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RESEARCH ARTICLE

Clinical characteristics and diagnostic workup in severe asthma: data from the database of the Italian Pediatric Respiratory Society

Running title: Italian database for pediatric severe asthma

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ABSTRACT

Although rare in children, severe asthma is responsible for a heavy burden on families and society. Being a rare condition, every center follows only a limited number of patients, and there is a solid rationale for setting up networks to collect data.

We present a first report on clinical features and diagnostic workup of children and adolescents with severe asthma included in the database of the Italian Pediatric Respiratory Society (Società Italiana per le Malattie Respiratorie Infantili - SIMRI).

24 Italian pediatric pulmonology and allergology centers took part in the study. Data were collected from October 2021 to October 2023 on a web-based platform.

207 subjects (60.4% males), with a median age of 13.9 years (range: 6.2-17.9 years) were recruited; 191 (92.2%) were sensitized to aeroallergens, 25.6% were overweight and 15.4% were obese. 60 patients (29%) showed a FEV1 value below 80% of the predicted.

The diagnostic workup included a chest CT scan in 78 patients (37.7%, range 0-83% in each center) and a bronchoscopy in 45 patients (21.7%, range 0-87%). The most frequent abnormal findings on chest CT were bronchial thickening and air trapping.

In conclusion, our study provides an overview of the main clinical characteristics of Italian children and adolescents with severe asthma enrolled in participating centers, and it underlines the variability between centers in the diagnostic workup of these patients.

IMPACT STATEMENT: This is the first report on pediatric severe asthma based on data collected through a large national database and describing some clinical features of recruited patients together with the diagnostic workup they underwent.

KEY WORDS

Adolescents; children; database; severe asthma.

INTRODUCTION

Although most children with asthma can be effectively treated with low doses of inhaled steroids, reaching a good level of symptom control, this is not true for the whole population of asthmatic children. Severe asthma is defined as the presence of troublesome asthmatic clinical manifestations despite treatment with high dose inhaled steroids plus a second controller or the persistent need for this therapy to maintain symptoms under control (1). Severe pediatric asthma has a prevalence that varies in different studies between 0.23 and 3.2% in the general population and between 2.11 and 10% among children with asthma (2). Despite being a rare condition, severe asthma is associated with a substantial burden in terms of direct and indirect costs. In the past decade, the introduction of biological drugs, which interfere with specific and well-known pathogenetic pathways, has significantly improved the management of severe asthma and the quality of life of children and families (3).

To optimize the use of available biologics and to contribute to the development of new drugs to treat those endotypes not targeted by the available ones, an essential step is represented by the complete and accurate characterization of children and adolescents with severe asthma (4). Since this condition is so rare, most pediatric centers only have a minimal number of subjects with severe asthma. For this reason, creating networks between centers is of the utmost importance to collect data and improve our understanding of severe asthma.

With this aim, we built a national multicenter web-based database promoted by the Italian Pediatric Respiratory Society including 24 centers distributed throughout the country. Here, we present the clinical and functional characteristics of children and adolescents with severe asthma at recruitment and their examinations within their diagnostic workup.

MATERIALS AND METHODS

Subjects

Between October 2021 and October 2023, children, and adolescents 6-17.9 years old, followed for at least 4 months for severe asthma in the 24 participating centers (**Figure 1**), were included in the database.

According to the European Respiratory Society and American Thoracic Society (ERS/ATS) definition (1) asthma was defined as severe if it required high doses of inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent loss of control or if it remained uncontrolled despite this therapy. For patients on biologic drug at recruitment these criteria had to be present before starting it. Alternative diagnoses (i.e. diagnoses that can masquerade as severe asthma) had to be excluded before inclusion in the database.

The study has been approved by the Pediatric Ethics Committee of Tuscany (protocols n.275/2021 and n. 14/2022), coordinating center for the SIMRI /IPRS and by all the Ethics Committee of the participating centers. Written informed consent was obtained from all the parents and from children >11 years old.

Data collection and analysis

REDCap (Research Electronic Data Capture), a web application for building and managing databases, was used to collect and store the data.

The database has been held and managed in collaboration with the Biostatistics, Epidemiology and Public Health Unit of the University of Padua**.**

The following data have been collected: demographic and clinical characteristics of the patients, lung function measurements, and instrumental investigations performed during the diagnostic workup. Spirometry data were analyzed using Global Lung Function Initiative (GLI) reference equations (5).

Continuous data have been described using mean and standard deviation or median and Interquartile Range (IQR), categorical data have been described as proportions.

RESULTS

Patients' features

Two hundred-seven children and adolescents (125, 60.4% were male) were included in the database. The parental country of origin was Italy for both parents in 135 patients, a foreign country (eastern Europe, South America, Africa, others non-EU) for both parents in 60 patients and mixed for 12 patients. Median age at inclusion was 13.9 years (Interquartile range, IQR 11.1-15.8).

The first appearance of wheezing or other respiratory symptoms of asthma in their personal history was reported at a median age of 3 years (IQR: 2.0-6.0 years), while a doctor-based asthma diagnosis was made at a median age of 6 years (IQR 5.0-7.0). Despite males being more numerous than females in the whole sample, the frequency distribution of age at diagnosis by sex clearly shows how in preschoolers the diagnosis was much more frequent in males, while it was more frequent in females after the age of 9 (**Figure 2**).

At inclusion in the database, 165 patients (79.7%) were treated with biologic therapy (48 with dupilumab, 22 with mepolizumab, 95 with omalizumab).

191 out of 207 patients (92.3%) were sensitized to aeroallergens: the most prevalent were dust mites (89.5%), followed by grasses (52.9%) and pets (51.8%) (**Table 1**); 81 of 99 patients sensitized to pets had prick and/or specific IgE positive for cat.

Of the 16 non sensitized patients, 9 have total IgE levels higher than 100 IU/ml (range 125-1541).

At inclusion, 25.6% of children and adolescents were overweight (BMI > 75 centile, according to Cacciari et al (6)), while 15.4% were obese (BMI >95 centile).

Lung function

Spirometric parameters at recruitment are reported in **Table 2**.

60 patients (29%) had a FEV_1 below 80% of the predicted value according to GLI. Distribution of FEV_1 (% predicted) is shown in **Figure 3**. 178 (86%) patients performed a reversibility bronchodilator test that in 45 cases (21.7%) showed a rise in FEV1 of at least 12%.

Diagnostic workup

Seventy-eight (37.7%) included patients performed a chest compute tomography (CT) scan as a part of their severe asthma diagnostic work-up. The proportion of patients undergoing chest CT scans largely varies among centers (in centers that recruited at least 6 patients, the value ranged between 0 and 64%). In 22 out of 78 cases (28.2%), the CT scan was normal. The most frequent anomalies reported in the remaining 57 patients were bronchial wall thickening (n=33) and air trapping (n=19). Other abnormal findings were small bronchiectasis in limited areas of the lungs (n=6), atelectasis (n=4), and mucus plugs (n=4).

Forty-five patients (21.7%) underwent bronchoscopy as part of their diagnostic workup, with a significant between-center variability (range 0-87%). 62% of these bronchoscopies were performed in one center.

DISCUSSION

In the present paper, we describe the demographic and clinical features as well as the instrumental investigations performed during the diagnostic workup in a cohort of Italian children and adolescents with severe asthma.

Although the first appearance of asthma symptoms in included subjects was reported at a median age of 3 years, the median age at diagnosis was 6 years. This result was not unexpected: to confirm asthma diagnosis, in fact, the international reference documents (GINA, ERS) (7,8) strongly recommend the use of objective tests (spirometry, bronchodilator reversibility, exhaled nitric oxide measurement), which require a level of cooperation that children usually can provide after the age of 5. Moreover, below the age of 5 years, many children present with episodes of wheezing mainly triggered by respiratory infections, and they outgrow this problem during school age (9). Noteworthy, there was a tendency for an earlier diagnosis in males and a later diagnosis in females, as it has been described in the general population of asthmatic children and adolescents (10).

In our cohort of children with severe asthma, the prevalence of aeroallergen sensitization showed a distribution similar to the one described in the general pediatric Italian population of asthmatic children (11,12). Although severe asthma in Italian children and adolescents was not associated with a different sensitization pattern, it is interesting to underline the higher prevalence of sensitization to pets. In keeping with this, a recent meta-analysis found an association between pet ownership and severe childhood asthma (13).

Overweight and obesity are well-known comorbidities of severe asthma. A recent report on the comorbidities of severe asthma in adult subjects with severe asthma included in a large international database (International Severe Asthma Registry) showed a prevalence of obesity of 42% (14). Our data in children, although showing a lower prevalence, still highlight the importance of overweight and obesity as comorbidity factors in severe asthma.

In our patient's lung function was assessed through spirometry. The mean values of spirometric parameters (FEV_1, FEV/FVC, FEF_{25-75}) were within the normal range, and only in about one-third of the cases FEV_1 values were below 80% of predicted. This result, which might be partly due to long term treatment with biologics in some of the children, is consistent with previous studies showing that spirometry is often normal in pediatric severe asthma, while other tests, such as lung clearance index, can show an earlier deterioration (15).

No consensus exists on which examinations should be performed within the diagnostic workup when severe asthma is suspected. ERS/ATS recommendations (1) and Global Initiative for Asthma (GINA) report (7) suggests performing a chest CT scan when the presentation is atypical. Moreover, especially in children, a balance of radiation risk versus potential treatment benefits should be considered before this imaging exam. The indications for an explorative bronchoscopy to assess airway anatomy and collect bronchoalveolar lavage are even more discussed, especially in children (16). For the time being, the role of bronchoscopy in asthmatic children should probably be limited to patients with persistent symptoms not responsive to appropriate anti-asthmatic therapy. Many studies highlight the pivotal role of bronchoscopy in identifying alternative causes of wheezing (e.g. airway abnormalities, airway tumours, vascular compressions, and foreign bodies) (17). In our study, these causes had to be excluded before including patients in the database. Some studies have investigated the role of bronchoalveolar lavage analysis in assessing airway inflammation and microbiologic profile in children with asthma, but data supporting the clinical efficacy of such analyses are still lacking (16,18).

In our database a large variability between centers has been documented for both CT (performed in 0 to 64% of children in centers with at least 6 patients included) and bronchoscopy (0 to 87%) translating the low consensus in the literature in the real-life context.

Looking into chest CT results, the most common findings were represented by airway thickening and air trapping. These findings have been previously reported in children with

severe asthma, and bronchial wall thickness is considered a marker of the remodeling process involving asthmatic airways (19,20). Bronchiectasis (small and distributed in limited lung zones) were reported only in 6 cases, but it is worth considering that the presence of larger or more diffuse bronchiectasis was an exclusion criterion in our study. Previous data from the literature show conflicting results on the association between pediatric severe asthma and bronchiectasis. Lo et al. (21) reported the presence of significant bronchiectasis in about one-third of children with difficult asthma who underwent a clinically indicated CT scan, while Saglani et al. (20) found no bronchiectasis in the chest CT scan performed in a similar population of asthmatic children.

Noteworthy, these previous studies' chest CT findings did not change patients' management. Therefore, based on the available evidence and also considering the risks related to radiation exposure in children, it is reasonable to stick with the indication of the ERS/ATS recommendations (1) that suggest performing CT scans in selected cases, especially in those presenting with atypical features.

CONCLUSIONS

In conclusion, our study provides an overview of important clinical and functional characteristics of Italian children and adolescents with severe asthma. Moreover, it provides insight into the between-center variability in the use of CT scan and bronchoscopy in the diagnostic work up of these patients. The use of a national database enabled data gathering on a significant number of subjects despite severe asthma being a rare condition. Furthermore, the database has the potential to be used prospectively, enabling the collection of longitudinal data from the patients that are followed over time.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

Antonio di Marco received fees for Deca and support for attending meetings from Recordati; Grazia Fenu received grants from Astrazeneca, GSK, Novartis, Sanofi; Michele Ghezzi received grants form Chiesi, Sanofi, GSK; Mattia Giovannini reports personal fees form Sanofi; Enrico Lombardi has received research grants from Boehringer, Novartis, Restech, and Sanofi; lecture fees from Angelini, Boehringer, Chiesi, GSK, and Recordati; travel grants from Chiesi; Advisory Board fees from Angelini, Chiesi, and Recordati; research equipment

from Cosmed; Amelia Licari received grants from GSK, Sanofi, NTC, Dompè, Novartis; Marcello Sandoni received travel grants from Dicofarm.

The other authors have no conflict of interest to disclose related to the manuscript content.

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Author contributions

SC contributed to study design and patient enrollment and wrote the first manuscript draft; FR was responsible for the database, designed the study, contributed to data analysis and critically revised the manuscript; MP was in charge for the management of the database; AF, DG, GL developed the database; AF updated the database when needed; LB, IB, SB, MB, GB, GC, FC, FC, AC, ADC, MDC,MD, ADM, EDP, SDP, VF, GF, VF, SF, SFR, MG, MG, MEG, AK, ML, SL, AL, EL, SM, FM, AM, FM, FM, RN, AN, MFP, MP, MR, GR, MS, LT, CT, MT, CT, AZ enrolled the patients, contributed to populate the database and critically revised the manuscript.

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Figure 1: Geographic distribution of participating centers

Figure 2. Distribution of age at asthma diagnosis in males and females

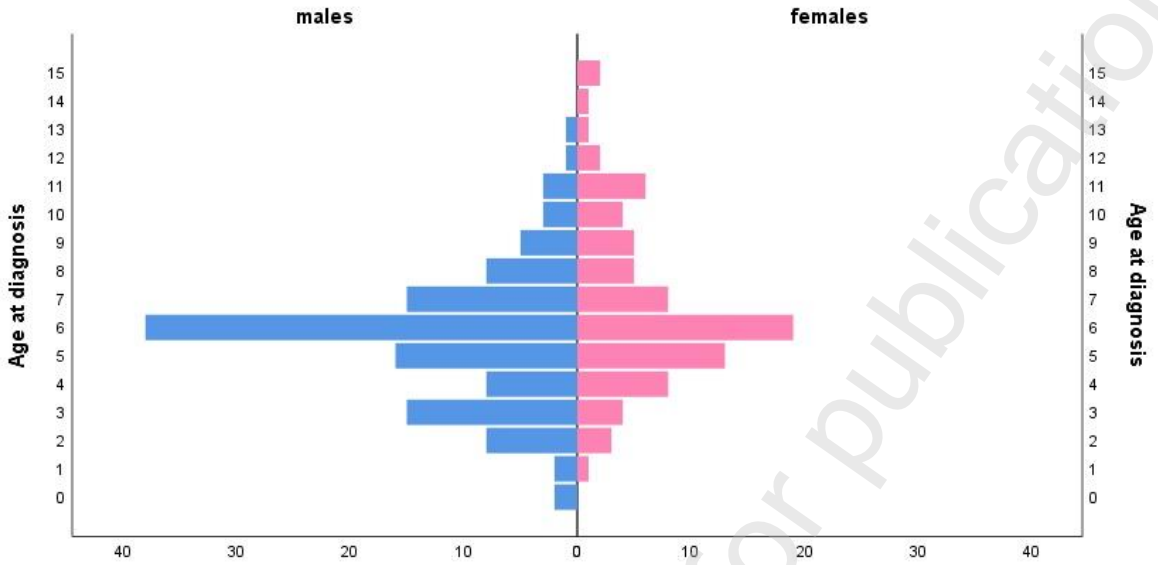

Figure 3: Distribution of FEV1 (% predicted) values in included patients.

In the box plot median and interquartile ranges (edges of the box) are presented, together with upper and lower values of the data (horizontal lines) and outliers (single points). A red line shows the cut of 80%.

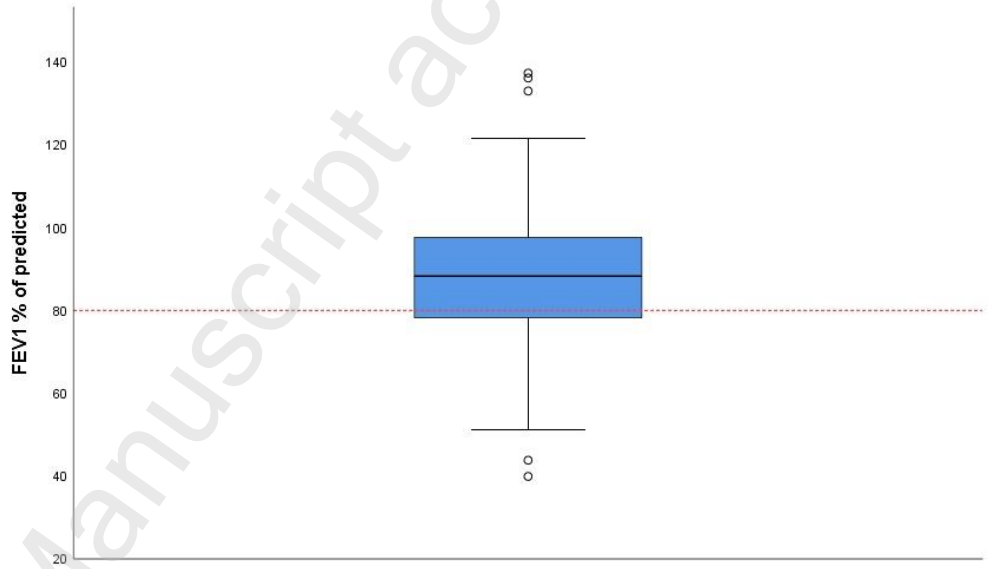

Table 1. Distribution of sensitization (skin prick test >= 3 mm or positive IgE) to aeroallergens

Aeroallergen	**Proportion of sensitized patients**
Dust mite	171/191 (89.5%)
Grasses	101/191 (52.9%)
Other herbaceous plants	63/191 (33.0%)
Tree pollen	83/191 (43.5%)
Pets	99/191 (51.8%)
Molds	52/191 (27.2%)

Table 2. Spirometric parameters at recruitment

	FEV_1 (%pred*)	FVC (%pred*)	FEV_1/FVC	FEF_{25-75} (%pred*)
Mean	87.95	93.57	94.17	76.07
SD	15.41	14.45	10.57	24.95

*According to Global Lung Function Initiative (GLI) reference values. FEV_1 : Forced expiratory volume in the first second; FVC: Forced vital capacity; FEF_{25-75} : Forced expiratory flow between 25% and 75% of forced vital capacity.