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Gender-Dependence of Airflow Limitation and Air Trapping in Children with Severe Asthma

Ronald L. Sorkness, Ph.D.,

University of Wisconsin School of Pharmacy, and Departments of Medicine and Pediatrics, Madison, Wisconsin

W. Gerald Teague, M.D.,

University of Virginia Department of Pediatrics, Charlottesville, Virginia

Madhuri Penugonda, M.D., and

Emory University Department of Pediatrics, Atlanta, Georgia

Anne M. Fitzpatrick, Ph.D.*

Emory University Department of Pediatrics, Atlanta, Georgia

For the National Institutes of Health, National Heart, Lung and Blood Institute's Severe Asthma Research Program (SARP)

SUMMARY

In this cross-sectional evaluation of 77 severe and 71 non-severe asthmatics ages 6–17, boys, unlike girls with severe asthma, exhibited adult-like patterns of air-trapping and post-bronchodilator airflow limitation, apparently coincident with the onset of the severe asthma phenotype.

Keywords

refractory asthma; difficult asthma; lung development

To the Editor

The National Heart Lung and Blood Institute's Severe Asthma Research Program (SARP) database is compiled from 10 centers with studies involving subjects with severe asthma¹, including the pediatric cohort at Emory University. A SARP study of airway physiology in adults with severe asthma found that, compared with non-severe asthmatics, the severe group exhibited marked air-trapping relative to the level of airflow limitation, and greater persistence of airflow limitation after maximal bronchodilation (PstBD).² Male gender and age were independent predictors of PstBD airflow limitation.² Previous studies indicate that the duration of asthma may be an important determinant of the severe asthma phenotype seen in adults^{3,4}, although deterioration of PstBD spirometry may occur at a younger age, especially in boys.⁵ In an earlier publication describing the first 75 children evaluated in SARP, we reported that children with severe asthma had significantly greater air-trapping and airflow limitation during bronchodilator hold, and more airflow limitation PstBD, indicating that at least some of the <18 year olds had patterns of airway physiology similar to adults with severe asthma.⁶ However that report was based on relatively few children with

*Please address correspondence to: Dr. Anne M. Fitzpatrick, Emory University Department of Pediatrics, 2015 Uppergate Drive, Atlanta, Georgia 30322, anne.fitzpatrick@emory.edu, Phone: 404-727-9112, Fax: 404-712-0920.

severe asthma and subsequently the SARP characterization procedures have been modified to provide a more detailed analysis of airway physiology. We therefore hypothesized that the impairment in lung function we have seen in adults with severe asthma might be identified in children, and related to duration of asthma, age, and gender.

The Emory SARP cohort currently includes data from 77 severe and 71 non-severe asthmatics ages 6–17 years. Characterization of airway physiology included baseline spirometry and plethysmographic lung volumes after a bronchodilator withhold, and again after maximal bronchodilation with up to 8 puffs of albuterol. Data were analyzed using repeated measures and single measure 2-way ANOVA models. The RV/TLC %predicted was log-transformed. Posthoc pairwise comparisons of interactive effects were done with the Fischer's Least Significant Difference test. Inclusive repeated measures ANOVA containing categorical variables for sex and asthma severity group revealed significant ($P<0.007$) group-by-sex interactions for both airflow limitation and air trapping, necessitating separation of the repeated measures analyses by subgroups, i.e., severity group effects within each gender and gender effects within each severity group. Figure 1 summarizes the pre/post-bronchodilator data for each subgroup.

Airflow limitation

Subjects in the non-severe asthma group had modest airflow limitation at baseline, with only 19% having FEV₁/FVC below the lower limit of normal ($<89\%$ predicted for boys and $<90\%$ predicted for girls⁷), and no differences between sexes ($P>0.4$; Fig 1A). The severe asthma group exhibited greater airflow limitation than the non-severe group ($P<0.0001$), with 54% of the girls and 73% of the boys having FEV₁/FVC %predicted below normal, and the boys significantly more obstructed than the girls ($P=0.017$). Airflow limitation improved after maximal bronchodilation in both severity groups, but the severe asthma subjects had a larger increase in FEV₁/FVC %predicted than did non-severes for both boys ($P<0.003$) and girls ($P=0.023$). The non-severes and the girls with severe asthma exhibited reversal of airflow limitation into the normal range (Fig. 1A), and there was no significant difference among these subgroups PstBD ($P>0.08$). However, the boys with severe asthma reversed incompletely, with a group median of 91% predicted, 46% of the group remaining below normal, and significantly different from the other subgroups ($P\leq 0.0001$; Fig. 1A).

Air-trapping was assessed with the plethysmographic RV/TLC ratio %predicted⁸ (Fig. 1B). There was no elevation in RV/TLC in the subjects with non-severe asthma, with group medians $<100\%$ predicted, no difference between sexes ($P>0.5$), and no significant change PstBD ($P>0.8$; Fig. 1B). The severe asthma group exhibited air-trapping compared with the non-severe group ($P<0.0001$), and the boys had significantly more air-trapping than the girls in the severe group ($P=0.023$; Fig 1B). Air-trapping improved in both sexes of the severe group after maximal bronchodilation ($P<0.0001$). After bronchodilation the girls with severe asthma had no residual air-trapping, having PstBD RV/TLC %predicted values similar to those of the non-severe subjects ($P>0.5$). In contrast, the boys with severe asthma had incomplete reversal of air-trapping, with PstBD RV/TLC %predicted persistently higher than those of the other subgroups ($P<0.005$; Fig 1B). Thus, boys with severe asthma had greater baseline airflow limitation and air-trapping than girls with severe asthma, and, unlike the girls, had incomplete reversal PstBD, indicating that the adult patterns of severe asthma are present in male children, while only partially developed in female children.

Age and other factors

The patterns of airflow limitation and air-trapping related to severity group and gender were apparent in each of the age tertiles of the cohort, and there were no significant main effects or interactive effects of age in the multivariate models ($P>0.2$). Multivariate models also

were employed to assess whether reported age of asthma onset, reported asthma duration, race, positive skin tests, blood eosinophils, serum IgE, or exhaled nitric oxide were associated with air-trapping or persistent airflow limitation, but none of these variables exhibited significant effects independent of those associated with male sex and the severe asthma classification in the models.

In summary, air-trapping and persistent airflow limitation-- characteristics of severe asthma in adults-- are present in boys with severe asthma. This pattern of disturbed airway physiology was identified in early school age in boys and surprisingly was not correlated with duration of asthma. In contrast, girls with severe asthma exhibit some air-trapping and airflow limitation during bronchodilator abstinence, but at a lesser magnitude than seen in boys, and generally reversible with bronchodilation.

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Abbreviations

ANOVA	analysis of variance using the general linear hypothesis model
FEV₁	forced expiratory volume in one second
FVC	forced vital capacity
FEV₁/FVC %predicted	the FEV ₁ /FVC ratio as a percent of the predicted value
RV	residual lung volume after maximal expiration
TLC	total lung capacity
RV/TLC %predicted	the RV/TLC ratio as a percent of the predicted value
PstBD	post maximal bronchodilation with albuterol
SARP	Severe Asthma Research Program

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Figure 1.

Airflow limitation (A; measured as FEV₁/FVC %Predicted), and air-trapping (B; measured as plethysmographic RV/TLC %Predicted) in male and female children with severe and non-severe asthma classifications, at medication-hold baseline (BSLN) and post-bronchodilation with albuterol (PstBD). Significant differences: ***vs baseline; **vs respective non-severe subgroup; *vs respective female, severe asthma subgroup. Boxes indicate median and interquartile range for each subgroup.