	31.1%	20.4%	33.3%
middle + high		74.1%	68.9%	79.6%	66.7%
1995					
Height (cm)	mean	133.58	134.67	135.15	135.07
	SE	0.20	0.90	0.83	0.90
Weight (kg)	mean	29.94	31.89	30.76	31.20
	SE	0.19	1.07	0.73	1.06
FVC (L)	mean	1.955	1.938	2.036	2.059
	SE	0.012	0.060	0.045	0.085
FEV_1 (L)	mean	1.791	1.762	1.830	1.851
	SE	0.011	0.052	0.041	0.071
$FEF_{25-75\%}$	mean	2.242	2.200	2.162	2.190
(L/sec)	SE	0.017	0.076	0.065	0.105
FEV_1/FVC (%)	mean	91.82	91.27	90.05	90.35
	SE	0.162	0.805	0.874	1.095
1997-95					
DHeight (cm)	mean	11.48	11.44	11.20	10.90
	SE	0.11	0.55	0.47	0.52
DWeight (kg)	mean	7.85	8.09	7.89	9.27
	SE	0.12	0.50	0.44	0.73
DFVC (L)	mean	0.503	0.523	0.439	0.438
	SE	0.010	0.044	0.035	0.061
$DFEV_1$ (L)	mean	0.416	0.414	0.349	0.302
	SE	0.009	0.041	0.033	0.049
$DFEF_{25-75\%}$	mean	0.467	0.413	0.420	0.287
(L/sec)	SE	0.015	0.063	0.060	0.070

As the first step in the analysis of data, we have carried out the univariate descriptive statistics of pulmonary function indices by categories of asthma symptoms and SLFG for each of the spirometric tests has been established. Subsequently, multivariate linear regression analysis has been used for choosing body variables being significant predictors of the pulmonary growth. Variables that were associated with pulmonary function in this analysis included baseline height and the baseline of a given pulmonary test, growth rate (difference in height between 1997 and 1995) and gender. In the second stage of the analysis, we used multivariate logistic regression (MLR) to calculate the odds ratio for the SLFG and asthma symptoms together with predictors of lung function growth and other potential confounders [18]. Descriptive and multivariate analysis were done with BMDP programs [19].

Table 2. ORs of SLFG for FVC, FEV_1 and $FEF_{25-75\%}$ by the categories of asthma-like symptoms (adjusted in multiple logistic model to gender, height and lung function at baseline survey, and body growth rate in the follow-up).

Predictors	SLFG (+) N	SLFG (–) N	Crude OR (95% CI)	Adjusted OR (95% CI)
FVC				
Without symptoms	168	704	1.00	1.00
New symptoms	9	36	1.05 (0.46–2.36)	1.25 (0.52–2.97)
Remitted symptoms	11	43	1.07 (0.51–2.21)	1.11 (0.51–2.21)
Continued symptoms	12	18	2.79 (1.24–6.24)	3.40 (1.32–8.77)
FEV_1				
Without symptoms	176	696	1.00	1.00
New symptoms	12	33	1.44 (0.69–2.96)	1.46 (1.02–2.10)
Remitted symptoms	16	38	1.67 (0.87–3.17)	2.06 (0.93–4.58)
Continued symptoms	12	18	2.64 (1.17–5.88)	3.46 (1.43–8.40)
$FEF_{25-75\%}$				
Without symptoms	172	700	1.00	1.00
New symptoms	13	32	1.65 (0.80–3.35)	2.03 (0.97–4.28)
Remitted symptoms	18	36	2.03 (1.08–3.80)	2.63 (1.38–4.99)
Continued symptoms	15	15	4.07 (1.84–8.98)	5.84 (2.53–13.5)

$SLFG_{FVC}(+) \leqslant 0.23$ L, $SLFG_{FEV1}(+) \leqslant 0.18$ L, $SLFG_{FEF25-75\%}(+)$ without lung function gain.

RESULTS

In the total study sample, there was 45 children with the new symptoms, 54 with symptoms remitted and 30 with continued symptoms (table 1). The children with new symptoms and with continued symptoms more frequently came from the families with lower parental education; the proportion of boys have been greater in those who had continued symptoms.

Mean crude spirometric gain (the difference 1997–1995) for FVC and FEV_1 over two-year follow up was smaller in children with continued or remitted symptoms when compared with children without symptoms or with the recent ones. Also the gain in $FEF_{25-75\%}$ was smaller in those subjects who reported continued symptoms. Interestingly, the children with continued symptoms had smaller gain in height but greater gain in weight over the follow-up period.

The slower lung function growth (SLFG) was found more often in children who presented the symp-

Table 3. ORs of the lung obstructive syndrome (FEV1/FVC⩽80% in 1997) in children by the occurrence of asthma-like symptoms over the follow-up.(Adjusted in the multiple logistic model to gender and parental education).

Predictors	FEV_1/FVC(%) ⩽80% N	>80% N	Crude OR (95% CI)	Adjusted OR (95% CI)
Without symptoms	29	843	1.00	1.00
New symptoms	4	41	2.84 (0.80-9.01)	2.99 (0.98-9.08)
Remitted symptoms	7	47	4.33 (1.63-11.0)	4.19 (1.71-10.3)
Continued symptoms	6	24	7.27 (2.45-20.6)	6.47 (2.38-17.5)

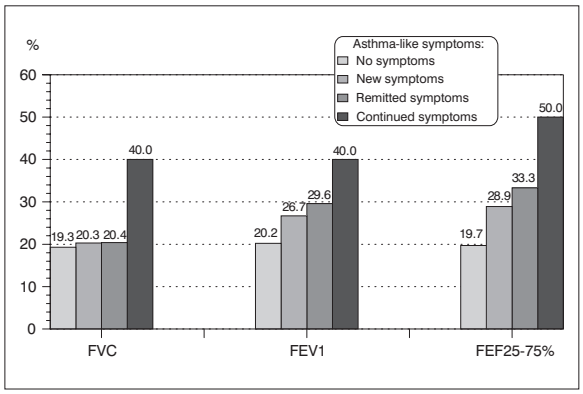

Figure 1. Prevalence of slow lung function growth for FVC, FEV_1 and $FEF_{25-75\%}$ by asthma-like symptoms.

toms. The odds ratios (OR) of SLFG(FVC), SLFG(FEV_1) and SLFG($FEF_{25-75\%}$) by the occurrence of asthma-like syndrome have been assessed using the multiple logistic regression model where the effects in terms of slower lung function growth have been adjusted to gender, baseline height, baseline lung function and height velocity of children over the follow-up (table 2).

Adjusted OR for SLFG(FVC) was significantly higher only in the children having the continued symptoms(OR=3.40; 95%CI: 1.32–8.77). There was a consistent trend of adjusted ORs for SLFG(FEV_1) with the category of symptoms, where OR was 1.46 (95%CI: 1.02 – 2.10) in children with recent new symptoms; 2.06 (95%CI: 0.93–4.58) in those with symptoms remitted, while 3.46 (95%CI: 1.43 – 8.40) in children who had persistent symptoms. The corresponding ORs for SLFG($FEF_{25-75\%}$) were 2.03 (95%CI: 0.97–4.28), 2.63 (95% CI: 1.38–4.99), and 5.84 (95%CI: 2.53–13.50).

The table 3 documents that the trend in ORs for obstructive syndrome (FEV_1/FVC%⩽80%) at the end of the survey (1997) by the category of asthmatic symptoms is very similar to that observed for FEV_1 and $FEF_{25-75\%}$. Figure 1 summarises the effect of asthmatic symptoms on the lung growth in the sample under study.

DISCUSSION

The study has shown lower lung function gain over the follow up in preadolescent children with asthmatic symptoms. The risk of the slower lung function growth (SLFG) in children did not result from the altered body growth since in addition to gender the effect was adjusted to potential confounders such as baseline lung function, baseline height and growth velocity over the follow-up.

The slower lung function growth has been associated in the strongest way with the persistent asthmatic symptoms. Children among whom the symptoms had remitted over the last two years showed significantly better FVC and FEV_1 gain than those with persistent symptoms. This may indicate a tendency for re-acceleration of lung function growth after remission of symptoms. However, the recovery process in terms of the lung function improvement probably has to take a longer time as children with symptoms remitted were still at the lower end of the $FEF_{25-75\%}$ population distribution for non-symptomatic children.

There are speculations on the nature of the slower lung function development in asthmatic children. There is a controversial hypothesis that the asthmatic children may loss elastic recoil of the lung [20,21]. However, some authors suggest that disorders of growth in children suffering from asthma are rather related with either increased resting energy expenditure or inadequate energy intake [22].

The results of this study is in agreement with the prospective study carried out by Borsboom et al. in the Dutch children aged 12.5 to 18 yr with or without a positive history of prepubertal respiratory symptoms [23]. The authors showed that adolescents with a positive history of prepubertal respiratory symptoms, even if they lose their symptoms, remain at a disadvantage with respect to their ventilatory function when they reach adulthood. Unfortunately, the authors did not specify the respiratory symptoms. Observations of Kelly et al. [24] are also in agreement with our study. They showed that lung function of young adults (at the age of 28 years) who had wheezing of variable frequency as children but ceased wheezing was es-

sentially normal, but lung function was increasingly abnormal in those who continued to wheeze. In the latter study it was evident that airways obstruction became more common as wheezing increased, however, the authors could find no evidence of decline in lung function related to bronchial reactivity.

It is difficult to explain the differential rate of regaining normal lung function growth in terms of $FEF_{25-75\%}$ after the remission of asthmatic symptoms. As most of asthmatic children are atopic, one can assume that in atopic children, despite the remission of symptoms, the bronchial inflammation process may be sustained over certain period of time. Clinical and cross-sectional studies confirmed the importance of atopy for lung function level. This was also confirmed by Sherill et al. [6] in a 6--year follow-up study of preadolescent children where atopy was associated with decreased the FEV_1/FVC ratio and appeared to be independent of clinical symptoms and airway responsiveness. In other studies, the degree of bronchial responsiveness correlated with the development of lung function [25]. However, neither bronchial responsiveness nor markers of bronchial inflammation were measured in our study.

The consistent association between degree of reversibility of asthma-like symptoms and lung function gain in preadolescent children confirmed the significance of the asthma-like symptoms in the natural history of ventilatory function. So it seems justified that even children with occasional and recent wheezing, should be classified as belonging to the asthmatic risk group with all implications both to the individuals and in terms of the quality of the epidemiological data used to establish the true prevalence of asthma. The observed slower lung function gain in preadolescence may have implications for the development of chronic lung disease later in adulthood and this has been suggested previously by many observations. The children with the slower lung function may eventually be more susceptible to environmental insults and be at an increased risk for the development of accelerated decline in FEV_1 later in life [26–28]. However, only the prolonged longitudinal measurements of lung function performed in subsequent years would show whether the airway function of the symptomatic children catch up lung growth and attain a level comparable with the general population.

CONCLUSIONS

1. The consistent association between reversibility of asthma-like symptoms and lung function gain in preadolescent children confirmed the clinical significance of the symptoms in the natural history of ventilatory function.

2. The observed slower lung function gain in preadolescence may have implications for the development of chronic lung disease later in adulthood. The children with the slower lung function may be more susceptible to environmental insults and be at an increased risk for the development of accelerated decline in FEV_1 later in life.

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