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SHORT COMMUNICATION

Gas trapping is associated with severe exacerbation in asthmatic children

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Summary
Background: Gas trapping suggesting small airway disease is observed in adult asthmatic suffering from severe asthma. The aim of the study was to assess whether gas trapping could be evidenced in asthmatic children with/without severe exacerbation and with/without symptoms during the past three months.
Methods and patients: Forced expiratory flows (FEV_1, FVC, $MEF_{25-75\%}$, $MEF_{50\%}$), plethysmographic lung volumes (TLC, FRC, RV) before and after bronchodilation (BD) were recorded in asthmatic children with documented airflow reversibility. Three groups were defined according to the presence during the last three months of 1) severe exacerbation (oral steroid: 3 consecutive days) 2) asthma symptoms without severe exacerbation and 3) without any symptom (GINA guidelines).
Results: 180 children (median 11.3 years, range 6.3–17.6, 57 girls) were included, 24 (13%) had at least one severe exacerbation, 58 (33%) had respiratory symptoms without severe exacerbation and 98 (54%) had no symptom during the past 3 months. Forced expiratory flows did not significantly differ in these three groups, while RV/TLC was significantly higher in the first group before and even after bronchodilation: before BD, 0.27 ± 0.07, 0.24 ± 0.05 and 0.23 ± 0.05, respectively ($p = 0.016$) and after BD, 0.25 ± 0.07, 0.21 ± 0.05, 0.21 ± 0.05, respectively ($p = 0.003$).

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Conclusion: In asthmatic children, gas trapping is associated with occurrence of a severe exacerbation during the last three months, suggesting a small airway disease that is not evidenced by forced expiratory flows.

Introduction

While studies have demonstrated that abnormalities of lung volumes (gas trapping) can be present in asymptomatic asthmatic children with normal spirometry,[1,2] systematic measurement of lung volumes is not recommended in current guidelines even in the more severe patients. Whether these abnormalities are associated with deleterious clinical or functional outcomes in children remains largely unknown, which may explain the absence of formal recommendation. Recently Sorkness and colleagues showed that severe asthma in adults is associated with lung hyperinflation[3] that deserves to be demonstrated in children since a normal lung function is considered as rule in childhood.[4] Overall, one may hypothesize that both uncontrolled symptoms and exacerbations may be associated with functional abnormalities. Consequently, the aim of our cross-sectional study was to assess whether asthma symptoms and/or severe exacerbation in the past three months were associated with functional abnormalities while the children were asymptomatic for one week at the time of assessment. To further evaluate whether the abnormalities are related to the persistence of increased bronchomotor tone and/or remodelling process, bronchodilator response was systematically tested.

Methods

All consecutive children suffering from asthma (diagnosis criteria of GINA guidelines: www.ginasthma.com) with a previously documented reversibility (>12% increase in FEV_1 or 50% decrease in sRaw) were studied in a period of disease stability (absence of any respiratory symptom over the last week) between December 1, 2008 and November 30, 2009. The study was approved by the Institutional Review Board of the French Language society for respiratory medicine — Société de Pneumologie de Langue Française, and children/parents gave their consent.

Due to the retrospective assessment of clinical events, the time interval to be chosen needed to allow accurate recall of symptoms and to be sufficient for severe exacerbation exposure. We chosen a three-month time-lag since this time interval is sufficient to isolate asthmatic patients with frequent exacerbations as suggested by Miller and colleagues.[5] Consequently, the following indices were recorded for the past three months: 1) duration of oral steroid treatment reported in the health record (a severe exacerbation was defined by an exacerbation requiring at least three days of systemic corticosteroid treatment), 2) number of days with symptoms (those defined in GINA guidelines for asthma control) assessed by parents, and 3) mean dose of ICS (given as beclomethasone equipotent daily dose as defined in GINA guidelines).

Bronchodilator treatment was withheld for 12 h before pulmonary function tests. Spirometry and body plethysmography (MasterScreen Body, Jaeger, Würtzburg, Germany) were performed as previously described,[1,6] according to international recommendations. A systematic assessment of the bronchodilator response (salbutamol, 400 μg) was performed. Special attention was ensured to obtained maximal expiratory effort for residual volume (RV) measurement. Reference values were those recommended by Stocks and Quanjer.[7]

We calculated that over one year the inclusion of 180 children would ensure a severe exacerbation group >20 children (540 months of follow-up with an exacerbation rate of 0.50/patient/year). Variables were expressed as mean ± SD, except when stated. The statistical tests used are detailed in the results. A two-tailed *P* value below 0.05 was considered statistically significant. Statistical analyses were performed using Statview® and MedCalc® softwares.

Results

Twenty-four children (13%) experienced at least one severe exacerbation, 58 (32%) had only mild respiratory symptoms and 98 (54%) had no respiratory symptom during the past three months. Their clinical and functional characteristics are described in Table 1. No difference in gender, age and atopic status was found between these three groups, while children with a severe exacerbation differed from the two other groups by a higher ICS treatment dose. Their pulmonary function tests show that gas trapping is evidenced in the children who experienced a severe exacerbation. Using receiver—operator characteristic curve analysis, a $(RV/TLC)_{Pre\text{-}BD}$ greater than 0.30 was the best threshold to identify these children ($p = 0.022$, AUC 0.65; 95% CI [0.57—0.72]), with a high specificity (92%) but a low sensitivity (38%).

Discussion

The main result of our study is the demonstration that a severe exacerbation within the previous three months is associated with subsequent gas trapping suggesting a small airway disease that is not evidenced by forced expiratory flows in asthmatic children. Our study emphasizes that lung volume measurement is probably a useful tool in asthmatic children because it has become increasingly clear that children at all levels of asthma severity can have relatively unimpaired FEV_1 values when clinically stable.[4] It has to be stated that lung volume abnormalities evidenced (isolated increase in residual volume) are mild, but the increase in RV in obstruction is deemed to be a marker of airway closure as stated in the ATS/ERS Task Force guidelines.[8] Lung volume assessment is not a routine test in several

Table 1 Characteristics of the three groups of asthmatic children.

	Severe exacerbation $n = 24$	Mild symptoms $n = 58$	No symptoms $n = 98$	P values[a]
Gender, girls/boys	10/14	20/38	27/71	0.35
Age, years: median [range]	10.8 [6.9–16.5]	11.7 [7.3–17.1]	11.6 [6.3–17.6]	0.18
Height, cm	143 ± 13	150 ± 14	149 ± 14	0.09
Weight, kg	38 ± 12	44 ± 15	42 ± 13	0.22
Skin prick tests				0.96
One positive test, *n*	4	12	24	
More than one, *n*	17	38	58	
Negative, *n*	2	6	11	
Non available, *n*	1	2	5	
Treatment				
ICS GINA categories, high/moderate/low/no ICS	7/8/5/4	6/14/24/14	10/24/26/38	**0.026**
ICS dose − BED, (μg/d)	357 ± 256	248 ± 271	202 ± 222	**0.020**
LABA, *n*	20	40	59	0.20
LRA, *n*	0	1	3	0.63

	Severe exacerbation $n = 24$		Mild symptoms $n = 58$		No symptoms $n = 98$		P values[a]	
	Pre-BD	Post-BD	Pre-BD	Post-BD	Pre-BD	Post-BD	Pre-BD	Post-BD
Spirometry								
FEV_1 (% pred) Zapletal	94 ± 15	105 ± 13	96 ± 12	108 ± 10	98 ± 15	107 ± 12	0.53	0.59
FEV_1 (% pred) Quanjer	90 ± 15	100 ± 12	92 ± 11	103 ± 11	93 ± 11	103 ± 11	0.46	0.47
FEV_1/VC (%)	77 ± 9	84 ± 8	75 ± 7	82 ± 6	76 ± 7	83 ± 7	0.54	0.63
FVC (% pred) Zapletal	103 ± 15	105 ± 13	106 ± 13	108 ± 10	106 ± 12	108 ± 13	0.58	0.59
FVC (% pred) Quanjer	101 ± 14	103 ± 13	105 ± 13	107 ± 11	104 ± 11	106 ± 11	0.38	0.28
$FEF_{25-75\%}$ (% pred) Zapletal	71 ± 23	91 ± 26	68 ± 18	88 ± 16	69 ± 16	89 ± 18	0.77	0.75
$FEF_{50\%}$ (% pred) Zapletal	69 ± 21	92 ± 24	68 ± 17	89 ± 15	69 ± 15	88 ± 17	0.91	0.70
Plethysmography								
sRaw, kPa s	0.96 ± 0.24	0.61 ± 0.15	1.09 ± 0.32	0.63 ± 0.14	1.03 ± 0.25	0.63 ± 0.15	0.13	0.81
TLC, % pred	105 ± 15	103 ± 14	106 ± 10	104 ± 10	105 ± 10	103 ± 10	0.84	0.14
FRC, % pred	102 ± 19	98 ± 19	104 ± 18	100 ± 15	105 ± 14	102 ± 15	0.63	0.96
RV, % pred	116 ± 42	106 ± 42	105 ± 31	93 ± 20	101 ± 25	91 ± 23	0.076	**0.044**
FRC/TLC	0.47 ± 0.06	0.47 ± 0.06	0.48 ± 0.06	0.47 ± 0.05	0.49 ± 0.05	0.48 ± 0.06	0.22	0.37
RV/TLC	0.27 ± 0.07	0.25 ± 0.07	0.24 ± 0.06	0.21 ± 0.05	0.23 ± 0.05	0.21 ± 0.05	**0.016**	**0.003**

BD denotes bronchodilator; ICS denotes inhaled corticosteroid; LABA denotes Long-acting beta-agonist; LRA denotes leukotriene receptor antagonist; BED denotes beclomethasone equipotent dose.
Results are expressed as mean ± SD, except when stated.
P values in bold are statistically significant.
[a] ANOVA or chi-2 test between the three groups (tested before [pre-BD] and after [post-BD] bronchodilation).

centers. For instance, Sorkness and colleagues described a large sample of severe asthmatic patients, but only 84/287 had lung volume measurements.[3] We and others previously demonstrated that gas trapping can be demonstrated in asthmatic children with normal forced expiratory flows.[1,2] In this study, we further show that gas trapping is more pronounced in children with a history of severe exacerbation in the past three months (high specificity but low sensitivity for the RV/TLC ratio). The practical consequence is that when a child exhibits an RV/TLC ratio before bronchodilation above 0.30, it can confidently be explained by an exacerbation in the previous three months.

Our study has inherent limitations due to its cross-sectional design and due to the retrospective assessment of clinical events. Weng and Levison studied a group of asthmatic children from acute attack to symptom free status and noted that abnormalities of static lung volumes were common in the interval phase,[9] consequently we cannot infer from our results that the observed abnormalities will persist. But one may hypothesize that the repetition of severe exacerbations will lead to a definitive loss of function.[10]

In conclusion, gas trapping is associated with occurrence of a severe exacerbation during the last three months in asthmatic children, suggesting a small airway disease that is not evidenced by forced expiratory flows.

Conflict of interest

The authors declare no conflict of interest.

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