

Problematic severe asthma: A proposed approach to identifying children who are severely resistant to therapy

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Children with problematic severe asthma (PA) are either difficult to treat because of the presence of aggravating factors or else severely resistant to therapy. We investigated a cohort of school-aged children with PA and compared these children to age-matched peers with controlled persistent asthma (CA). The aims were to characterize features of children suffering from PA and identify children who were severely resistant to therapy. In this cross-sectional, multicenter comparison of children with different manifestations of persistent asthma, PA was defined as insufficient asthma control despite level 4 treatment, according to GINA. The protocol included questionnaires, spirometry, methacholine provocation, measurement of fraction of nitric oxide in exhaled (FE_{NO}) and nasal air, blood sampling for inflammatory biomarkers and atopy, and computerized tomography of sinuses and lungs (in the PA group only). Of the 54 children with PA, 61% had therapy-resistant asthma, with the remaining being difficult to treat because of identified aggravating factors. Children with PA more often had parents with asthma ($p = 0.003$), came from families with a lower socioeconomic status ($p = 0.01$), were less physically active ($p = 0.04$), and had more comorbidity with rhinoconjunctivitis ($p = 0.01$) than did the 39 children with CA. The former also exhibited lower FEV_1 values ($p = 0.02$) and increased bronchial hyper-responsiveness ($p = 0.01$), but there were no differences in atopy ($p = 0.81$) or FE_{NO} ($p = 0.16$). A non-invasive protocol, involving a standardized and detailed clinical characterization, revealed distinguishing features of children with PA and enabled the identification of children with therapy-resistant asthma.

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Abbreviations: BHR, Bronchial hyper-responsiveness; BMI, Body mass index; CA, Controlled persistent asthma; CAMP, Childhood Asthma Management Program; CI, Confidence interval; CT, Computed tomography; $DRS_{methacholine}$, Slope of the dose-response curve for provocation with methacholine; EG., *exempli gratia* (for example); EPX, Eosinophilic protein x; Et.al, et alii (and others); FEF_{50} , Forced expiratory flow at 50% of forced vital capacity; FE_{NO} , Fraction of nitric oxide in exhaled air; FEV_1 , Forced expiratory volume during one second; FRC, Functional residual capacity; FVC, Forced vital capacity; GA²LEN, Global Allergy and Asthma European Network; GERD, Gastro esophageal reflux disease; GINA, Global initiative for asthma; HCU, Health care utilization; HRCT, High-resolution computerized tomography; I.E, Id est (that is); ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; IQR, Inter-quartile range; kU_A/l, Kilounits of antibody per liter; LABA, Long-acting β -2 agonist; LTRA, Leukotriene receptor antagonist; nNO, Fraction of nitric oxide in nasal air; OR, Odds ratio; PA, Problematic severe asthma; PD20, The dose of methacholine producing a 20% reduction in FEV_1 ; PPB, Parts per billion; RV, Residual volume; SABA, Short acting β -2 agonist; SD, Standard deviation; TLC, Total lung capacity.

Introduction

A GA²LEN task force, the Problematic Severe Asthma in Childhood Initiative, has proposed the term 'problematic severe asthma' (PA) to designate children who suffer from chronic symptoms and/or severe exacerbations despite treatment with several drugs (1, 2). The group of children with PA is heterogeneous with respect to contributory factors, airway inflammation (3), pulmonary function (4), and clinical symptoms (5). These patients require extensive health care (5), experience a reduced quality of life, and represent a clinical challenge to the pediatrician. Previous investigations on such patients, both adults (6) and children (5, 7), have varied with regard to definitions, geographic and ethnic backgrounds, criteria for inclusion, and study design.

The recently introduced term 'problematic severe asthma' (PA) makes a distinction between two sub-groups of patients, i.e., children who are difficult to treat because of unidentified exacerbating factors (e.g., allergens or environmental hazards, comorbidities, psychological and social issues, and/or poor adherence) and those with no identifiable aggravating factors but, nonetheless, severe resistance to asthma therapy. This distinction is of considerable clinical significance, because the first of these groups should not be subjected to invasive diagnostic procedures or therapy beyond what is recommended by guidelines before the exacerbating factor(s) has been attended to; whereas for children with truly severe asthma, invasive procedures and application of novel treatment strategies may be justified.

Accordingly, establishing a standardized clinical protocol for investigating children with PA is certainly needed, but will require international multicenter trials. Such a protocol should include identification and treatment of comorbidities; a survey of triggering factors and of ongoing exposure to allergens and other detrimental environmental factors; assessment of adherence and response to prescribed treatment; health care utilization (HCU); and an overall evaluation of current asthma control (8). Furthermore, the protocol should include objective assessments of the different features of asthma pathophysiology; lung function, bronchial hyper-responsiveness, airway inflammation, and the atopic phenotype.

In the present observational, cross-sectional study, we applied a standardized and extensive clinical protocol involving the parameters discussed earlier. We provided a detailed and individualized characterization of a cohort of

school-aged children with PA and compared these children to age-matched peers with controlled persistent asthma (CA).

The objectives were to identify distinguishing features of children suffering from PA and to differentiate between children who were difficult to treat and those who were severely resistant to therapy, according to the newly proposed definition of PA (2).

Methods

Design

In this multicenter, cross-sectional investigation, children 6–18 yr of age with PA were compared to age-matched peers with CA. These two conditions were defined in accordance with the GINA guidelines (9), which take into account the severity of the underlying disease, as indicated by the need for treatment and degree of symptom control achieved (10). Children with vocal cord dysfunction, cystic fibrosis, immunodeficiencies, serious neurological disease or who had undergone major lung surgery or been born prematurely (at < 36 wk of gestational age) were excluded. In addition, our subjects were required to have been free from airway infections or exacerbation of their asthma during the 2-wk period prior to examination. Information was collected at each patient's regular clinic or at our own research clinic in connection with two or three visits during the period of January 2007–February 2009. Written informed consent was obtained from all participants, and this study was pre-approved by our regional board of ethics.

Subjects

Allergists working at 27 pediatric clinics throughout Sweden were invited to refer children with PA and age-matched peers (± 12 months) with CA for this investigation. Fifteen of these clinics (five at university hospitals and 10 at general hospitals) from all regions of the country responded. In addition, journal charts from four clinics were systematically reviewed by one of the authors (BN) to identify children with CA. The children identified and referred in this manner were then invited by mail, telephone, or verbally in connection with a visit to their doctors to participate and, following reassessment of their medical histories, medication and adherence to prescribed treatment, final selection of the participants was performed according to the criteria documented in Table 1. The children

Table 1. Criteria for inclusion of children suffering from problematic severe asthma (PA) and controlled persistent asthma (CA)

Problematic severe asthma (PA)	Controlled persistent asthma (CA)
Major criteria (all required) A diagnosis of asthma by a pediatric allergist Daily high-dose administration of ICS (≥ 800 μg budesonide or ≥ 400 μg fluticasone/mometasone per day) in combination with LABA and/or LTRA* Minor criteria observed within the preceding 12-month period (minimum of at least one required) - at least one emergency hospitalization - at least two emergency out-patient visits - at least one oral treatment with corticosteroid - at least twelve exacerbations of asthmatic symptoms per year or symptoms present continuously for at least 3 months - symptoms that limited daily activities (including sport or leisure activities) more than twice a week for at least three consecutive months - nocturnal symptoms more than twice a week for at least three consecutive months	Major criteria (all required) A diagnosis of asthma by a pediatric allergist Daily low- to medium-dose administration of ICS (≥ 100 to ≤ 400 μg budesonide or ≥ 50 to ≤ 200 μg fluticasone per day). Use of either LABA or LTRA was acceptable Minor criteria observed within the preceding 12-month period (all required) - no hospitalization - no emergency out-patient visits - no oral corticosteroid treatment - less than five exacerbations of symptoms† - occasional symptoms related to strenuous exercise only, otherwise no symptoms - no nocturnal symptoms

ICS, inhaled corticosteroid; LABA, long-acting β -2 agonist; LTRA, leukotriene receptor antagonist.

*High-dose administration of ICS for at least 6 months during the preceding year; previous use of LABA or LTRA only was considered acceptable if this treatment was discontinued because of inefficacy or the occurrence of unacceptable side-effects.

†An increase in the ICS dosage for a maximum of 2 wk in connection with asthma exacerbations was considered acceptable.

who admitted that they could miss more than three doses of prescribed medication per week were considered ineligible for inclusion.

Procedures

A mobile team consisting of two of the authors (JK and BN) visited the participating clinics and conducted the interviews and the majority of the procedures at site, utilizing brought equipment, to ensure standardized collection of biologic samples and data.

Questionnaires and clinical examination

The children and their parents were interviewed by two of the authors (JK and BN) using a standardized questionnaire, which was a modified version of the one employed in the Environmental and Childhood Asthma Study (11). The questionnaire includes enquiries regarding demographic data; family history; indoor environment; exposure to tobacco smoke, pets, and outdoor pollution; level of physical activity; symptoms or previous diagnosis of rhinoconjunctivitis (sneezing, congestion, secretions, itchiness, seasonal variation) and/or gastroesophageal reflux disease (GERD) (heartburn, regurgitation, upper abdominal pain); occurrence of atopic disease; anaphylactic reactions; use of asthma medication; adherence to medication (evaluated with a three-point scale ranging from missing on the average < 1 to missing > 3 doses of prescribed medications per week); asthmatic

symptoms and their exacerbations (8); triggering factors; and utilization of health care services. One of the investigators (BN) observed the ability of each child to use the inhaler properly. The percentiles of age- and sex-adjusted body mass indices (BMI) were calculated utilizing published algorithms (12).

Nitric oxide

Employing a NIOX™ apparatus (Aerocrine AB, Solna, Sweden), the fraction of exhaled nitric oxide (FE_{NO}) was measured prior to spirometry, at an exhalation flow rate of 50 ml/s, in accordance with international guidelines (13). Using nasal air samples obtained during breath-holding following maximal inhalation, nasal NO (nNO) was determined with this same apparatus (14). A nNO value greater than 105 ppb was considered indicative of the absence of primary ciliary dyskinesia (15).

Pulmonary function and assessment of bronchial hyper-responsiveness

Treatment with short-acting (SABA) and/or long-acting (LABA) β -2 agonists and/or leukotriene antagonists (LTRA) was withheld for 8, 24, and 72 h, respectively, prior to measurement of baseline pulmonary function and provocation with methacholine. Spirometry was performed with a Vitalograph® 2120 (Vitalograph®, Ennis, Ireland), in accordance with published recommendations (16) and using the reference values

reported by Polgar (17) (Table 3). Bronchial hyper-responsiveness (BHR) to a challenge with methacholine was assessed utilizing a Spira nebuliser (Spira Respiratory Care Centre, Hämeenlinna, Finland) (18). The dose of methacholine causing a 20% reduction in FEV₁ (PD₂₀) (19) and the slope of the dose-response curve ($DRS_{\text{methacholine}}$) were calculated (20). Nebulised salbutamol (0.2 mg/kg, maximally 5 mg) was administered following methacholine provocation and FEV₁ recorded 15 min later. Static lung volumes were determined at each local hospital and expressed as percentages of the locally applied reference values.

Analyses in blood and urine

Following application of local anesthesia (EMLA cream, Astra Zeneca, Sweden), samples of venous blood were collected and the white blood cells and C-reactive protein (CRP) examined. In addition, the levels of immunoglobulin E (IgE) antibodies directed specifically against the Phadiatop[®] mixture of common inhaled allergens (birch, timothy, mugwort, cat, dog, horse, and mold (*Cladosporium herbarum*)); against house dust mite (*Dermatophagoides pteronyssinus*); and against food allergens (fx5[®] = cow's milk, egg white, soy bean, peanut, cod fish, and wheat) (ImmunoCAP System[™], Phadia AB, Uppsala, Sweden) were determined. Sera that demonstrated a positive reaction to Phadiatop[®] or fx5[®] (defined as a level of IgE antibodies ≥ 0.35 kU_A/l) were analyzed further for IgE antibodies toward the individual allergens present in these mixtures. Atopy was defined as a level of antibodies toward Phadiatop[®] and/or fx 5[®] ≥ 0.7 kU_A/l. Eosinophilic protein X (EPX) in morning urine was analyzed with the EDN ELISA kit (Medical & Biological Laboratories Co., Naka-Ku Nagoya, Japan), for which the lowest level of detection is 0.62 ng/ml, and expressed as nanogram EPX per millimole urine creatinine.

CT scanning of sinuses and lungs

To exclude differential diagnoses or confirm comorbidities, children suffering from PA underwent CT of their nasal sinuses and lungs at their local hospitals. These investigations were performed within 3 months after inclusion in the study and all images were evaluated by the same radiologist (ML). Sinus CT scans were scored and presented according to the Lund-MacKay system (21, 22). The lungs were examined with high-resolution CT (HRCT) using a standardized protocol (23), and the number of children with a

significant differential diagnosis detected in this manner is indicated. Additional details concerning this examination will be described in a subsequent paper.

Statistical analyses

All information obtained was recorded on a specially constructed, computerized form for subsequent analysis with the Statistical Package for Social Sciences version 16.0 (SPSS, Chicago, IL, USA). The values are presented as means and standard deviations or minimal and maximal values (min-max) for continuous data and as medians and inter-quartile ranges (IQR) for data not demonstrating a normal distribution. Categorical data are presented as percentages. For all comparisons, a two-tailed probability of ≤ 0.05 was considered statistically significant. Groups of variables that exhibited a normal distribution were compared utilizing Student's t-test, while for skewed variables the Mann-Whitney's test was used. For associations between two categorical variables a chi-square test was applied. Correlations were assessed employing the Spearman's test. Binary logistic regression analyses (Tables 4 and 5) were conducted to further analyze applicable categorical variables which demonstrated significant differences between PA and CA in the univariate analysis (Table 2). Controlled persistent asthma or PA were used as the dichotomous dependent variable, CA was assigned a value of 0 and PA was assigned a value of 1, and odds ratios (OR) were estimated along with 95% confidence intervals (95% CI). Adjustments were made for possible confounding factors; age, gender, and ethnicity (model A) and in model B, the variables that came out with a significant result in model A were analyzed together. The history and trigger score (the sum of scores of the individual variables included in model A, each of which was assigned a value of 0 = no or 1 = yes) were calculated to integrate information provided by the different variables concerning each patient's history. Regression analyses of history score and trigger score were performed to assess the OR associated to PA or CA with every stepwise increase in each of these scores. Furthermore, an exploratory univariate regression analysis of applicable categorical variables in Table 6 was carried out to calculate OR associated to different subgroups of children with PA. Children classified as severely resistant to therapy (assigned a value of 0) or children classified as difficult to treat (assigned a value of 1) were used as the dichotomous dependent variable.

Features of problematic severe asthma

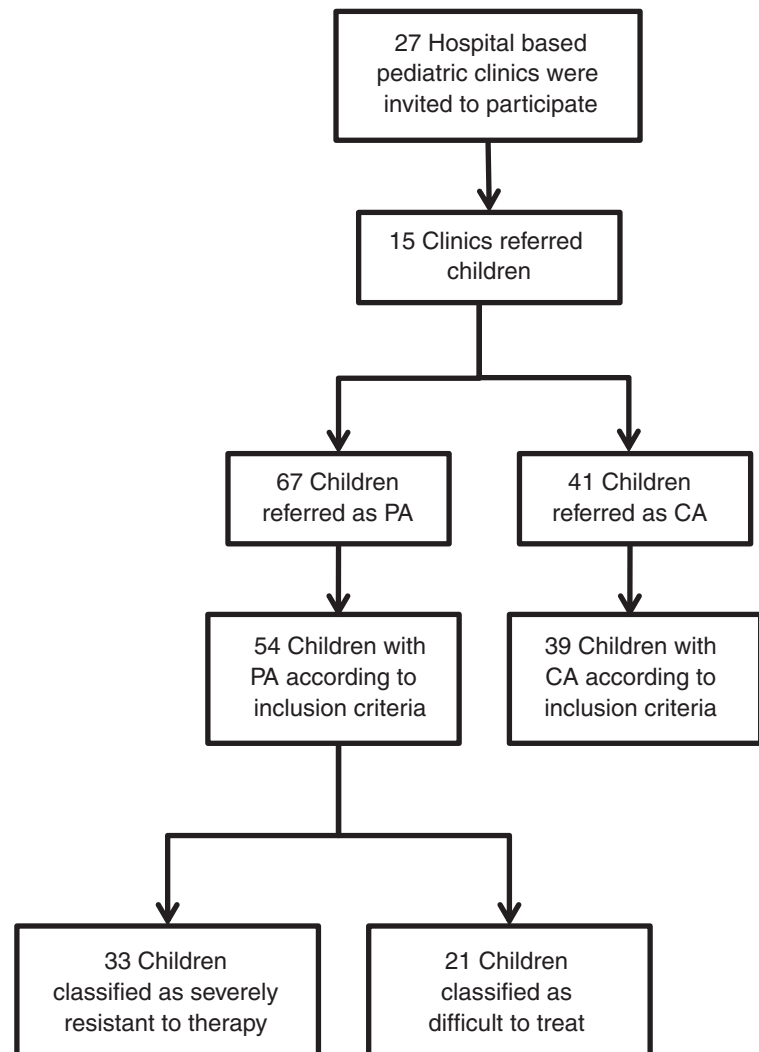


Fig. 1. Flow of patients from referral to final classification. PA, problematic severe asthma; CA, controlled persistent asthma.

Results

Of the 67 children with suspected PA, six did not fulfill any of the minor criteria for inclusion. Three others born prematurely, one with a diagnosis of immunodeficiency, and another who had undergone major pulmonary surgery were also excluded. Of the 56 remaining children, two withdrew after inclusion, leaving a total of 54 subjects from 15 pediatric clinics all over Sweden. Of the 41 age-matched children with CA referred for comparison, two were excluded because of poor asthma control, leaving 39 subjects in this group. Most of these children (i.e., 25 of those with PA and 31 with CA) came from the Stockholm region. A flow chart is provided in Fig. 1. Children with PA and CA were similar with regard to age, gender distribution, and BMI, and the majority of children in both groups were Caucasians (Table 2). In line with the inclusion criteria, children with PA were prescribed more inhaled corticosteroids (median

800 vs. 320 μ g budesonide equivalents daily) and oral corticosteroids (median 2 vs. 0 bursts per year). Furthermore, 80% of children with PA were taking three controller medications (Inhaled corticosteroid (ICS), LABA, LTRA) and 79% required treatment with SABA more than twice weekly. By comparison, 65% of the children with CA were taking two controller medications.

Characteristic features of children with PA compared to children with CA

Patient history, comorbidities, and adherence. Demographical and clinical characteristics of children with PA, together with a univariate comparison to children with CA are provided in Table 2. Children with PA more frequently had parents with asthma ($p = 0.003$) and without formal education beyond high school ($p = 0.01$) and were also less physically active ($p = 0.04$) than those with CA (Table 2).

Table 2. Detailed clinical assessment of children with problematic severe asthma (PA) and controlled persistent asthma (CA)

Parameter	PA	CA	p-value
Number of patients	54	39	
Demographic features			
Mean age, years (s.d.)	13.1 (3.0)	13.8 (2.9)	0.28
Females, %	39	41	0.84
Body mass index, mean percentile (s.d.)	63 (28)	55 (29)	0.15
Both parents Caucasians, %	83	92	0.20
Parental income 3 or less on a 4-point scale, %	89	69	0.03
Parents without education beyond high school, %	46	19	0.01
At least one parent with asthma, %	64	33	0.003
Clinical characteristics, health care utilization, and triggering factors			
Median age at the time of diagnosis with asthma, years (IQR)	2 (1–4)	3.5 (1–6)	0.12
Physically active >5 h/wk, %	28	49	0.04
Two or more emergency out-patient visits during the past year, %	44	0	n.a.
Median number of scheduled doctor appointments/year	3	1	< 0.001
Hospitalized during the preceding 12-month period, %	22	0	n.a.
Median number of lifetime hospital admissions for asthma	2	0	n.a.
Symptoms triggered by physical activity, %	85	85	0.94
Symptoms triggered by viral airway infection, %	93	77	0.03
Symptoms triggered by birch–grass pollen, %	74	49	0.02
Symptoms triggered by animal dander, %	65	63	0.88
Symptoms triggered by food, %	33	23	0.28
Symptoms triggered by fog/humid air, %	56	21	0.001
Symptoms triggered by cold air, %	61	26	0.001
Symptoms triggered by tobacco smoke, %	51	29	0.04
Symptoms triggered by perceivable odors, %	43	34	0.42
Exposures and comorbidities			
At least one family member smokes, %	40	21	0.05
Exposure to heavy traffic, %	15	31	0.07
Dampness in the home, %	22	8	0.06
Pets at home, %	17	13	0.61
Rhinoconjunctivitis, %	89	67	0.01
Atopic eczema, %	82	69	0.17
Food allergy, %	70	62	0.37
History of anaphylactic reaction, %	28	39	0.28
Gastroesophageal reflux, n	3	0	n.s.

n.a.: Statistical comparison not relevant because the observed differences reflect the inclusion criteria.

s.d., standard deviation; IQR, inter-quartile range; n.s: not significant.

For the 48 children who underwent a sinus CT, the median Lund–MacKay score was two, with nine children demonstrating a score > 5. No significant correlation between these scores and symptoms of rhinoconjunctivitis was observed. The HRCT of the lungs conducted on 50 children with PA did not reveal any relevant differential diagnoses. The nNo values obtained for 77 patients, 46 of whom had PA, were all above 115 ppb.

With respect to adherence, 59% and 44% of those with PA and CA, respectively, reported that they missed on the average less than one dose of controller medication per week ($p = 0.14$) and 39% vs. 51% reported that they missed 1–3 doses per week ($p = 0.24$).

Pulmonary function and bronchial hyper-responsiveness. Spirometry and provocation with methacholine revealed that the children with PA

exhibited lower FEV₁ ($p = 0.02$), FEF₅₀ ($p = 0.002$) and FEV₁/FVC values ($p < 0.001$), and more pronounced BHR ($p = 0.01$) than those with CA (Table 3).

Inflammatory biomarkers and assessment of allergic sensitization. The white blood cell counts and CRP, EPX, and FE_{NO} values also documented in Table 3 show that the children with PA had elevated numbers of circulating neutrophilic ($p = 0.03$) and eosinophilic ($p = 0.01$) cells in comparison with those with CA. No difference was seen with respect to EPX and FE_{NO} either when all patients in both groups were compared or when subgroup analysis was performed on the atopic patients. Most of our subjects with PA or CA were atopic (82% and 80%, respectively; $p = 0.81$), with equal frequencies of sensitization to inhaled and food allergens, as well as to three or more allergens (data not shown).

Regression analysis. Regression analyses provided in Tables 4 and 5 demonstrate that several variables concerning patient history and triggering factors were independently associated to PA. Furthermore, every stepwise increase in history score and trigger score was associated with an OR for suffering from PA of 2.53 (95% CI: 1.6–4.0) and 2.63 (95% CI: 1.7–4.1), respectively.

Children with problematic severe asthma resistant to therapy

In attempt to identify children with PA resistant to therapy, we excluded those patients subjected to possible aggravating factors, including untreated rhinoconjunctivitis ($n = 4$), current exposure to tobacco smoke ($n = 12$), untreated symptoms of GERD ($n = 5$), the presence of pets in the home despite sensitization to such pets ($n = 3$), sensitization to molds and reported exposure to a problematic and/or humid indoor climate ($n = 4$). After these exclusions, 33 (61%) of the children with PA were designated as suffering from severe therapy-resistant asthma. These children had parents with higher income ($p = 0.002$) and education ($p = 0.004$) and exhibited a non-significant trend toward higher FEV₁ ($p = 0.06$) and lower FE_{NO} ($p = 0.06$) compared to those who were difficult to treat because of exacerbating factors (Table 6). An exploratory univariate regression analysis of children with PA demonstrated that children with parents without education beyond high school and children with FE_{NO} > 19 p.p.b. had increased OR of having asthma that was difficult to treat because of identifiable exacerbating factors (OR = 6.07 (95% CI: 1.66–22.12, $p = 0.006$) and OR = 3.85 (95% CI: 1.19–12.87, $p = 0.03$), respectively).

Discussion

In the present observational investigation, we applied a standardized and comprehensive clinical protocol to provide a detailed characterization of school-age children with different manifestations of persistent asthma. We compared children with PA, as recently defined by a GA²LEN initiative (2) to children with CA and aimed at identifying hallmarks associated to children with PA. Our main findings were that the characteristic features of children suffering from PA concern hereditary factors, socioeconomic status, comorbidity with rhinoconjunctivitis, degree of physical activity, triggering factors, pulmonary function, and BHR. Moreover, we found that a detailed approach to each individual patient is helpful in distinguishing

Table 3. Measurement of pulmonary function, response to provocation with methacholine and values for various biomarkers in our children with problematic severe asthma (PA) and controlled persistent asthma (CA)

	PA	CA	p-value
Dynamic spirometry (n)	54	39	
Baseline FEV ₁ , % of predicted	82 (20)	90 (11)	0.02
Baseline FVC, % of predicted	101 (18)	103 (16)	0.60
Baseline FEF ₅₀ , % of predicted	69 (28)	85 (18)	0.002
FEV ₁ /FVC × 100	78 (10)	85 (7)	<0.001
Static lung volumes (n)*	45	30	
TLC, % of predicted	106 (15)	104 (15)	0.45
RV, % of predicted FRC	133 (60)	125 (55)	0.60
RV/TLC × 100	23 (8)	20 (8)	0.14
FRC, % of predicted	120 (24)	111 (28)	0.20
Methacholine provocation (n)	32 [†]	39	
Median DRS _{methacholine} (IQR)	18 (1.5–65)	3 (0.4–26.9)	0.01
PD20 < 2 µmol, %	69	33	0.003
PD20 negative, %	16	31	0.14
FEV ₁ post-salbutamol, % of predicted	89 (16)	92 (11)	0.44
Biomarkers (n)	54	39	
Total WBC (10 ⁹ × L ⁻¹)	6.7 (2.1)	5.9 (1.4)	0.05
Neutrophils (10 ⁹ × L ⁻¹)	3.2 (1.4)	2.7 (0.7)	0.03
Eosinophils (10 ⁹ × L ⁻¹)	0.5 (0.4)	0.3 (0.2)	0.01
Median CRP (IQR)	0 (2)	0 (0)	0.14
EPX, ng × mmol ⁻¹ creatinine	203 (165)	152 (106)	0.15
Median FE _{NO} , ppb (IQR)	21 (10–40)	17 (9–26)	0.16
Median total IgE, kUA/l (IQR)	283 (118–853)	280 (66–700)	0.51

Abbreviations in order of appearance: FEV₁, forced expiratory volume during 1 second; FVC, forced vital capacity; FEF₅₀, forced expiratory flow at 50% of forced vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; DRS_{methacholine}, slope of the dose–response curve for provocation with methacholine; IgE, immunoglobulin E; IQR, inter-quartile range; PD20, The dose of methacholine producing a 20% reduction in FEV₁; WBC, white blood cells; CRP, C-reactive protein; EPX, eosinophilic protein x; FE_{NO}, fraction of nitric oxide in exhaled air; PPB, parts per billion; IgE, immunoglobulin E; kUA/l, kilounits of antibody per liter.

The values presented are means (standard deviation), unless otherwise indicated.

*Static spirometry was conducted on a separate occasion on each local hospital's pulmonary function laboratory. All children were invited to perform this investigation. However, nine children in both groups did not turn up for their scheduled appointment and therefore results from these children are missing.

[†]Fifteen children with PA were not subjected to provocation with methacholine because their baseline FEV₁ was <70% of predicted. Another seven children with PA did not undergo methacholine provocation because they had taken β-2 agonist on the same day ($n = 3$), because of technical problems with the equipment ($n = 2$) or in accordance with the recommendation of their physician based on the severity of their asthma ($n = 2$).

between those whose asthma is problematic because of identifiable exacerbating factors and those whose disease is resistant to conventional therapy.

We found, somewhat unexpectedly, that neither allergic sensitization nor increased FE_{NO} is the characteristic feature of children with PA. This finding is in contrast to Fitzpatrick et al. (7) who studied an inner-city, predominantly African-American, population and found that atopy and increased exhaled nitric oxide are features of

Table 4. Regression analysis of factors in the patient history associated to problematic severe asthma (PA) or controlled persistent asthma (CA)

Parameter	n	Model A: (adjusted for age, gender, and ethnicity)			Model B: (multivariate analysis)		
		OR	95% CI	p-value	OR	95% CI	p-value
Parents without education beyond high school	85	3.39	1.20–9.53	0.02	3.60	1.07–12.17	0.04
At least one parent with asthma	92	3.87	1.58–9.50	0.003	3.45	1.18–10.10	0.02
At least one family member who smokes	92	2.67	1.01–7.07	0.048	1.65	0.44–6.17	0.45
Rhinoconjunctivitis	93	3.74	1.20–11.67	0.02	3.46	0.90–13.34	0.07
Parental income of 3 or less on a 4-point scale	82	2.95	0.88–9.92	0.08			
Physically active ≤ 5 h/wk	93	2.15	0.88–5.21	0.09			
History score*	93	2.53	1.60–4.02	<0.001			

OR, odds ratio; CI: confidence interval.

PA or CA was used as a dichotomous dependent variable in the binary logistic regression analysis. CA was assigned a value of 0 and PA was assigned a value of 1. Analysis was conducted on the applicable categorical variables which demonstrated significant differences between PA and CA in the univariate analysis presented in Table 2.

Model A: OR estimated for each variable using different models, but all adjusted possible confounding factors: age, gender, and ethnicity.

Model B: The four variables that came out with a significant result in Model A were analyzed together.

*The sum of the scores of all the individual variables included in Model A, each of which was assigned a value of 0 = no or 1 = yes.

Table 5. Regression analysis of factors triggering asthma symptoms in children with problematic severe asthma (PA) and controlled persistent asthma (CA)

Parameter	n	Model A: (adjusted for age, gender, and ethnicity)			Model B: (multivariate analysis)		
		OR	95% CI	p-Value	OR	95% CI	p-Value
Viral airway infection	93	3.55	0.99–12.67	0.05	4.25	0.95–18.98	0.06
Birch-grass pollen	92	2.76	1.09–6.95	0.03	2.80	1.01–7.76	0.048
Fog/humid air	90	4.87	1.83–12.97	0.002	4.34	1.46–12.88	0.008
Cold air	93	4.23	1.64–10.94	0.003	3.12	1.10–8.83	0.03
Tobacco smoke	89	2.44	0.97–6.12	0.08			
Sum of all triggers (trigger score)*	93	2.63	1.67–4.14	<0.001			

OR, odds ratio; CI, confidence interval.

PA or CA was used as a dichotomous dependent variable in the binary logistic regression analysis. CA was assigned a value of 0 and PA was assigned a value of 1. Analysis was conducted on the categorical variables which demonstrated significant differences between PA and CA in the univariate analysis presented in Table 2.

Model A: OR estimated for each variable using different models, but all adjusted for possible confounding factors: age, gender, and ethnicity.

Model B: The four variables that came out with a significant result in Model A were analyzed together.

*the sum of the scores of all the individual triggering factors included in Model A, each of which was assigned a value of 0 = no or 1 = yes.

severe childhood asthma. The severe asthmatic children in the study by Fitzpatrick demonstrated increased sensitization toward house dust mites and weed mix, allergens that occur rarely in Sweden. In contrast, there were no difference with regard to sensitization to animal dander, tree, and molds compared to their control group with mild-to-moderate asthma. Moreover, a large proportion of the children with mild-to-moderate asthma in the Fitzpatrick study did not receive daily medication and represent a more healthy control group compared to the control group in our study.

The comorbidity between childhood asthma and rhinoconjunctivitis is well established (24). However, the observation that patients with PA report clinical symptoms of rhinoconjunctivitis more often than those with CA has only been reported in adults (25). This finding is of partic-

ular interest in light of our observations that the frequency of atopic sensitization was equal in both of these groups and that the sinus CT for most of our children with PA was normal. Thus, neither allergic sensitization nor chronic sinus disease, but rhinitis *per se* appears to be associated with the development of PA, a finding in concordance with the concept of the united airways (26).

In this broadly recruited and well-characterized cohort of children, we found that 39% of children with PA were exposed to exacerbating factors that could be treated or at least partially eliminated. This finding provides support for the clinical utility of the recently formulated definition of PA. Moreover, these exacerbating factors were not disclosed in connection with routine care by experienced pediatric allergists, which further emphasizes the usefulness of an

Table 6. Univariate comparison between the children with problematic severe asthma whose disease was severely resistant to therapy and those who were difficult to treat because of identified exacerbating factors

	Severely resistant to therapy (n = 33)	Difficult to treat (n = 21)	p-Value
Age, years	13.3	12.9	0.6
Females, %	49	24	0.07
Body mass index, percentile	60	69	0.26
Both parents Caucasian, %	91	71	0.13
Median income (on a 4-point scale)	3	1	0.002
Parental education beyond high school, %	70	28	0.004
At least one parent with asthma, % parent with asthma, %	69	57	0.39
Physical activity >5 h/wk, %	30	24	0.60
Rhinoconjunctivitis, %	88	91	0.77
Atopic, %	79	86	0.52
Median dose of ICS, µg (IQR)	800 (800–800)	800 (800–1040)	
Missed <1 dose controller medication/wk, %	55	67	0.38
Missed 1–3 doses controller medication/wk, %	42	33	0.5
FEV ₁ , % predicted	86	76	0.06
Median DRS _{methacholine} (IQR)	49 (1.4–94.6)	17 (3.6–24.1)	0.5
Eosinophils (10 ⁹ × L ⁻¹)	0.4	0.5	0.8
Median FE _{NO} , ppb (IQR)	15 (10–38)	32 (16–42)	0.06
Median total IgE, kU _A /l (IQR)	219 (44–885)	290 (140–1196)	0.39

Abbreviations in order of appearance: ICS, inhaled corticosteroids; IQR, inter-quartile range; FEV₁, forced expiratory volume during 1 second; DRS_{methacholine}, slope of the dose–response curve for provocation with methacholine; FE_{NO}, fraction of nitric oxide in exhaled air; ppb, parts per billion; IgE, immunoglobulin E; kU_A/l, kilounits of antibody per liter.

The values presented are means, unless otherwise indicated.

*Compliance was self-estimated on a three-point scale, ranging from missing <1 to missing >3 doses of prescribed medications per week.

extensive and standardized clinical protocol. In addition, our results indicate that children with PA, low socioeconomic background and high FE_{NO} have increased probability of having asthma, which is difficult to treat because of aggravating factors.

For the 61% of our children with severe therapy-resistant asthma and for whom no aggravating factors could be identified, our present findings have a number of implications. These children might benefit from more invasive procedures, such as bronchoscopy, that provide more detailed characterization of their disease. In addition, they could be candidates for novel therapeutic options, such as anti-IgE treatment and to participate in studies on other treatment alternatives currently in the pipeline. Finally, future studies on underlying mechanisms of severe childhood asthma should not include children who are difficult to treat because of identifiable exacerbating factors.

One limitation of the present investigation is that fewer children with CA than with PA were involved. Because of the problematic nature of their disease, the children with PA were easily motivated to participate. In contrast, those with CA were both more difficult to identify and to recruit, being less strongly motivated to undergo the extensive study protocol (which actually involved an even larger number of examinations than those described here). Moreover, many

asthmatic children with adequate control of their symptoms had discontinued treatment with ICS and were therefore not even considered for inclusion.

Despite this limitation, we are convinced for the following reasons that our findings are generally applicable. In the first place, all subjects were included on the basis of strictly defined criteria, with two of the authors (JK and GH) taking sole responsibility for the final inclusion. Moreover, our observations concerning heredity (7), socioeconomic factors (27), HCU (5), triggering factors (6), lung function (4, 7, 28), and BHR (29) are comparable to those of previous studies. The frequency of atopic sensitization observed here is similar to that in the CAMP study (28), as well as to preliminary findings on children with persistent asthma recruited from a large Swedish birth cohort (30) upon follow-up at 8 yr of age (Inger Kull, PhD, personal communication, April 2010). Finally, the characteristics of our children with PA and CA agree well with the findings from a population-based study in Norway (29). Taken together, these considerations indicate that our subjects were representative of children with different manifestations of persistent asthma.

As adherence to prescribed medication was determined by self-assessment, this information might be somewhat unreliable. This reliability might have been improved by, for example,

examining pharmacy records, which might have allowed us to identify more children with asthma that was severe because of non-adherence to medication. Nonetheless, the approach employed here represents current clinical practice in Sweden and the lack of any differences in adherence between the groups (PA vs. CA or children who were severely resistant to therapy vs. those who were difficult to treat because of aggravating factors) suggests that this shortcoming did not exert any major impact on our findings.

Although we have included more children than were involved in previous investigations of a similar nature (7, 29), our study population was probably too small to reveal all of the differences that might exist between our groups of patients. At the same time, our study design has certain significant advantages. Our subjects with PA were all identified and treated by senior consultant pediatric allergists at 15 different hospital-based clinics throughout Sweden. Moreover, despite the multicenter design, the questionnaire was administered and the majority of examinations conducted by the same two investigators (JK and BN) employing the same equipment. The procedures employed here, most of which are common in current clinical practice, were applied thoroughly and systematically to characterize each individual patient.

Conclusions

This observational investigation shows that a comprehensive and standardized clinical assessment discerns specific features of children with PA and allows the identification of those who are severely resistant to therapy. Furthermore, the major characteristics of children with PA concern hereditary factors, socioeconomic status, comorbidity with rhinoconjunctivitis, degree of physical activity, triggering factors, pulmonary function, and BHR, but not sensitization to specific allergens or circulating levels of biomarkers of inflammation such as FE_{NO} and EPX. Finally, rhinitis *per se* is associated with the severity of asthma, further emphasizing the concept of the united airways.

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Appendix

The Swedish network of pediatric allergists working with severe asthma consists of the following individuals:

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