Allergol Immunopathol (Madr). 2014;42(6):507–509

Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica

www.elsevier.es/ai

EDITORIAL

Identifying severe asthma in pediatrics: The glass half full or half empty

One of the main limitations in adequately identifying severe asthma (SA) in pediatric patients is undoubtedly the lack of consensus regarding its definition. The severity of asthma depends on two closely related concepts: the underlying physiopathological alterations on one hand, and the lack of disease control on the other.[1]

In view of the existing terminological confusion, the World Health Organization (WHO) in 2009 established a task force with the aim of proposing a uniform definition of asthma severity,[2] which contemplated the level of treatment needed to achieve control of the disease. This initiative was also incorporated by the Global Initiative for Asthma (GINA) in its revision of 2014.[3] The term ''problematic severe asthma'' has been proposed in reference to patients who are unable to achieve control despite maximum treatment effort, and includes both difficult to control asthma and asthma resistant to treatment.[4]

Why is it important to identify pediatric patients with SA? A first reason could be its prevalence. Few studies have analyzed the prevalence of SA in the pediatric population. Lang et al. found the prevalence at 10 years of uncontrolled SA in a Norwegian cohort to be 0.5% for the general population and 4.5% among asthmatics.[5] Nordlund et al., using the definition proposed by the WHO and a different methodological approach, found the prevalence at 12 years in a cohort of Swedish children to be 0.23% (2.1% in asthmatics).[6] The article published in this issue of the journal by Plaza-Martín et al.[7] is the first study on the prevalence of SA in pediatric patients in Spain. During a period of three months, pediatric pneumology and allergy units from 30 Spanish hospitals analyzed 12,376 asthmatic patients and identified SA (according to medical criterion) in 8.8% of the cases (95% CI: 8.3–9.3%). Among these, difficult to control SA was diagnosed in 24.2% (95% CI: 21.7–26.8%) – representing 2.2% of the asthmatic subjects.

Another clear reason why it is important to identify SA in pediatric patients is its consequences. In effect, children with SA suffer important morbidity. In the mentioned study,[7] during the preceding year the patients with SA suffered 6.0 ± 5.0 exacerbations, and in the previous 6 months 20% had been admitted to hospital, 63% required emergency care, and 40% had made four or more unscheduled visits to their doctor, with a strong impact upon quality of life. This situation evidently implies important social and healthcare costs associated to SA – the amount totaling about 5380 euros/year in Spain. This sum is more than 10 times the cost of mild asthma, without taking into account the indirect costs, which are not negligible.[8] On the other hand, SA in pediatric patients is not without mortality.[9] Another no less relevant aspect is the middle- to long-term sequelae of the disease. Fitzpatrick et al.,[10] during the follow-up of pediatric patients with SA enrolled in the National Heart, Lung, and Blood Institute Severe Asthma Research Program, recorded a post-bronchodilator test reduction in FEV1 in 46% of the cases, and in 29% of the patients the decrease was over 1% annually – this suggesting progressive airflow limitation. Tai et al.[11] in turn found 44% of the patients with SA in childhood to develop chronic obstructive pulmonary disease by 50 years of age, with an odds ratio (OR) of 31.9 (95% CI: 3.4–269).

And how can we identify pediatric patients with SA? We first need to know the characteristics of the disorder, which differ from those of adult SA.[7,12–14] Pediatric SA tends to be more common in males, in patients with several years of asthma, with atopic conditions (increased IgE titers and exhaled nitric oxide levels, and greater aeroallergen sensitization), with lung function relatively within normal limits, and an improved bronchodilator response. On the other hand, adequate evaluation is required of each and every one of the dimensions of this complex and heterogeneous syndrome (symptoms, lung function, inflammation, and even quality of life), particularly taking into account that the association among them is weak and not substitutable but complementary.[15] The symptoms can be evaluated using previously validated questionnaires (though accepting their limitations), such as the CAN in Spain, which defines poor control as a score of ≥ 8, with sensitivity and specificity performance in the range of 70%.[16] The gold standard for assessing lung function in asthma is FEV1, but the cut-off points used to define severity are based on expert

http://dx.doi.org/10.1016/j.aller.2014.10.001

opinion and have not been duly validated. Furthermore, most children with SA have normal or almost normal FEV1 values (FEV1 >80% of the predicted value). Alteration of the FEV1/FVC ratio is more sensitive in this respect.[17] Serial pre- and post-bronchodilation measurements are needed in our patients, since bronchodilation is correlated to airway inflammation parameters and is a risk factor for the development of fixed airflow obstruction. Since the lungs of children are growing, the data should be presented graphically, as in the case of the body weight and height curves, using percentiles[18] that are available for this purpose (Global Lung Function Initiative; www.lungfunction.org). Although inflammatory parameters as such are not used for classifying the severity of asthma, increased exhaled nitric oxide levels are common in patients with SA, and are directly related to the risk of exacerbation, poor adherence and/or performance of the inhalatory technique and scant asthma control, and are predictive of the loss of lung function.[19,20] Regarding quality of life as the ultimate concern in asthma treatment, Nordlund et al.[21] found a PAQLQ (S) score of <6.2 to distinguish severe problematic asthma with a sensitivity of 85% and a specificity of 97%. This dimension of asthma probably should be included in the assessment of our patients.

A number of factors condition the correct identification of patients with SA, such as the existence of disagreement among specialists in classifying the severity of asthma, probably due to variability in interpretation of the symptoms and lung function, and even to variability in the attributed importance of the symptoms versus lung function[22]; heterogeneity in assessing asthma control among patients, parents and physicians[23]; the importance of adding objective measures – particularly those referred to lung function – to symptoms evaluation in order to better classify the severity of asthma and not underestimate the disease (which would lead to undertreatment)[24,25]; and the high percentage of pediatricians who do not routinely use lung function tests in evaluating their asthma patients.[26] We therefore need to develop and implement strategies such as adequate training of the healthcare professionals; therapeutic educational measures targeted to our patients and/or their caregivers; and structural and institutional improvements designed to overcome the existing problems and ensure better identification of SA in pediatric patients – with a view to offering optimum treatment capable of reducing morbidity and of avoiding deleterious effects upon lung growth and function. Let's fill the glass!

References

1. Blakey JD, Wardlaw AJ. What is severe asthma? Clin Exp Allergy. 2012;42:617–24.
2. Bousquet J, Mantzouranis E, Cruz AA, Aït-khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation of Severe Asthma. J Allergy Clin Immunol. 2010;126:926–38.
3. From the Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA); 2014. Available from: http://www.ginasthma.org/
4. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, de Benedicits FM, Melén E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36:196–201.
5. Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-kaas M, Mowinckel P, et al. Severe asthma in childhood: assessed in 10 year olds in a Barth cohort study. Allergy. 2008;63:1054–60.
6. Nordlund B, Melén E, Schultz ES, Grönlund H, Hedlin G, Kull I. Prevalence of severe childhood asthma according to the WHO. Respir Med. 2014;108:1234–7.
7. Plaza-Martín AM, Vennera MC, Galera J, Herráez L, PREX Study Group. Prevalence and clinical profile of difficult-to-control severe asthma in children: results from pneumology and allergy units in Spain. Allergol Immunopathol (Mar). 2014;42:510–7.
8. Blasco Bravo AJ, Pérez-Yarza EG, Lázaro de Mercado P, bonillo Perales A, Díaz Vázquez CA, Moreno Galdó A. Costes del asma en pediatría en España: un modelo de evaluación de costes basado en la prevalencia. An Pediatr (Barc). 2011;74:145–53.
9. Sánchez-Bahillo M, García-Marcos L, Pérez-Fernández V, Martínez-Torres AE, Sánchez-Solís M. Evolución de la mortalidad por asma en España, 1960–2005. Arch Bronconeumol. 2009;45:123–8.
10. Fitzpatrick AM, Gerald Teague W, National Institutes of Health/National Heart. Lung and Blood Institute's Severe Asthma research Program. Progressive airflow limitation is a feature of children with severe asthma. J Allergy Clin Immunol. 2011;127:282–4.
11. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax. 2014;69:805–10.
12. Fitzpatrick AM, Gerald Teaque W. Severe asthma in children: Insights from the National Heart Lung, and Blood Institute's Severe Asthma Research Program. Pediatr Allergy Immunol Pulmonol. 2010;23:131–8.
13. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011;127:382–9.
14. Jenkins HA, Cherniack R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. Chest. 2003;124:1318–24.
15. Sardón-Prado O, Korta-Murua J, Valverde-Molina J, Fernández-Paredes JJ, Mintegui J, Corcuera-Elosegui P, et al. Association among lung function, exhaled nitric oxide, and the CAN questionnaire to asses asthma control in children. Pediatr Pulmonol. 2010;45:434–9.
16. Pérez-Yarza EG, Badía X, Badiola C, Cobos N, Garde J, Ibero M, et al. Development and validation of a questionnaire to asses asthma control in pediatrics. Pediatr Pulmonol. 2009;44:54–63.
17. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying asthma severity in children. Mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med. 2004;170:426–32.
18. Spahn JD, Cherniack R, Paull K, Gelfand EW. Is forced expiratory volumen in one second the best measure of severity in childhood asthma? Am J respir Crit Care Med. 2004;169:784–6.
19. Turner S. Exhaled nitric oxide and the management of childhood asthma – yet another promising biomarker ''has been'' or a misunderstood gem. Paediatr Respir Rev. 2014, http://dx.doi.org/10.1016/j.prrv.2014.07.005.
20. van Veen IH, ten Brinke A, Sterk PJ, Sont JK, Gauw, Rabe KF, et al. Exhaled nitric oxide predicts lung function decline in difficult-to-treat asthma. Eur Respir J. 2008;32:344–9.
21. Nordlund B, Konradsen JR, Pedroletti C, Kull I, Hedlin G. The clinical benefit of evaluating health-related quality-of-life in children with problematic severe asthma. Acta Paediatr. 2011;100:1454–60.
22. Baker KM, Brand DA, Hen J. Classifying asthma. Disagreement among specialist. Chest. 2003;124:2156–63.

23. Shefer G, Donchin M, Manor O, Levy-Hevroni R, Schechter A, Cohen R, et al. Disparities in assessments of asthma control between children, parents, and physicians. Pediatr Pulmonol. 2014;49:943–51.
24. Stout JW, Visness CM, Enright P, Lamm C, Shapiro G, Gan VN, et al. Classification of asthma severity in children. The contribution of pulmonary function testing. Arch Pediatr Adolesc Med. 2006;160:844–50.
25. Cowen MK, Wakefield DB, Cloutier MM. Classifying asthma severity: objective versus subjective measures. J Asthma. 2007;44:711–5.
26. García-Marcos L, Castro-Rodríguez JA, Montaner AE, Garde JG, Bernabé JJM, Belichón JP, Spanish Pediatric Asthma Study Group. The use of spirometers and peak flow meters in the diagnosis and management of asthma among Spanish pediatricians. Results from the TRAP study. Pediatr Allergy Immunol. 2004;15:365–71.

J. Valverde-Molina
Pediatric Pneumology, Hospital Universitario los Arcos del Mar Menor, San Javier, Murcia, Spain
E-mail address: Jose.valverde@neumoped.org