Features of severe asthma in young children from Romania

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Abstract

Asthma is the most frequent chronic disease of childhood. In spite of significant improvement of treatment options and diagnostic tools, asthma remains in many patients uncontrolled. The term of "severe asthma" seems to be rather a large umbrella for a heterogeneous group of diseases. This paper is presenting our experience in two respiratory disease clinics that evaluate asthmatic children. Current study was designed to test an algorithm for daily practice in a special group of patients: children with previously diagnosed asthma or recurrent-wheezing, evaluated by family physician or pediatrician as severe disease ("Asthma Decalogue in Children"). Out of 313 referrals (during a six months inclusion time) we had 202 children completing study per-protocol. 49 (22.69%) had severe disease, but only 8 had severe asthma (3.7% of total patients and 18.6% of severe patients). They were older, with less male predominance and with more frequent rhino-conjunctivitis and D vitamin deficiency than other asthmatic children with less severe disease. Asthma Decalogue in Children seems to be an efficient tool to differentiate severe asthma from the rest of children with reactive airway diseases.

Keywords: *severe asthma, children, algorithm*

Rezumat

Caracteristicile astmului sever la copiii de vârstă mică din România

Astmul este cea mai frecventă boală cronică a copilăriei. În ciuda îmbunătățirii semnificative a opțiunilor de tratament și instrumentelor de diagnostic, astmul rămâne la multi pacienți necontrolat. Termenul de „astm sever" pare a fi mai degrabă o „umbrelă" mare pentru un grup heterogen de boli. Această lucrare prezintă experiența noastră în două clinici de boli respiratorii care evaluează copiii astmatici. Studiul actual a fost conceput pentru a testa un algoritm pentru practica de zi cu zi la un grup special de pacienți: copii diagnosticați anterior cu astm bronșic sau wheezing recurent, evaluați de către medicul de familie sau pediatru ca boală severă („Decalog Astmul la Copii"). Din 313 copii referiți (într-o perioadă de incluziune de șase luni) am avut 202 copii care au completat studiul per-protocol. 49 (22,69%) au avut boli grave, dar numai 8 au avut astm sever (3,7% din totalul de pacienți și 18,6% dintre pacienții severi). Ei au fost mai mari ca vârstă, sexul masculin fiind mai puțin predominant și rino-conjunctivita și deficitul de vitamina D au fost mai frecvente decât la alți copii astmatici cu boală mai puțin severă. „Decalogul Astmul la Copii" pare a fi un instrument eficient pentru a diferenția astmul sever de restul copiilor cu boli reactive ale căilor respiratorii.

Cuvinte-cheie: *astm, copii, algoritm*

Background and aim

Asthma is one of the most important chronic diseases. Worldwide there are 300 million patients of various ages and racial backgrounds[6]. In childhood, asthma is the disease with the most notable impact due to high prevalence and increased direct (medications, medical visits, emergency care, hospital admissions, and tests) and indirect costs (workdays lost and patient travel or transfer costs)[9]. In all climate settings asthma is the most common chronic disease in children[25]. Many of the asthmatic children exhibit a mild disease that can be fully controlled[1, 6]. Tailoring asthma treatment to the level of actual disease control and future risk has been implemented in various guidelines generated by expert-panel efforts like GINA or ICON[1,5].

In spite of significant improvement of treatment options and diagnostic tools, asthma remains in many patients uncontrolled, but really severe asthma is unusual. Several factors were involved in a suboptimal control of asthma in children: lack of treatment standardization, lack of parental knowledge about disease and understanding of treatment recommendations, lack of medical information and education provided to parents, high costs of medicine and devices, emotional, lifestyle and non-adherence issues, unreasonable expectations of parents or patients[10]. In 5 up to 10% of patients control cannot be achieved in spite of aggressive treatment[6].

Regional or national task-forces[19] were implemented to address the severe asthma issue. In 2009 a World Health Organization Task-Force[26] was commissioned to discuss the issue of severe asthma. They suggested a three-group stratification of severe asthma: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma. The term of "severe asthma" seems to be rather a large umbrella for a heterogeneous group of diseases, than a unique entity[7,8]. Recently, a complex effort (Global Allergy and Asthma Network of Excellence (GALLEN), Mechanisms of the Development of Allergy (Me-DALL) and Allergic Rhinitis and its Impact on Asthma (ARIA) groups) was organized to address the difficult area of severe allergic diseases, including severe asthma[26]. The concept of "problematic-severe-asthma" has risen and two major groups of asthmatic children were identified: difficult-to-treat asthma and therapy-resistant asthma.

There were published few papers on asthmatic children from Romania[27,28,29] but only two papers are addressing the problematic of severe asthma in children[27, 30]. Our paper is aiming to evaluate features of severe asthma in very young and preschool children from Romania.

Table 1 History data

FAMILY HISTORY	PERSONAL MEDICAL HISTORY
1. family history of asthma	1. personal history of rhinitis
2. family history of recurrent wheezing	2. personal history of atopic dermatitis
3. family history of allergies	3. personal history of allergies
4. family history of smoking	4. personal history of chronic cough
	5. exclude personal history of significant co-morbid conditions (CF, BDP, PCD, congenital abnormalities of respiratory tract, ABPA, CHD, GERD)

Material and method

Prospective study of patients from two tertiary-referral asthma clinics: were included in our study all children with previously diagnosed asthma or recurrent-wheezing phenotype, up to 10 years of age. All these children were referred by GP or pediatrician because of severe or uncontrolled disease. None of these children were steroid-naïve.

Initial evaluation was complex, in order to validate diagnosis. A pre-designed check-box list with relevant data (medical and family history – Table 1) and complete clinical examination were performed in order to exclude alternative diagnosis. After clinical features of patients were evaluated, co-morbid conditions were excluded or fully documented. Anthropometric data were collected and BMI was calculated. A special focus was on rhinitis[18] and atopic dermatitis. In asymptomatic children during initial visit family was instructed to perform a video-recording during an exacerbation of symptoms.

Questions regarding family history of asthma or allergic diseases were reviewed. A special section of the initial evaluation was regarding triggers of symptoms. Parents were questioned about exercise-induced symptoms, about viral-induced asthma[13], about smoking habits of family, about housing conditions and pollution in their area[16], about pets and other possible indoor triggers, about diet[15] and vitamins, especially D vitamin[14].

In selected patients a complex rage of tests (PFT's, chest radiology or HRCT in selected cases, sweat-test, immunology tests, ENT, serum 25OH vitamin D, total-IgE and allergy screening-panel, skin prick-tests, ECG, heart and abdominal ultrasound, and oesophageal pH-metry) were performed to validate asthma diagnosis and exclude differentials.

At first visit, an extensive training for device use, inhalation technique and trouble-shooting was implemented. Parents and school age children were questioned about previous problems with inhalation devices and were asked about device preference, if there was any. A brief review of guideline recommendations about age-specific devices was presented in undecided parents[4].

Both parent and child were instructed about normal routine regarding medication delivered via the selected device. A short video, device-specific (recorded in clinic, in Romanian) was presented. After presentation the parent and/or child were evaluated for the acquired skills. They had to demonstrate proficiency of device use. Anti-static strategy was presented for all patients that were assigned for plastic spacer (Volumatic® and Baby-haler® GSK or Optichamber Phillips/Respironics) use. Post-inhalation measures (device cleaning, rinsing the mouth, gargling, bicarbonate use etc.) were presented and were reinforced at each visit. Because many pMDI's used in Romania do not have a counter, parents were instructed to evaluate the amount of remaining medication by flotation technique.

Written action plan in Romanian language was personalized for each patient.

For asthma monitoring and treatment outcome we used Childhood Asthma Control Test (C-ACT). Cut-off points used were 20 and above for well-controlled asthma, 13 to 19 for uncontrolled asthma and 12 and below for very-poorly controlled asthma[3].

Protocol evaluation was performed at two, four and six months after start of treatment that was initiated at first visit. Patients fully controlled by any treatment approach were reevaluated per-protocol only once more, because main end-point of study was to evaluate the spectrum of difficult (uncontrollable) asthma in young children. Once they reached sustainable control (two consecutive visits with controlled disease) they were followed outside the study group.

233 children were reevaluated up to six times. 17 patients were excluded because they were older than 10 years at referral. 216 children were included in our study.

They were 56.7 months old on average with extremes of 4 to 125 months, 153 (70.83%) were boys and 182 (84.26%) were inner-city children. For 202 (93.53%) the evaluation per-protocol was completed.

153 (70.83%) had identifiable factors for not achieving control (non-adherence, parental denial of disease, no basic knowledge about disease and approach of an asthma patient, no written action-plan, inadequate treatment, inadequate delivery system for age or coordination).

49 (22.69%) had severe disease that generated multiple planned or unplanned visits and exacerbations. In 6 children (12.24%) of this group another diagnosis was documented (CF, VCD and BPD) and asthma or other recurrent-wheezing phenotypes were excluded. The remaining 43 children (87.76%) had uncontrolled asthma, but really difficult-to-treat or refractory asthma was documented only in 8 children (3.7% of included patients, but 18.6% of children with more severe disease and no identifiable factors). In these children there was not possible to achieve control (frequent exacerbations in spite of step five treatment for at least two months - high-dose ICS plus LABA or LTRA, according to NHLBI guidelines17) and ACT score was low.

Figure 1. *Study outline*

1. Start from scratch (all presumed severe asthma children should be reassessed from baseline).
2. Medical history should be performed in a standardized way.
3. Perform complete clinical assessment and evaluate video-recordings performed by family in oligo-symptomatic children.
4. Mandatory multidisciplinary approach: ENT, allergology and gastroenterology consults should be arranged.
5. Optional multidisciplinary approach: cardiology, genetics, neurology and psychology consults could be scheduled in selected patients.
6. Screening tests: pulmonary function tests, CBC, inflammation tests, serum 25OH vitamin D, total IgE, skin prick-tests, ECG, chest radiology, FeNO, sweat test, oesophageal pH-metry.
7. Selected tests for non-responders: CFTR genotyping, Doppler heart ultrasound, bronchoscopy and nasal-mucosa biopsy.
8. Education, inhalation technique and device management evaluation.
9. Start treatment at stage five NHLBI guidelines (high-dose ICS + LABA or LTRA).
10. Reevaluate at 2 and 6 weeks (for non-response) and at 3 months interval for at least one year since last exacerbation for responders.

Figure 2. *Asthma Decalogue in Children*

Results

313 referrals in an out-patient clinic during a six-month period (October 2011-March 2012) were evaluated (Figure 1).

This group was particular compared with general aspects of young children with recurrent wheezing. They didn't present male dominance (50% girls), they presented rhino-conjunctivitis and atopic dermatitis. Another feature of this group was the high exacerbation rate as compared with asthma group as a whole and even with those with more severe disease and poor control.

This group presented, more often than control group, severe side effects induced by intense regimens of prescribed medication. In 2 (25%) from severe asthma preschoolers versus 1 case (0.65%) in children with non-severe asthma were documented significant side effects, like depression and/or psychotic episodes associated with initiation of chronic LTRA treatment.

All uncontrolled children were evaluated for eosinophilic inflammation by FeNO and had a vitamin D metabolism evaluation. 4 (50%) had elevated FeNO (mean 81 ppb). FeNO correlated very powerful with ACT score (r = -0.993)[24]. Other 4 patients presented with normal FeNO (mean 7.3 ppb) and were suspected as non-eosinophillic inflammatory phenotypes. They were started on azythromycin, 3 times/ week for at least 3 months. 2 (25%) with severe allergic asthma were given Omalizumab and 2 (25%) received a combination of oral steroids and high-dose ICS fixed-combination. 7(87.5%) were vitamin D-deficient with an average value of (22.74 nmol/L) and were receiving 2000 UI vitamin D/day continuously during the entire study period.

Discussion

According to literature data, ACT is preferable to the ACQ in clinical practice[4]. New data have suggested that neither the ACT, nor the ACQ are useful for the assessment of uncontrolled asthma[4]. In our study we used ACT for uniform evaluation.

Difficult asthma in children is a heterogeneous group of diseases and sometimes is an umbrella for a wide variation of co-morbid conditions.

Structured approach of a child with suspected severe asthma can be performed in a ten steps process (Figure 2). Most important steps are the first two: start from scratch and get the basics right!

All patients should be reevaluated from zero. A structured questionnaire should be provided before the first visit. Parents should have enough time to answer the questions. During first visit parents should bring the completed questionnaire and answers should be thoroughly reviewed. As screening tool we used the API

(asthma predictive index)[11]. In young children this scoring system seems to be a very efficient tool[12].

Treatment should focus on achieving asthma control because this approach has major advantages for patients and significantly outweighs potential risks and side effects[20]. Patients can benefit of a tailored anti-inflammatory strategy by means of FeNO measurements in compliant, device-proficient and trained patients. The children with potential non-eosinophilic inflammation should be treated with step V + azithromycin. Vitamin D deficiency could be a factor for poor control in children with asthma[21, 22] as in adult asthmatics[23].

Conclusions

Previously reported data in Romanian children described severe disease in a smaller proportion (1.5%)[27] that one seen in our study (3.7% patients). Reported data present a lower frequency of asthma-associated severe rhino-conjunctivitis (in 60-63.6%)[28, 29] in these children, compared with 75% in our study.

Children with severe asthma were allergic in a smaller proportion than a general group of children with asthma and most of them had significant vitamin D deficiency.

Approach of a child with potential difficult-to-treat asthma should be generated in a structured way (pre-designed protocol):

1. Initial visit for complete clinical evaluation and personal + family history evaluation (pre-printed flow-chart is advisable!).

2. Tailored examination schedule to rule-out alternative diagnosis.

3. Optimal treatment regimen (drug and device optimization according to age and preferences) in a step-wise approach according to guidelines, starting at step V and titrating scheme according to response.

4. Educational and complex psychological support for both parents and children. ■

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