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Characterization of severe asthma in the pediatric population

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Abstract
Introduction and objectives: Relationship between the causal mechanisms of pediatric severe asthma and severity of symptoms would be helpful for developing personalized strategies for treatment and prevention.
Materials and methods: For this study, 698 medical histories of asthmatics between 6 and 18 years of age were reviewed in a period of 2 years. Variables analyzed were: age, sex, ethnicity, perinatological history, allergy history, asthma predictive index (API), exposure to tobacco, heavy traffic or epithelium, lung function, age of onset of symptoms, hospitalization admissions/PICU, systemic corticosteroids, daily symptoms control, device prescribe for daily control, and adherence.
Results: A total of 86 children with severe asthma were included (12.3%). Mean age 13.3 +/− 1.86 years, sex ratio1:1, mean age of symptom onset 2.765 +/− 3.06 years, mean IgE 1076.18KU / L +/− 1136, mean eosinophils 604c / mcl +/− 511.9, mean of FEV1 93.15% +/− 16.3. Evidently, 70 children (81.4%) had positive API, 68 (79.1%) rhinitis, 34 (39.5%) atopic dermatitis. 73 (83.9%) sensitized to inhalants and 56 (65.1%) to dermatophagoides, 39 (45.3%) passive smokers, 19 (22.1%) exposure to heavy traffic; 55 (64%) showed symptoms with exercise, 35 (40.7%) had audible wheezing. The mean systemic corticosteroid cycles/year was 3.63 +/− 3.23, mean PICU admissions 0.36 +/− 0.83, mean hospital admissions 4.31 +/− 5.3, average emergency room visits/year 19.44 +/− 16.28. 38 (56.7%) had good adherence, 44 (51%) used an MDI device and 39 (45.3%) used dry powder.
Conclusions: Children with severe asthma meet the following criteria: premature, positive API, rhinitis, atopic dermatitis, high IgE, eosinophilia, passive smokers, exposure to heavy traffic, decreased lung function, and low adherence to controller medication.

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Introduction

The characterization of severe asthma in the pediatric population is currently one of the greatest challenges faced by professionals working with asthmatic patients. Establishing the relationship between the causal mechanisms of the disease and the severity of the symptoms would be helpful for developing more effective personalized strategies for treatment and prevention. Although there are many studies that aim to describe the development of asthma, there are few publications that relate epidemiological and clinical factors to the phenotype of severe asthma[1]. The International ERS/ATS guidelines define severe asthma in people older than 6 years as asthma that requires medication in step 4–5 GINA [high doses of inhaled corticosteroids (ICS)+long-acting beta-agonists (LABA) and/or antileukotrienes (LTRA)] during the previous year or systemic corticosteroids (SCS) for >=50% of the previous year to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy[2].

Severe asthma represents approximately 5–10% of childhood asthma, and is associated with a higher consumption of economic resources and greater morbidity and mortality compared with moderate or mild asthma[3]. In 2011, Ferreira et al.[4] estimated that the cost of asthma in children under 15 years of age in Spain would be around € 403/year for mild asthma and up to € 5,930/year for severe asthma.

Authors such as Belgrave[5] believe that the phenotype of severe asthma could be related to a certain genetic predisposition linked to environmental factors; however, the specific nature of this gene–environment interaction remains unknown. These same authors are currently working on a project to characterize asthma patients by entering routine, biological, genetic, environmental, and phenotypic health care data into powerful computational tools. These tools are used to analyze data sets to find endotypes that could determine the different asthmatic phenotypes, which could be used to predict optimal health outcomes and develop treatment strategies.

Other authors, such as Berry et al.[6], have directed their studies toward the search for biomarkers, describing four main types of different asthma phenotypes: all of the T2 pathways, such as eosinophils in peripheral blood, exhaled nitric oxide, periostin, and IgE. However, these have not been shown to reflect the underlying causal mechanism that could predict the severity of the disease. The search for personalized treatment compels us to study the tools that help us identify genetic, molecular, and environmental mechanisms, as well as demographic characteristics that allow us to predict the behavior of asthma in each individual, and thus identify the most severe phenotypes in order to offer an effective and timely treatment [4, 5].

Identifying the distinctive characteristics of children with severe asthma would be useful not only for improving scientific knowledge about asthma risk factors and phenotypes, but also for improving treatment by developing a more personalized medical strategy.

Our objective is to describe the clinical and epidemiological characteristics of children with severe asthma in our study area, and to establish the risk factors that may influence the condition.

Methods

Retrospective multicenter observational study describing the clinical and epidemiological characteristics of patients between 6 and 18 years of age with a diagnosis of severe asthma, attended at the pediatric pneumoallergy clinic in two hospitals in Tarragona between January 2017 and December 2018. Severe asthma is defined as asthma which requires medication in step 4–5 of GINA (high doses of ICS+LABA and/or ALT during the previous year) or SCS for >=50% of the previous year to prevent it from becoming uncontrolled or that remains uncontrolled despite this treatment.

The databases of both hospitals were reviewed and those medical histories that met all the inclusion criteria, shown in Table 1, were analyzed.

The following variables were analyzed: age, sex, ethnicity, perinatological history, personal history of allergic/respiratory pathology, asthma predictive index (API), epidemic environment (exposure to tobacco or heavy traffic, exposure to epithelium), allergic sensitization, and lung function. We also analyzed the diagnosis measured by forced expiratory volume in the first second (FEV1), natural history of the disease (age of onset of symptoms, age of diagnosis), severity criteria such as hospitalization admissions/PICU and treatment with SCS, control of symptoms (night cough, audible wheezing, symptoms with exercise), device used as a base treatment (MDI or dry powder), and adherence measured by the Morisky–Green test, which is a simple questionnaire, widely used in chronic diseases, that consists of four questions that must be answered with "no" for the patient to be considered adherent. Heavy traffic was defined as those houses located on avenues or main roads with a large amount of traffic. As it was a retrospective study, an exemption from informed consent was requested from the research ethics committee of our center, which was approved (ref. CEIM: 214/2020).

The statistical analysis was carried out with the program SPSS version 22.0. The normal distribution of the variables was verified using the Kolmogorov–Smirnov and Saphiro–Wilk tests. A descriptive analysis of qualitative variables expressed in frequencies and percentages was performed. The quantitative variables were expressed as means and

Table 1 Inclusion/Exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients of both sex	Aged under 6 years and over 18 years
Aged between 6 and18 years	Not having any bronchodilator test in history
History of asthma+positive bronchodilator test	Have another chronic disease
Controller medication in step 4–5 of GINA in the previous year or SCS for at least >=50% of the time in the previous year	Have a diagnosis of immunodeficiency

Legend: SCS: systemic corticosteroids; GINA: Global Initiative for Asthma.

standard deviation or median and range. Chi-square test and Student's t test were applied to determine the statistical significance of the qualitative variables. Student's t test was used to compare quantitative variables. A multivariate analysis was performed to statistically adjust the confusion. The level of statistical significance was set at $p \leq 0.05$.

Results

A total of 698 medical histories of asthmatics between 6 and 18 years of age were reviewed, of which 86 patients (12.3%) met the criteria for severe asthma. Table 2 describes the general characteristics of the sample, the criteria for severity, and symptom control. The table shows a mean age of 13.3 +/− 1.86 years with a 1:1 male: female ratio, mean age of symptom onset of 2.765 +/− 3.06 years, mean IgE of 1076.18 KU / L +/− 1136, mean eosinophils of 604c / mcl +/− 511.9, and mean of FEV1 93.15% +/− 16.3.

Table 2 General characteristics of the study population.

General characteristics	Results (n=86)
Median age; years +/− SD	13.3 +/− 1.86
Gender:	
Male n (%)	40 (46.5%)
Female n (%)	46 (53.5%)
Ethnicity: n (%)	
Spanish	72 (83.7%)
Árabs	11 (12.8%)
South-American	3 (3.5%)
Mean age of symptom onset: years +/− SD	2.76 +/− 3.06
Mean age of asthma diagnosis: years +/− SD	8.5 +/− 2.69
Asthma Predictor Index (API): n (%)	
Positive	70 (81.4%)
Other allergic diseases: n (%)	
Food Allergy	13 (15.1%)
Atopic Dermatitis	34 (39.5%)
Rhinitis	68 (79.1%)
Exposure Tobacco Smoke (ETS): n (%)	39 (45.3%)
Heavy traffic: n (%)	19 (22.1%)
Gestational age: n (%)	
Term	69 (80.2%)
Preterm	16 (18.6%)
Type of delivery: n (%)	
Vaginal	64 (74.4%)
Caesarean section	19 (22.1%)
Respiratory distress at delivery: n (%)	12 (14%)
Laboratory markers: media +/− DE	
Total IgE (KU/L)	1076.18 +/− 1136.3
Eosinophil levels in peripheral blood (c/mcl).	604 +/− 511.9
Neutrophils % in peripheral blood.	47.1 +/− 15.4
Positive skin prick test: n (%)	73 (83.9%)
House dust mist	56 (65.1%)
Olive pollen	21 (24.4%)
Alternaria alternata	16 (18.6%)
Dog epithelium	14 (19.1%)
Cat epithelium	13 (17.8%)
Epithelium exposure	32 (41%)
FEV1 at the time of diagnosis: media +/− SD	93.15% +/− 16.3
Severity criteria: media +/− SD	
SCS cycles/year	3.63 +/− 3.23
Hospital admissions	4.31 +/− 5.29
PICU admissions	0.36 +/− 0.83
Emergency room visits/year	19.44 +/− 16.28
Control of symptoms:	
Symptoms with exercise: n (%).	55 (64%)
Audible wheezing: n (%)	35 (40.7%)
Night cough: n (%)	31 (36%)
Symptomatic days/week: media +/− SD	1.8 +/− 1.5
Treatment	
Age at the start of ICS: year +/− SD	6.3 +/− 3.91
Age at the start of LTRA: year +/− SD	6.36 +/− 3.96
Treatment with MDI: n (%)	44 (51.1%)
Treatment with dry powder: n (%)	39 (45.3%)
Adherence (Morisky test): n (%)	
Adherent	38 (56.7%)
Non-adherent	29 (43.3%)
MDI adherent	23 (60.5%)
Dry powder adherent	15 (39.5%) P:0,394

Legend: SCS: systemic corticosteroids; PICU: pediatric intensive care unit; ICS: inhaled corticosteroids, LTRA: antileukotrienes receptor antagonist; MDI: inhaled medium dose.

Of the 86 patients, 70 children (81.4%) had positive API, 68 (79.1%) rhinitis, and 34 (39.5%) atopic dermatitis. A total of 73 (83.9%) were sensitized to inhalants and 56 (65.1%) to dermatophagoides, 39 (45.3%) were due to exposure to tobacco smoke (ETS), and 19 (22.1%) lived in areas of heavy traffic. A total of 55 (64%) showed symptoms with exercise, and 35 (40.7%) had audible wheezing. The mean SCS cycles/year was 3.63 +/− 3.23, mean PICU admissions was 0.36 +/− 0.83, mean hospital admissions 4.31 +/− 5.3 and average emergency room visits (ER)/year 19.44 +/− 16.28. Of the 86 patients, 38 (56.7%) had good adherence, 44 (51%) used an MDI device, and 39 (45.3%) used dry powder.

Table 3 describes the statistical comparisons between epidemiological and clinical variables with risk variables according to a multivariate analysis. When the use of SCS is compared with all the variables, we obtain statistically significant results in prematurity ($p=0.05$), high IgE ($p=0.026$), and neutrophilia ($p=0.03$). When all the variables are compared with visits to the ER visit/year, we obtain statistically significant results in prematurity ($p=0.028$), atopic dermatitis ($p=0.046$), rhinitis ($p=0.033$), exposure to heavy traffic ($p=0.008$), eosinophilia ($p=0.036$), and low FEV1 ($p=0.016$). When all the variables are compared with hospitalizations in <3 years,

Table 3 Statistical comparisons between epidemiological and clinical variables with risk variables according to a multivariate analysis.

	Preterm N=16	API+	Food allergy N=13	Atopic dermatitis N=34	Rhinitis N=68	Passive smoker N=39	Heavy traffic N=19	IgE>=500 N=38	Totals Eo>=500 N=32	Neutrophils >50% N=9	Epithelium exposure N=32	Non adherent N=29	FEV1 <80% N=19	Sensitized N=73
SCS/year	5+/−3,53	3,88+/−3,47	3,2+/−2,03	3,56+/−2,76	3,4+/−3,06 2,5 (12)	4,12+/−3,44	1,06+/−0,78	3,89+/−3,29	3,3+/−1,82	3,29+/−1,7	3,06+/−2,7	4,6+/−3,65	5,6+/−4,09	2,75+/−2,6
Mean (SD)	**P=0,05**	P=0,093	P=0,599	P=0,062	P=0,932	P=0.146	P=0,318	**P=0,026**	P= 0,073	**P=0,03**	P=0,834	P=0,73	P=0,149	P=0,12
ER visit/year	7 (49)	7 (57)	4 (51)	15 (50)	12 (56)	19 (49)	5,5 (39)	19 (56)	21,5 (34)	16 (27)	9 (57)	12 (49)	30 (35)	5 (57)
Median (range)	**P=0,028**	P=0,298	P=0,38	**P=0,046**	**P=0,033**	P=0,283	**P=0,008**	P= 0,595	**P=0,036**	P=0,933	P=0,211	P=0,676	**P=0,016**	P=0,71
Hospitalizations <=3 years	0 (2)	0 (6)	0 (7)	0 (6)	0 (7)	1 (7)	0 (7)	0 (7)	0 (7)	0 (0)	1 (7)	0 (6)	0 (6)	0 (7)
	P=0,001	**P=0,000**	P=0,025	P=0,60	**P=0,000**	P=0,815	**P= 0,000**	P=0,616	P=0,638	P=0,716	P=0,103	P=0,809	**P=0,000**	P=0,28
Median (range)														
Hospitalizations >3 years	1,5 (6)	1'5 (14)	0 (10)	1 (14)	1,5 (14)	2 (14)	1 (3)	2 (14)	3 (10)	1 (3)	2 (14)	1 (14)	1 (14)	1 (11)
Median (range)	**P=0,001**	**P= 0,027**	P=0,716	P=0,97	**P=0,002**	P=0,242	**P=0,000**	P=0,972	P=0,672	P=0,757	P=0,141	P=0,643	**P=0,000**	P=0,12
PICU with <=3years	0 (2)	0,357+/−0,68	0	0	0	0	0	0	0	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)
Median (range)	P=0,26	0 (2)								P=0,17		P=0,13	**P=0,011**	P=0,116
PICU with > 3years	0 (1)	0 (2)	0(2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (1)	0 (1)	0 (1)	0(1)	0 (1)	0 (2)
Median (range)	P=0,952	P=0,265	P=0,92	**P=0,036**	P=0,440	**P=0,024**	P=0,117	P= 0193	P= 0,963	**P= 0,039**	**P=0,029**	P=0,95	P=0,440	P=0,567
Ager of symptom onset	1,5 (3)	2 (13)	2 (13)	2 (13)	1 (13)	1 (3)	1 (13)	1 (6)	1,5 (3)	3 (4)	1 (6)	1 (3)	1 (6)	2 (13)
Median (range)	P=0,710	P=0,515	P=0,951	P=0,762	P=0,258	P=0,06	P=0,093	P=0,573	P=0,588	P=0,419	P=0,132	P=0,76	P=0,304	P=0,62
Age at the start of LTRA	5,44+2,83	5,91+/−3,22	6+/−4,8	5,59+/−3,62	6,34+/−4,11	6+/−3,64	9+/−4,98	4,2+/−2,59	3,9+/−2,38	4,6+/−2,4	6,27+/−4,41	7,9+/−4,23	5,6+/−2,51	6,44+/−3,89
Mean (SD)	P=0,336	P=0,474	P=0,691	P=0,33	P=0'94	P=0,634	P=0,173	**P=0,012**	P=0,13	P=0,301	P=0,406	P=0,404	P=0,98	P=0,741
Age at the start of ICS	6,5+/−2,38	6,74+/−3,18	5,9+/−4,5	5,7+/−3,67	6,5+/−4	5,88+/−3,77	8,6+/−5,07	4,47+/−2,73	5+/−2,94	5,2+/−0,84	6,27+/−4,41	7,9+/−4,56	3,8+/−2,59	7,05+/−3,35
	P=0,44	**P=0,540**	P=0,17	**P=0,08**	P=0,45	P=0,753	P=0,374	P=0,089	P=0,683	P=0,556	P=0,733	P=0,29	P=0,225	P=0,35
Symptomatic days/week	2+/−1,86	1,6+/−1,5	1,7+/−1,6	1,32+/−1,3	1,79+/−1,62	2,07+/−1,59	1,83+/−1,6	2,03+/−1,57	2+/−1,6	3,44+/−1,3	1,67+/−1,51	1,86+/−1,5	1,78+/−1,54	1,775+/−1,5
	P=0,54	P=0,03	P=0,79	P=0,021	P=0,93	P=0,10	P=0,87	P=0,32	P=0,271	**P=0,036**	P=0,39	P=0,34	P=0,97	P=0,90
Audible wheezing.	6 (37,5%)	31 (44,3%)	4 (30,8%)	15 (44,1%)	30 (44,1%)	19 (48,7%)	5 (26,3%)	16 (42,6%)	13 (40,6%)	4 (44,4%)	13 (40,6%)	11 (37,9%)	9 (47,4%)	31 (42,5%)
n (%)	P= 0,448	P= 0,602	NA	NA	P= 0,34	P=0,158	P=0,146	**P=0,027**	P=0,81	P=0,91	P=0,713	**P=0,033**	P=0,884	P=0,25
Symptoms with exercice	11 (68,8%)	43 (63,2%)	8 (66,7%)	20 (62,5%)	46 (71,9%)	30 (76,9%)	13 (76,5%)	26 (72,2%)	23 (71,9%)	7 (77,8%)	22 (71%)	21 (72,4%)	12 (63,2%)	46 (66,7%)
n (%)	P=0,908	P=0,155	NA	NA	P=0,348	**P= 0,02**	P=0,341	P=0,43	P=0,08	P=0,43	P=0,248	P=0,784	P=0,022	P=1,00
Night cough	6 (37,5%)	23 (32,9%)	4 (30,8%)	9 (26,5%)	24 (35,3%)	17 (43,6%)	9 (47,4%)	12 (31,6%)	8 (25%)	4 (44,4%)	13 (40,6%)	15 (51,7%)	6 (31,6%)	25 (34,2%)
n (%)	P=0,827	**P= 0,022**	NA	NA	P=0,889	P=0,254	P=0,953	P=0,81	P=0,29	P=0,35	P=0,115	P=0,378	P=0,355	P=0,61

NA= Not aplicable.

we obtain statistically significant results in prematurity (p=0.001), API+(p=0.000), rhinitis (p=0.000), exposure to heavy traffic (p=0.000), and low FEV1 (p=0.000). When all the variables are compared with hospitalizations in >3 years of life, we obtain statistically significant results in prematurity (p = 0.001), API+(p=0.027), rhinitis (p=0.002), exposure to heavy traffic (p=0.000), and low FEV1 (p=0.000). When all the variables are compared with PICU admissions, we obtain statistically significant results in atopic dermatitis (p=0.036), ETS (p=0.024), neutrophilia (p=0.039), exposure to epithelia (p=0.029), and low FEV1 (p=0.011). When all the variables are compared with symptomatic days/week, we obtain statistically significant results in neutrophilia (p=0.036). When all the variables are compared with audible wheezing, we obtain statistically significant results in high IgE (p=0.027) and low adherence (p=0.033). When all the variables are compared with night cough, we obtain statistically significant results in API+(p=0.022).

Discussion

This study shows that children with severe asthma, in a cut off average age of 13.3 years, meet the following significant characteristics: premature with positive API, rhinitis, atopic dermatitis, elevated IgE, and eosinophilia in peripheral blood with exposure to heavy traffic and ETS, decreased FEV1, and low adherence to controller medication.

Part of our results are in keeping with Fitzpatrick[7] in 2016 showing that children with severe asthma have a high degree of atopy reflected by increased blood eosinophils and higher concentrations of total serum IgE and a decline in FEV1 values compared with children having non-severe asthma.

In the publication of Rosas-Salazar[8], prematurity shows an association with asthma just in atopic children and without specifying asthma severity. This study shows that in severe asthma children, prematurity is the risk factor significantly related to more severity criteria, such as requiring oral steroids, emergency room visits, and hospitalizations regardless of age or atopy, history, and obviating the bias due to admissions for pulmonary bronchodysplasia. This finding represents an important step in the identification of epidemiological risk factors for the development of severe asthma.

Another significant factor affecting greater asthma severity is the ETS as a severity criterion for PICU, this result is in concordance with Shah S and cols[9] showing that asthmatic children admitted in PICU because of status asthmaticus with previous ETS deteriorate and recover slower than non-ETS-exposed patients. This can be related to impairs histone deacetylase-2 (HDAC2) function via phosphoinositide-3-kinase (PI3K) signaling activation, which could contribute to corticosteroid-insensitive inflammation in children with severe asthma, as recently suggested by Kobayashi[10]. Exposure to heavy traffic also is a significant severity criterion for emergency room visits/year and admissions, in keeping with Eun Lee[11] that shows that exposure to high levels of outdoor air pollution without air purifier was associated with moderate/severe asthma when mild intermittent asthma was considered as a reference. The consistent results of these studies provide stronger evidences of the need to reduce ETS and air pollution for a better control of asthma.

In this study, using a multivariate analysis to statistically adjust the confusion, severity biological biomarkers such as elevated IgE, eosinophilia and neutrophilia in peripheral blood proved to be statistically significant risk factors for both asthma severity criteria and poor symptom control. Also, clinical biomarkers such as positive API, rhinitis, and atopic dermatitis proved to be statistically significant criteria for severe asthma. These results are comparable to Rosas-Salazar[8] in which asthmatic patients had a history of atopy, although it was not described in relation to severity, but opposite to Eun Lee[11] and the SARP III cohort[3] who did not observe a relationship between atopy and severe asthma. This disparity in results could be explained because asthma has a specific genetic component and its interaction with environmental factors seems to be the key in the development of the disease[12].

Regarding pulmonary function, our study showed that FEV1 <80% is a statistically significant risk factor for presenting more exacerbations that require emergency room visits, hospital admissions or PICU, similarly to several publications[11,13,14]. Besides, a non-adherence of 43.3% was observed showing statistically significant results of worse control of the symptoms of severe asthma and maybe that could explain a lower pulmonary function.

Finally, this study has several limitations. In our cohort study, pediatric severe asthma represented 12.3% of the total number of asthma patients treated at pediatric pulmonology clinics with more similar presentation in boys than in girls. This places us at higher limits of prevalence, more similar to the results of the ATS guideline[15] (5-10%) than those published in GEMA 5.0[16], which describe a prevalence ranging between 0.5% and 5%. This is probably because it is a coastal area, which is classically related to greater exposure to perennial aeroallergens (65.1% sensitized to dermatophagoides) and therefore, greater predisposition to developing severe asthma, and also because it is a selected sample of the population of patients who have been monitored in specialty asthma clinic with a certain degree of severity.

Another limitation is the fact that is a retrospective study and the information is obtained by medical records, so there are data that we do not have access to. Also, the results cannot be generalized to all children with severe asthma, since children with mild and moderate asthma were not included. This study was not controlled and the predicted factors could be affected by factors such as adherence of treatment; however, to optimize accuracy, we used a multivariate analysis to adjust the confusion.

In conclusion, this study provides us with useful and simple tools about how to recognize potential risk factors for developing severe asthma in children when they meet the following criteria: premature, atopy, high IgE, exposure to tobacco, and heavy traffic, decreased pulmonary function, and low adherence to controller medication.

More studies are needed that include a larger number of variables and are designed homogeneously to give more conclusive results.

Conflict of interest

No conflict of interest is reported by the authors.

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