Clinical Case Report

Medicine®

OPEN

Different evolution in the treatment of a severe persistent asthma in 2 twins

Case report and review of the literature

Ileana Ioniuc, MD, PhD[a], Ingrith Miron, MD, PhD[a], Ancuta Ignat, MD, PhD[a], Vasile Valeriu Lupu, MD, PhD[a,*], Cristina Gavrilovici, MD, PhD[a], Magdalena Starcea, MD, PhD[a], Elena Cristina Mitrofan, MD, PhD[b], Alina Murgu, MD, PhD[a]

Abstract

Rationale: Asthma is a multifactorial disease with complex genetic inheritance. In children under the age of 5 years, the diagnosis of asthma is a challenge.

Patient concern: We present the case of twin sisters under the same treatment for persistent asthma, but with different evolution over the time.

Diagnoses: One of the sister is diagnosed with severe persistent bronchial asthma associated with bronchiectasis and dyslipidemia and the other one only with mild persistent asthma.

Interventions: At each admission the treatment for the exacerbations and the underlying respiratory infections was represented by antibiotics, short-acting β2 agonists, and, sometimes, oxygen and systemic corticosteroids. As chronic treatment, they received in the last period inhaled corticosteroids associated with long-acting β2 agonist.

Outcomes: Until the age of 6.5 years, they had similar diagnoses and treatment; from this point one was asymptomatic, with normal pulmonary function tests. The other one had a more complicated evolution which led to a severe crisis by the age of 10 years old.

Lessons: Although asthma is a multifactorial disease with complex genetic inheritance, the genetics has its limits. Our twins had a similar onset with the same genetic inheritance, with the same risk factors, with the same comorbidities and with the same treatment. In this context, different evolutions of severe persistent asthma require more extensive genetic investigations.

Patient concern: We present the case of twin sisters under the same treatment for persistent asthma, but with different evolution over the time.

Abbreviations: BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PMN = polymorphonuclear leukocytes, SD = standard deviation.

Keywords: children, persistent asthma, severe asthma crisis, twins

1. Introduction

Asthma is defined as a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing. Asthma is the most common cause of chronic noninfectious disease in childhood. Spirometry is considered to be the "gold standard" of measuring airway caliber in cooperative children, because this can be used to diagnose, manage, and monitor asthma.[1,2]

In children under the age of 5 years, the diagnosis of asthma is a challenge, because wheezing can occur without asthma, and also, because confirmatory lung function tests cannot be performed.[3]

The diagnosis of asthma in young children is based largely on symptoms (wheezing, cough, difficult breathing, activity limitation, and nocturnal symptoms) and frequency, combined with a clinical assessment of family history and physical examination.[1,4]

2. Case report

This is the case of 2 sisters from a term (37 weeks) twin pregnancy, weighing 2000 and 2200 g, respectively, on birth, both with APGAR = 8, natural birth, artificially fed from birth, and fed a diversified diet starting at 6 months old. There is no family history of respiratory disease, apart from a cousin 22 years old, known with asthma. The 2 sisters had multiple respiratory infections, without exposure to cigarette smoke or polluted environment. We present the case of the first twin (T1, 10 years old), whose evolution was more complicated. Informed consent was obtained from the parents upon each admission.

Editor: N/A.

All authors contributed equally to this paper.

The authors report no funding and conflicts of interest.

[a] Pediatrics Department, University of Medicine and Pharmacy "Grigore T. Popa", [b] Clinic of Pulmonary Disease, Iasi, Romania.

[*] Correspondence: Vasile Valeriu Lupu, Pediatrics Department, University of Medicine and Pharmacy "Grigore T. Popa," Str. Universitatii, nr. 16, Iasi, 700115, Romania (e-mail: valeriulupu@yahoo.com).

Medicine (2017) 96:49(e8820)

Received: 11 October 2017 / Received in final form: 27 October 2017 / Accepted: 31 October 2017

http://dx.doi.org/10.1097/MD.0000000000008820

At the age of 8 months, she was admitted for acute bronchiolitis, and at the age of 1 year for viral pneumonia. Subsequently, she had frequent upper and lower respiratory infections, approximately 1 episode per month, more often in winter, most of them accompanied by wheezing, treated in the outpatient unit, until the age of 3 years and 6 months old. She had daily morning and night cough between the episodes of wheezing.

When she was 3.5 years old, T1 was admitted for another episode of viral pneumonia complicated with bacterial infection, with fever, productive cough, expiratory dyspnea, generalized retraction, sibilants, and crackling rales. The full blood count was normal, CRP absent, the ESR and fibrinogen were also within normal limits. Chest x-ray revealed that the interstitium was greatly accentuated in the left perihilar and hilar-basal regions. The administered treatment consisted in the association of ampicillin with gentamicin, salbutamol, inhaled corticotherapy, and mucolytics.

Thus, on her first admission in our clinic, when she was 3 years and 7 months old, T1 was overweight + 5 SD, she had rare cough, lung auscultation with rare bilateral sibilants on deep inspiration. The full blood count was normal, with eosinophils 8% ($720\,mm^{-3}$); ESR 5 mm/h; no eosinophils in nasal secretion or in the laryngotracheal aspiration; transaminase, urea, phosphocalcic, and lipid metabolism were normal, sweat test 11 mEq/L Na, 14 mEq/L Cl, normal immunogram, alpha-1 antitrypsin was normal, anti-IgM-Toxocara antibodies was positive. The administered treatment included salbutamol, inhaled corticosteroids, and albendazole. The diagnosis was toxocariasis with pulmonary manifestations, moderate persistent bronchial asthma, lambliasis, and first degree obesity. The treatment recommended upon discharge was inhaled corticosteroids (beclomethasone) in medium dose, albendazole 10 mg/kg of body weight/d for 10 days, and a liver protector. At this time we could not perform an allergic panel or cutaneous testing for allergens.

On her second admission in our clinic, at the age of 3 years and 8 months, T1 came in for a wheezing and expiratory dyspnea episode, for which she received salbutamol. In addition, the child had morning cough approximately 2 to 3 d/wk and night cough. The clinical examination was normal, except for the overweight and morning cough. The full blood count was still normal; nasal eosinophils were present; urea, transaminase, glycemia, and lipids were normal, the cutaneous test was negative, and total IgE < 100 U/L. The discharge diagnoses were: moderate persistent bronchial asthma, partially controlled, allergic rhinitis, and first degree obesity. The treatment recommended upon discharge was salmeterol/fluticasone propionate 25/125 μg, 1 puff twice/d by baby-inhaler.

On her third admission, at the age of 3 years and 9 months, symptoms were very rare during the daytime, and disappeared altogether during the night. This was considered to be a good asthma control, and the patient was recommended to continue the therapy with salmeterol/fluticasone propionate 25/125 μg, 1 puff twice/d and she was discharged with the diagnosis of moderate persistent bronchial asthma with good control, allergic rhinitis, and overweight.

On her fourth admission, after a month, when she was 3 years and 10 months old, she was admitted for fever, productive cough, dyspnea, and wheezing. The lung auscultation revealed disseminated sibilant and crackling rales. White blood cells = 1120 mm-3, PMN = 67%, ESR = 35 mm/h, CRP positive, in the laryngotracheal aspiration eosinophils were absent, with numerous PMNs, and culture positive for *Branhamella catarrhalis*. The x-ray revealed an infiltrative aspect on both pulmonary areas; the tuberculin skin test was negative. The recommended treatment consisted of amoxicillin/clavulanate potassium, corticosteroids, salbutamol, and mucolytic agents. The diagnoses were moderate persistent bronchial asthma, with the moderate severity exacerbation, viral pneumonia possibly with *B catarrhalis*, allergic rhinitis, overweight, and the patient was recommended to continue the treatment with salmeterol/fluticasone propionate 25/125 μg for another 3 months.

At the check-up at the age of 4 years and 5 months, T1 was asymptomatic under treatment with salmeterol/fluticasone propionate 25/125 μg. The clinical examination revealed only overweight, and according to the step down therapy, treatment with salmeterol/fluticasone propionate 25/50 μg was recommended.

The child T1 came back at the age of 6 years without intercritical treatment, interrupted without medical approval, for the previous 12 months. She had 2 to 3 exacerbations a month needing salbutamol and morning cough for 2 to 3 weeks. The clinical examination revealed irritating cough, rough vesicular breath sounds, and disseminated sibilant rales. The full blood count was normal, ESR = 35 mm/h, eosinophils were present in the nasal secretions, anti-IgM-*Toxocara canis* antibodies were present (1/100). During her hospitalization, she was administered sulperazone, corticosteroids, salbutamol, and albendazole. She was discharged with the diagnoses of moderate persistent bronchial asthma, medium exacerbation, interstitial pneumonia, allergic rhinitis, toxocariasis, and first degree obesity. The treatment recommended upon discharge included salmeterol/fluticasone propionate 25/125 μg. On this admission, spirometry was attempted, but the girls did not collaborate.

When she was admitted at the age of 6 years and 5 months, T1 had morning cough 1 to 2 episodes/month, cough caused by effort, sneeze, and nasal obstruction. The iontophoresis was normal, as well as the immunogram, IgE 65 UI/mL, and the spirometry revealed the persistence of a distal obstructive syndrome. (FVC = 94%; FEV1 = 85.7%; MEF50 = 80%; MEF25 = 50%, step up). She was discharged with the diagnoses of severe bronchial asthma, allergic rhinitis and first degree obesity. The treatment recommended at home was: fluticasone propionate/salmeterol xinafoate 25/125 μg, 1 puff twice/d, for 1 month and montelukast, 5 mg/d. The allergen panel for both twins was negative.

Up to this age, the 2 sisters came in together for admissions, with similar diagnoses and treatments. When they came in at the age of 6 years and 5 months, the twin sister T2 was asymptomatic, and spirometry was normal. Starting that moment, their treatment was differentiated and she was recommended fluticasone propionate 25/125 μg 1 puff twice a day, for 1 month.

After that, the 2 sisters never returned to our clinic. T1 came twice to a different clinic for medium exacerbations, for which she was administered hydrocortisone hemisuccinate, salbutamol, and antibiotics, and she received chronic therapy with montelukast sodic and medium dose inhaled corticotherapy with partial control of the symptoms. For the daily cough, the exacerbations needing salbutamol—1 episode/wk, the cough caused by effort, and nasal obstruction, she was recommended treatment at home with montelukast 5 mg/d and fluticasone propionate 25/125 μg when necessary.

Actually, the first twin (T1, 10 years old) was admitted in the intensive care unit for inefficient cough, wheezing, expiratory dyspnea, and alteration of her general state.

The onset of the exacerbation was 36 hours before the present admission in the intensive care unit originally with cough

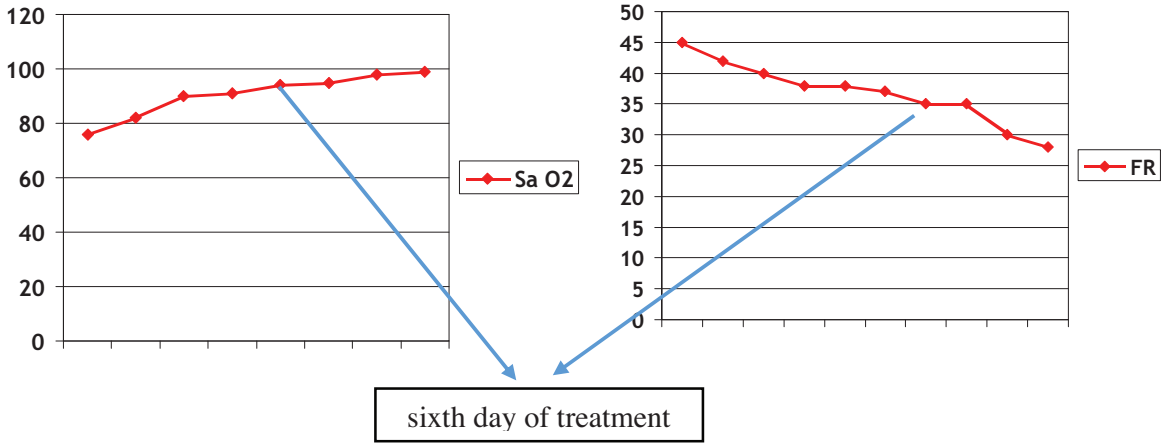

Figure 1. (A) Evolution of SaO_2 under treatment. (B) Evolution of the respiratory rate under treatment.

enhancement, gradual aggravation of her functional respiratory syndrome, and general state.

Upon admission in the intensive care ward, T1 was in a critical general state, had expiratory dyspnea, with respiratory rate of 45 min^{-1}, perioral-nasal cyanosis, generalized retraction, wheezing, bilateral sibilant and stertor, heart rate 150 min^{-1}, arterial blood pressure 110/60 mm Hg, $SaO_2 = 84\%$.

In our clinic, after 48 hours, the patient had an influenced general state, respiratory rate of 28 min^{-1}, coarse vesicular breath sounds, disseminated crackling and sibilant rales on both pulmonary areas, SaO_2 94%, daytime, and productive cough.

Her biological parameters were: full blood count—white blood cells = 37.3100 mm-3, PMN = 92.3%, Hb = 15.8 g/dL, platelets = 530000 mm-3; ESR = 27 mm/h, fibrinogen = 438 mg/dL, CRP > 6; total cholesterol = 219 mg/dL, LDL cholesterol = 125.5 mg/dL, triglycerides = 360 mg/dL, and normal glycemia.

The thoracic x-ray revealed a bilateral interstitial infiltrates, dilated bronchi grouped in a cluster located in the left basal region.

Following the administered treatment, the patient had a favorable evolution, with the improvement of the SaO_2 and of the respiratory rate (Fig. 1A and B).

Based on the clinical and lab data, the following diagnoses were set: severe bronchial asthma with severe crisis, superinfected basal bronchiectasis, superinfected bacterial viral pneumonia, first degree obesity (BMI, 30), and dyslipidemia.

The treatment administered in the intensive care ward consisted in third generation cephalosporins, dexamethasone, salbutamol, lactic calcium, Peritol, and O_2 therapy. In our clinic, she received systemic corticotherapy in descending dose for 7 days, then inhaled corticotherapy, aminophyllinum orally for 5 days, association of clindamycin to third generation cephalosporins for 10 days, antacid, lactic calcium, ACC, aerosols with ACC, and physiological saline twice a day.

3. Discussion

A new guideline for asthma management and prevention in children of 5 years and younger has been published.[3] It addresses risk factors associated with asthma, the diagnosis, management and pharmacological treatment of asthma (education, control, pharmacotherapy, and the management of acute exacerbations).

Asthma has become more prevalent in recent years. The prevalence of asthma in early childhood at Northern Portugal was 10.7%.[5] The same study showed that environmental context (urban, suburban, or rural), gender and family asthma history was associated with asthma prevalence.[5] Risk factors for asthma were urban location, male gender, and having an asthmatic parent.[5]

Risk factors for asthma exacerbations include uncontrolled asthma symptoms, exposure to specific allergens, viral infections, tobacco smoke, air pollution, socioeconomic problems, certain foods and food additives such as sulfur dioxide, and emotional factors. Our twins had family history asthma and history of repeated respiratory infections, without exposure to tobacco smoke or air pollution.

A diagnosis of asthma should be considered when a young child presents symptoms like cough, wheezing, difficult or heavy breathing or shortness of breath, reduced activity, past or family history, therapeutic trial with low dose inhaled corticosteroids, and as-needed short-acting $beta_2$-agonist.[3]

There are no tests to diagnose asthma with certainty in children 5 years and younger. A therapeutic trial with short acting bronchodilators and inhaled glucocorticosteroids for at least 8 to 12 weeks may be suggestive for the presence of asthma.[6] First spirometry that our girls have collaborated was at the age of 6 years and 5 months, when a spirometry was modified, and the other normal.

Asthma is a multifactorial disease with complex genetic inheritance. Some studies reported more than a hundred genetic variants positioned throughout the genome that are implicated in asthma susceptibility.[7]

There are studies that examined the phenotypic expression of asthma. In Danish twins, the correlation between the ages at onset of asthma was higher in monozygotic twins than that in dizygotic twins, and with a heritability of age at onset of asthma of 35%.[8] It was demonstrated that if the first member of a twin pair develops asthma at an early age, then the co-twin also has a higher risk of developing asthma at an early age.[8] In our case, the onset was early for both twins, but the evolution was different.

Several twin studies have shown that the risk of atopy as well as the variation in serum total IgE has moderate-to-high heritability.[9–11] In our patients, skin tests were negative and total IgE were within normal limits.

The incidence of asthma is increasing, particularly in our country. The epidemiological studies suggest that infection with *T canis* contributes to the development of atopic diseases, including asthma. The genetic pattern and the frequency of exposure may influence the relationship between allergy and this infection. The induction of a Th2-cell mediated immune response with high production of IgE, the airways inflammation, and the accumulation of eosinophils can represent the common pattern of these 2 diseases. In our case, the treatment with albendazole does not improve the course of the underlying disease.[12]

"Hygiene theory" claims that the infectious agents have protective influence for asthma by initiating a Th1 type immune defense mechanism. Today, it is known that certain viral or bacterial infection occurring mainly in children at risk of atopy can trigger asthma by deviating the immune response to the Th2 line.[13] Viral or bacterial infection aggress the bronchial epithelial cell that intervenes in the immune response by expressing at least 10 members of the toll-like receptor (TLR 1–4).[13] This could be mechanism that practically differentiates the evolution of the disease in our twins.

Searching on PubMed, we did not find similar case reports.

4. Conclusion

Although asthma is a multifactorial disease with complex genetic inheritance, the genetics has its limits. Our twins had a similar onset with the same genetic inheritance, same risk factors, same comorbidities, and same treatment. In this context, different evolutions of severe persistent asthma require more extensive genetic investigations.

Acknowledgments

We would like to thank the staff in Intensive Care Unit, in Radiology Department, and Laboratory Unit, from the "St. Mary" Children Emergency Hospital, Iasi, for their help in managing these patients.

References

[1] Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 2007;175: 1304–45.
[2] van den Wijngaart LS, Roukema J, Merkus PJFM. The value of spirometry and exercise challenge test to diagnose and monitor children with asthma. Respirol Case Rep 2015;3:25–8.
[3] Global Initiative for Asthma (GINA). 2017 Pocket Guide for Asthma Management and Prevention in Children 5 Years and Younger Available at: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed October 1, 2017
[4] Belhassen M, De Blic J, Laforest L, et al. Recurrent wheezing in infants: a population-based study. Medicine (Baltimore) 2016;95:e3404.
[5] Branco PT, Nunes RA, Alvim-Ferraz MC, et al. Asthma prevalence and risk factors in early childhood at Northern Portugal. Rev Port Pneumol (2006) 2016;22:146–50.
[6] Potter PC. Current guidelines for the management of asthma in young children. Allergy Asthma Immunol Res 2010;2:1–3.
[7] Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol 2008;8:169–82.
[8] Thomsen SF, Duffy DL, Kyvik KO, et al. Genetic influence on the age at onset of asthma: a twin study. J Allergy Clin Immunol 2010;126:626–30.
[9] Bazaral M, Orgel HA, Hamburger RN. Genetics of IgE and allergy: serum IgE levels in twins. J Allergy Clin Immunol 1974;54:288–304.
[10] Thomsen S.F. The contribution of twin studies to the understanding of the aetiology of asthma and atopic diseases. Eur Clin Respir J. 2015; 2. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4653279/ Accessed October 5, 2017.
[11] Blumenthal MN, Bonini S. Marsh DG, Blumenthal MN. Immunogenetics of specific immune responses to allergens in twins and families. Genetic and environmental factors in clinical allergy University of Minnesota Press, Minneapolis, MN:1990;132–42.
[12] Pinelli E, Brandes S, Dormans J, et al. Infection with the roundworm Toxocara canis leads to exacerbation of experimental allergic airway inflammation. Clin Exp Allergy 2008;38:649–58.
[13] Murgu A, Gotia S. The infection - risk factor for asthma in children. Revista Românå de Pediatrie 2012;LXI:329–39.