Sequential Pulmonary Function Measurements in an Infant Treated with Idiopathic Pulmonary Hemosiderosis

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Pulmonary hemosiderosis is characterized by widespread hemorrhage in the alveolar spaces of the lungs [1]. It can occur as a primary disease of the lung or secondary to other systemic disorders. The most important clinical manifestations are pulmonary symptoms associated with iron deficiency anemia. The chest radiograph may show variable findings – from minimal infiltrates to large confluent shadows as seen in pulmonary edema. The definitive diagnosis is established by the demonstration of hemosiderin-laden macrophages in bronchoalveolar lavage or on lung biopsy.

The main treatment of patients with idiopathic pulmonary hemosiderosis is corticosteroids. If the response to corticosteroids is not sufficient or there are repeated relapses, inhaled steroids and immunosuppressive drugs such as azathioprine, hydroxychloroquine, cyclophosphamide or chlorambucil may be added [2]. In severe cases intravenous gammaglobulin has been found to be beneficial [3]. The course of the disease is variable, and the prognosis is generally poor with a mean survival of 2.5–3 years after onset. In adults and older children, lung function tests are useful for following the course of the disease and demonstrate decreased lung compliance, reduced lung volumes, and airflow obstruction. In infants, pulmonary function tests are more difficult to perform. However, valuable information may be obtained, particularly by measuring respiratory system compliance and lung volumes. We describe our experience using pulmonary function measurements in the management of an infant with severe idiopathic pulmonary hemosiderosis.

Patient Description

A 6 month old infant was referred to our department with a 2 month history of blood-streaked vomiting. The child was suspected to have an allergy to cow's milk protein and received a cow's milk protein-free diet without improvement prior to admission. He was born to healthy non-consanguineous parents of Ashkenazi Jewish* origin after a normal pregnancy and delivery.

On admission his weight was 7.3 kg and his height 65 cm (both 25th percentile). On physical examination he was pale with a respiratory rate of 60 breaths per minute. Auscultation showed that the lungs were clear and the heart sounds normal. Chest radiography showed bilateral alveolar infiltrates. Laboratory investigations revealed hemoglobin of 7.7 g/dl and hematocrit of 30%. The white blood cell and differential leukocyte counts as well as the platelet count were normal. The serum iron level was 15 µg/dl (normal 60–180), total iron binding capacity was 432 µg/dl (normal 250–450), and the ferritin level was below 10 ng/ml (normal 25–400). Clotting studies were normal. Routine serum biochemistry including liver and renal function tests was normal. Serological studies including antinuclear factor, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane, antireticulin, and anti-endomysial antibodies were all negative. Serum immunoglobulin levels, complement, T and B cell number and function were normal. Heart echocardiography was normal. Bronchoscopy revealed normal anatomy of the bronchial tree, but a small amount of fresh blood was noted in the trachea and both main bronchi. Histology of the bronchoalveolar lavage, using the Prussian blue stain, showed large amounts of hemosiderin-laden macrophages, which confirmed the diagnosis of pulmonary hemosiderosis.

Treatment was begun with intravenous methylprednisolone 4 mg/kg with progressive improvement after 1 week, followed by oral prednisone 2 mg/kg/day. Attempts to reduce the dose of prednisone resulted in an immediate exacerbation of the disease with respiratory distress, low oxygenation and a drop in hemoglobin level requiring hospitalization. Neither high dose pulses of methylprednisolone (30 mg/kg) nor the addition of hydroxychloroquine or methotrexate resulted in clinical improvement. A trial with high dose inhaled beclomethasone dipropionate (1500 µg/day) failed to provide any therapeutic effect. Moreover, the child developed cushingoid facies with hirsutism and systemic hypertension.

Infantile pulmonary function tests were performed using the Sensor Medics 2600 system. Respiratory system compliance and respiratory system resistance were measured by means of the end-inspiratory occlusion technique as described previously [4]. Functional residual capacity was measured by the classical open circuit "N_2 washout technique" in which N_2 is washed out from the respiratory system with 100% O_2 inhaled through a face mask. Pulmonary function studies showed severely reduced respiratory sys-

* Of East-European origin

Sequential pulmonary mechanics measurements

Age (mos)	Weight (kg)	Respiratory rate (min)	Tidal volume (ml)	Functional residual capacity (ml)	Crs/kg (ml/cmH_2O)	Rrs (ml/cmH_2O/sec)	Treatment
13	8	80			0.65	0.048	Prednisone 2 mg/kg
14	8.2	80	67		0.74	0.036	Prednisone 2 mg/kg, azathioprine 3 mg/kg, gammaglobulin
15	8.2	40	74		1.24	0.041	Prednisone 2 mg/kg, azathioprine 3 mg/kg, gammaglobulin
22	9.3	38	79	196	1.35	0.030	Prednisone 1 mg/kg, azathioprine 3 mg/kg, gammaglobulin
25	10.2	37	82	222	1.12	0.022	Prednisone 1 mg/kg, azathioprine 3 mg/kg, gammaglobulin
28	10.6	34	98	305	1.42	0.015	Prednisone 1 mg/kg, azathioprine 3 mg/kg, gammaglobulin
33	11.7	36	102	321	1.49	0.025	Prednisone 0.5 mg/kg, azathioprine 3 mg/kg, gammaglobulin
38	12.7	28	115	327	1.98	0.015	Prednisone 0.5 mg/kg, azathioprine 3 mg/kg, gammaglobulin
42	13.7	27	128	314	1.72	0.015	None

Rrs = respiratory system resistance, Crs = respiratory system compliance.

tem compliance as well as lung volumes [Table]. Azathioprine 3 mg/kg/day was added together with monthly intravenous gammaglobulin 400 mg/kg, which was increased to 2 g/kg. With this regimen the child became less symptomatic and the hemoglobin stabilized. Chest radiography showed the same alveolar pattern. However, pulmonary function tests showed gradual improvement in respiratory system compliance and functional residual capacity [Table]. The dose of prednisone was gradually reduced. After 27 months of treatment, the child did not suffer any exacerbations, the hemoglobin level was stable, and physical growth normalized. Azathioprine and IVIG were then discontinued. More than 3 years after the onset of the disease and 6 months after cessation of therapy, the child was asymptomatic and his physical examination normal even though chest radiographs still showed some increased interstitial markings.

Comment

This case of an infant with idiopathic pulmonary hemosiderosis demonstrates the usefulness of pulmonary function measurements in the clinical evaluation and therapeutic decision making. The diagnosis of this disorder was based on the presence of hemosiderin-laden macrophages on bronchoalveolar lavage in the absence of anatomic airway anomalies, or cardiac, renal or collagen vascular disease. The treatment with prednisone and methylprednisolone was associated with partial remission of the disease. However, all attempts at reducing the dose of steroids failed. Inhaled steroids, hydroxychloroquine and methotrexate were not found to be beneficial. We therefore started, in accordance with previous reports, treatment with oral azathioprine [2] and monthly IVIG [3], which resulted in clinical improvement and enabled reduction of the steroid dose.

Although IVIG is often administered in autoimmune diseases [5], this is only the second report of the use of IVIG in idiopathic pulmonary hemosiderosis. Nguyen et al. [3] described a case of severe idiopathic pulmonary hemosiderosis with recurrent exacerbations after cessation of steroid therapy in which remission was achieved with IVIG. This 4 year girl was first treated with a dose of 400 mg/kg IVIG per day for 5 days, and then one dose every 2 weeks for 3 months. The child remained healthy without medications during a follow-up period of one year. However, in our case it is difficult to determine to what degree each of the medications contributed to the child's recovery since they were administered concurrently.

Chest radiography continued to show bilateral infiltrates despite clinical improvement. However, the infant's pulmonary function measurements provided additional objective data that correlated with the clinical improvement. These sequential measurements assisted in the decision to reduce the drug therapy despite the persistence of radiological abnormalities. Of the measured variables, respiratory system compliance was the parameter that most accurately reflected the degree of pulmonary involvement. Starting at a low level, there was persistent improvement until it reached normal values in the final tests. Tidal volume and functional residual capacity increased and respiratory system resistance decreased accordingly. Pulmonary function studies have been shown to be useful in the evaluation and follow-up of children with chronic lung diseases. In infants and young children, these measurements are more complex, require special equipment but provide an objective assessment of pulmonary function. They have been used in neonatal intensive care units to follow the progression of chronic lung disease in both ventilated and non-ventilated patients. They were also found to be effective in the follow-up of infants with chronic interstitial pneumonitis. It seems that these tests can also be very helpful in idiopathic pulmonary hemosiderosis.

In conclusion, despite their complexity, pulmonary function tests provide valuable additional information and therefore should be recommended in the management of infants with significant lung disease. Further investigations are warranted to evaluate the efficacy of gammaglobulin therapy for idiopathic pulmonary hemosiderosis.

IVIG = intravenous immunoglobulin

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