

Lung Function in Hyper IgE Syndrome

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Summary. Pneumatocoles and bronchiectasis are secondary complications of respiratory infections in patients with hyper IgE syndrome (HlgES). We report on a patient with HlgES and recurrent pneumonias since 1 year of age, with progression to pneumatocoles and bronchiectasis and fatal outcome, with disseminated infection and suspected allergic bronchopulmonary aspergillosis, who was subjected to sequential spirometric assessment. We describe the early beginning of respiratory infections, difficulties in the management of pulmonary sequelae and the impact of an early functional diagnosis and follow-up of the patient regarding a disease for which lung function has not been fully described. **Pediatr Pulmonol.** © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Recurrent pulmonary infections with the formation of bronchiectasis and pneumatocoles may be clinical manifestations of some primary immunodeficiencies.¹ Hyper IgE syndrome (HlgES) is a rare primary immunodeficiency caused by mutations of the *STAT-3* gene (autosomal dominant inheritance) involving deficiency of multiple cytokine transduction, reduction of Th-17 cell differentiation, and insufficient IL-17 production.² Patients can present chronic eczema, skin abscesses, recurrent respiratory infections, and high serum levels of IgE (2,000 IU/ml or more).^{3,4} The main causes of pneumonia are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, with possible progression to bronchiectasis and pneumatocoles, usually due to disorders of lung remodeling.^{3,5,6} However, there are few studies describing the spirometric findings of this disease, which could improve its management.

We report on a patient with autosomal dominant HlgES, recurrent pneumonia, severe pulmonary failure, and fatal outcome, whose pulmonary function was evaluated by sequential spirometry.

We emphasize the difficulties in the management of pulmonary complications that may be limiting the survival of these patients and the importance of an early lung function diagnosis for providing a better follow-up.

CASE REPORT

The patient was a 15-year-old white boy who started to present chronic eczema and severe recurrent infections since 2 months of age, affecting the skin, ears, sinuses, lungs, and liver, most of them caused by *Staphylococcus aureus*. He was referred to our primary immunodeficiency clinic at 3 years of age. His physical examination was remarkable for scaly facial eczema, rales, and splenomegaly. He presented cranial dysmorphisms such as prominent forehead, macrocephaly, broadened nasal bridge, and mild prognathism. His

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family history was unremarkable. Serum immunoglobulin levels were normal, except for IgE, which was very high (9,080 IU/ml). Pneumococcal antibodies were normal. HIV serology was negative and sweat chloride concentration was normal. When the patient was 13 years old, an X-ray of the teeth showed retention of primary teeth. Computed tomography of the lungs showed multiple pneumatoceles and bronchiectasis, with air-trapping signs in the left lung, which was lower than the right one (Fig. 1A,B). Surprisingly, the first spirometry showed a restrictive pattern which gradually evolved to an obstructive pattern and worsening of pulmonary saturation at rest.

Although *STAT-3* genetic testing was not performed, the clinical presentation was consistent with HIGES and the patient started therapy with prophylactic sulfamethoxazole-trimethoprim at 40 mg/kg/day and intravenous gammaglobulin at 400 mg/kg/day every 21 days. Eczema improved and the number of sinopulmonary infections was reduced, but the patient presented a progressive worsening of dyspnea and limitation of exercise. Evaluation of lung function showed reduction of FVC, FEV1, and FEF25-75, elevation of RV (229% of predicted). The Tiffenau index was normal, but decreased progressively in spite of treatment (Table 1).

At age 10, the patient underwent resection of the right middle lobe due to two large pneumatoceles and bronchiectasis. During the postoperative period he developed pneumothorax, subcutaneous emphysema, and a bronchopleural fistula, with slow clinical improvement and prolonged hospitalization. The patient persisted with severe dyspnea and limitation of exercise.

At age 15, the patient presented persistent fever, cyanosis, dyspnea, and suspected allergic bronchopulmonary aspergillosis. Counterimmunoelectrophoresis of blood was positive only for *Aspergillus fumigatus* and the sputum culture was negative for *Aspergillus fumigatus* and any other fungus. Specific IgE for *Aspergillus fumigatus* was elevated (20.3 IU/ml). However, an invasive aspergillosis could not be ruled out. He was treated with itraconazole and prednisone for 3 months with clinical improvement and a progressive reduction of antibody titers to *Aspergillus fumigatus*. However, he

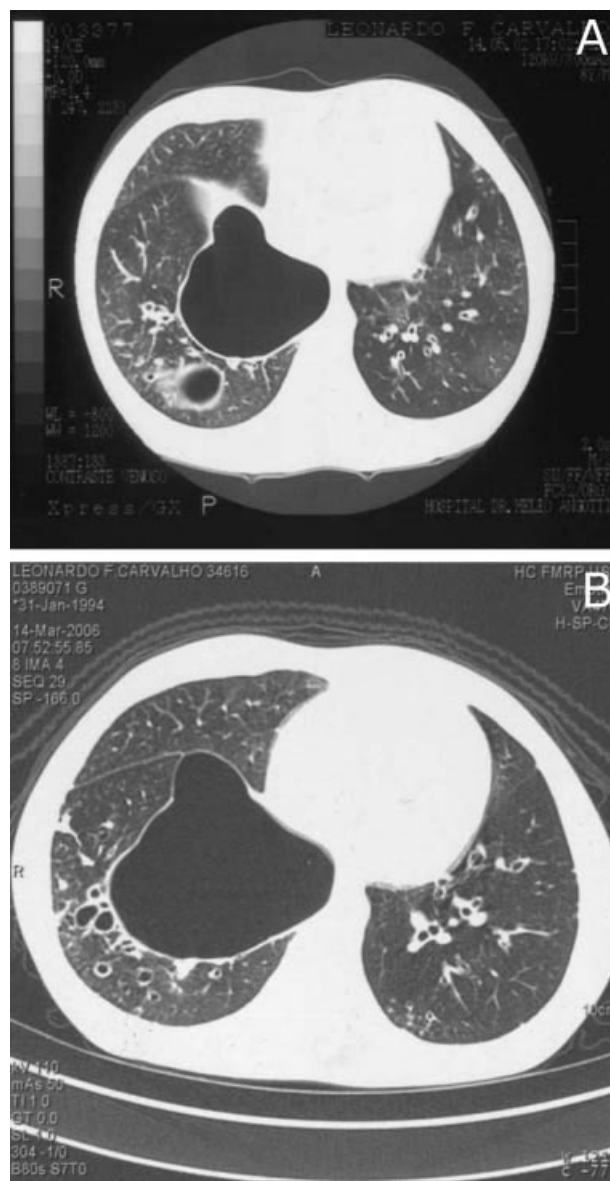


Fig. 1. Tomographic image showing a large cyst, various bronchiectasias and air trapping on the left at 8 years of age (A) and at 12 years of age (B), revealing increased bubble size but without additional radiologic lesions.

TABLE 1—Anthropometric and Pulmonary Function Measurements of the Patient Obtained During the Follow-Up Period

Parameters/age	8 years	10 years	12 years	14 years
Height (cm)	117	128.5	129.5	134.5
Body mass index	17.9	20	20.8	21.2
FVC (% of predicted)	70	56	37	39
FEV1 (% of predicted)	61	48	35	32
FEV1/FVC (%)	78	71	78	68
FEF25-75 (% of predicted)	34	32	27	18

experienced a sustained and progressive functional deterioration.

At age 16, the patient was admitted with fever, cyanosis, and severe dyspnea and he underwent chest drainage due to a pleural exsudate. He died a few days after admission due to respiratory failure and sepsis. *Pseudomonas aeruginosa* and *Staphylococcus aureus* were found in sputum and blood and *Aspergillus fumigatus* was found in the pleural drain.

DISCUSSION

HlgES is a multi-systemic disease characterized by serum levels of IgE usually higher than 2,000 IU/ml, chronic eczema, abnormalities of the musculoskeletal system, joint hypermobility, prominent forehead, macrocephaly, broad nasal bridge, retention of primary teeth, and recurrent infections, especially of skin and lungs.^{7,8} Pulmonary involvement is one of the main causes of the fatal outcome and life limitation of these patients due to both infection and subsequent pulmonary destruction. However, despite a large number of studies involving genes, cytokines, interleukins, and lymphocyte differentiation, little is known about the course of pulmonary function of these patients.

The main pathogens involved in infections are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenza*, especially in the beginning of the disease. However infections due to *Pseudomonas aeruginosa* and *Aspergillus fumigatus* may occur after parenchymal damage. Chronic and recurrent infections can cause bronchiectasis and pneumatoceles in 70% of affected patients due to disorders of the lung remodeling.^{1-6,9,10} Freeman et al.¹¹ reviewed autopsies of six women with HlgES and recurrent pneumonia caused by *Pseudomonas aeruginosa* and several fungi. Four of them underwent lobectomy and one of them underwent pneumectomy. Three patients died due to pulmonary bleeding and three patients died due to secondary brain infection caused by *Aspergillus* sp and *Scedosporium* sp.

Pneumonias should be treated aggressively in order to prevent pulmonary sequelae. Sulfamethoxazole-trimethoprim is frequently used in a prophylactic way to prevent infections by *Staphylococcus aureus* and intravenous gammaglobulin may reduce the number of infections. However, the use of other immunomodulator agents is controversial.¹² This is a disease that may progress to severe respiratory impairment. However, despite the complexity of signs and symptoms, little has been reported about the physiologic respiratory findings of these patients, information that could be of help for treatment and prognostic evaluation. Our patient had usual infections that were treated appropriately with a

satisfactory clinical response, although he rapidly reached a fatal outcome.

Surgical management of these sequelae is accompanied by risks and difficulties of lung re-expansion.¹³ Our patient underwent surgical treatment because of the difficult control of infections due to pneumatoceles and bronchiectasis and in order to exclude pulmonary regions with a shunt, but no improvement was obtained.

Furthermore, functional deterioration was present from the beginning. Despite the diffuse bronchiectasis and the signs of air trapping, only FEF25-75 and FVC values presented a significant fall, showing predominant impairment of the small airways. This finding was in contrast to those observed in most cases of bronchiectasis, which show a fall in FEV1 and FEV1/FVC in an initial phase.¹³ We question whether the extensive pulmonary destruction and the early death of our patient could have been predicted based on his intense functional deterioration, indicating that his disease was progressing despite the apparent clinical control. There are no reports in the literature about the pulmonary functional evolution of patients with HlgES. There are sporadic reports of ventilatory difficulty in intubated patients, with the occurrence of bronchoconstriction,¹⁴ but we did not detect any studies providing additional information. On this basis, we wonder what the initial pulmonary alteration would be in the disease in question: Pulmonary destruction leading to obstruction and increased RV caused by bronchiectasis, or involvement of the small airways.

On the basis of the present findings and on the scarcity of literature data, we emphasize that patients with HlgES and recurrent respiratory infections should be monitored yearly with spirometry and high resolution computed tomography of the lungs, procedures that would allow an early diagnosis of the sequelae, since clinical evaluation may be flawed for this purpose. We emphasize the importance of lung function abnormalities in order to draw the attention of other authors to these changes and thus try to establish a functional pattern for this disease. For other pulmonary diseases it is possible to predict a worse outcome by spirometric evaluations and to introduce a more aggressive treatment, especially when an inflammatory process of small airways is detected. We wonder if the same would also apply to HlgES. Thus further studies of pulmonary function in HlgES are needed in order to determine whether functional monitoring can be used as a prognostic index and to estimate the response to treatment, since spirometry is a noninvasive and easily available diagnostic tool. In this respect, spirometry could be very useful since pulmonary involvement is one of the main limiting factors regarding the quality of life of these patients.

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