Idiopathic pulmonary haemosiderosis in a child with Down’s syndrome: case report and review of the literature

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Abstract. We report the case of a female child with Down’s syndrome affected by idiopathic pulmonary haemosiderosis (IPH), who was successfully treated with hydroxychloroquine. First-line conventional treatment of IPH is traditionally based on systemic corticosteroids; however, many steroid-sparing agents are being increasingly used as adjuncts to corticosteroids in children with recurrent or refractory bleeding. The use of these drugs is particularly promising for maintenance treatment, because it tends to avoid the adverse effects of long-term corticosteroids. (Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 58-61)

Key words: pulmonary haemosiderosis, Down’s syndrome, hydroxychloroquine, bronchoalveolar lavage

Introduction

Idiopathic Pulmonary haemosiderosis (IPH) is a serious and potentially fatal disease which occurs predominantly in infants and children below 10 years of age. The diagnosis is suggested by the triad haematemesis, anaemia and pulmonary infiltrates, and is confirmed by the finding of haemosiderin-laden macrophages (siderophages) in bronchoalveolar lavage fluid (BAL) (1).

Case report

A female child aged 4 years 7 months with Down’s syndrome was referred to our centre with recurrent pneumonia and suspected haemolytic anaemia. She was born at term; during the first days of life she was diagnosed with ventricular septal defect, atrial septal defect and patent ductus arteriosus. At approximately two months of life she was referred to surgery with intestinal ischemia and necrotizing enterocolitis. Heart defects were surgically corrected at 70 days of life.

Before the admission she had a six month history of recurrent respiratory infections concomitant to episodes of suspected haemolytic anaemia and needed five hospital admissions to treat acute anaemia and/or respiratory distress. Repeated laboratory investigations revealed microcytic hypochromic anaemia (Hb lower value: 5.5 g/dl) with mild reticulocytosis (reticulocytes: 2.9-5.8%). Furthermore, an increase of both total and unconjugated bilirubin was found (7.44 mg/dl and 6 mg/dl, respectively). Serum vitamin B12 and folate concentrations were normal. Direct Coombs test, irregular antibodies to red blood cells, Hb electrophoresis, faecal occult blood and routine urinalysis were all negative. Blood glucose-6-phosphate dehydrogenase and pyruvate kinase were within the range of normality. There was no detectable blood loss from skin,
urine or stools. Anaemia was treated with oral iron supplements and two red blood cells (RBC) transfusions.

On admittance, physical examination did not reveal any abnormality, with the exception of a mild splenomegaly and a 92-94% oxygen saturation in room air; breath sounds were clear. She had no cough nor dyspnoea in the previous weeks; targeted questioning led to the mother’s recall of three episodes of mild haemoptysis with cough in the last two years. Laboratory investigations showed RBC 4770 x 10^9/l, Hb 12.8 g/dl, MCV 81.5 fl, white blood cells 6.18 x 10^9/l, platelet count 369 x 10^9/l. Inflammatory markers were normal. Urinalysis and kidney function tests were normal.

Chest radiography showed diffuse alveolar infiltrates (Figure 1A), and computed tomography scan revealed bilateral lung consolidations, interalveolar septal thickening and ground-glass opacities (Figure 1B).

Flexible bronchoscopy was performed: BAL showed 580,000 cells/ml (lymphocytes 5%, neutrophils 60%, macrophages 35%); numerous haemosiderin-laden macrophages (HLMs) were detected (>60%). Microbiological analysis for bacteria, mycobacteria and viruses were negative.

Anti-glomerular basement membrane antibodies, antinuclear antibodies, anti double-stranded DNA antibodies, cytoplasmatic staining and perinuclear staining anti-neutrophil cytoplasm antibodies, C3 and C4 were negative. Anti-transglutaminase and anti-endomysial antibodies were within the range of normality. Echocardiography showed normal heart anatomy and function, and no signs of pulmonary hypertension. Abdominal and renal ultrasound did not reveal any abnormality.

The diagnosis of idiopathic pulmonary haemosiderosis was made and immunosuppressive treatment with prednisone was started (initial dosage 25 mg/day, tapered after two weeks to 5 mg/day and then to 5 mg/day on alternate-day maintenance therapy) (Figure 2).

A further episode of haemoptysis with cough occurred after seven months: therefore, the child was admitted to our ward and the dosage of prednisone was temporarily increased (15 mg/day). One month later, the dosage was tapered to 5 mg on alternate days, and then stopped. Hydroxychloroquine at the dosage of 6 mg/kg/day was started (Figure 2). In the following year, only one episode of haemoptysis has occurred, which was treated with only a single course of prednisone (1.5 mg/kg/day).

**Discussion**

PH is defined as an abnormal accumulation of haemosiderin in the lungs, which results from a diffuse alveolar haemorrhage (2). It can be a primary pulmonary process or can be related to several dis-

![Fig. 1. (A) Chest X-ray shows bilateral alveolar infiltrates. (B) Computed tomography reveals bilateral lung consolidations, interalveolar septal thickening and ground-glass opacities](image)
The diagnosis of idiopathic PH (IPH) is made after having ruled out any other possible aetiology.

The differential diagnosis of PH includes other causes of diffuse alveolar haemorrhage, such as pulmonary capillaritis and acute idiopathic pulmonary haemorrhage (3). Pulmonary capillaritis can be found in association with pulmonary-renal syndromes, such as Goodpasture’s syndrome, systemic lupus erythematosus, Wegener’s granulomatosis, microscopic polyangiitis (4). Furthermore, the integrity of pulmonary capillaries can be impaired by increased pulmonary venous pressure: thus, an echocardiography is warranted to exclude any sign of pulmonary hypertension.

IPH is characterized by diffuse infiltrates, anaemia and HLMs in sputum, gastric aspirates, BAL or lung tissue: in our patient, microcytic hypochromic anaemia, concomitant with recurrent respiratory infections, was the presenting sign of the disease (5), and was initially suspected to be a haemolytic process, due to the mild transient elevation of total and unconjugated bilirubin.

The co-occurrence of PH and celiac disease (CD) was first described in 1971 (6): the patho-

![Fig. 2. Trend of haemoglobin levels during follow-up showing response to therapy. RBC-T: red blood cells transfusion. IPH: idiopathic pulmonary haemosiderosis](image)

...genetic link between the diseases is still not clear. It has been documented that gluten-free diet can have beneficial effects on lung disease: thus, patients with IPH should be screened for CD even in the absence of gastrointestinal symptoms. Recently, the association of PH with CD and retinitis pigmentosa was reported: for this reason, ophthalmic examination should be performed in patients with suspected PH (7).

It has been shown that PH could also be induced by cow milk, leading to the so-called Heiner syndrome (8). However, the association has been challenged as cow milk avoidance does not always produce the remission of symptoms and because CD and Heiner syndrome can co-exist. Finally, other possible mechanisms underlying PH are chemicals, such as trimellitic anhydride, propylthiouracil, insecticides (1).

The association between Down’s syndrome and PH is rare, having been reported only twice (9, 10), and no underlying mechanism has been proposed for this association. However, it has been shown that patients with Down’s syndrome have a high rate of respiratory problems (11).
First-line conventional treatment of IPH is based on systemic corticosteroids (3); however, many steroid-sparing agents, including cyclophosphamide, azathioprine, hydroxychloroquine, and intravenous immunoglobulin, have been used as adjuncts to corticosteroids in children with recurrent or refractory bleeding. Treatment with oral corticosteroids is generally indicated in the control of the acute phase of the disease: however, long-term corticosteroids should be avoided, due to the risk of important side effects.

The decision to use hydroxychloroquine as maintenance treatment in our patient was due to its efficacy and safety profile. The efficacy of hydroxychloroquine for maintenance treatment has been previously documented in children, even though the appropriate dose and the treatment schedule have not yet been definitively established (1, 12-14). It has also been suggested that long-term immunosuppressive treatment (i.e. hydroxychloroquine and azathioprine) may improve the prognosis of IPH in children (13, 14). In addition, hydroxychloroquine treatment for IPH has very few reported side effects (one case unilateral sensorineural hearing loss (15), and no cases of visual impairment). Finally, this drug offers the advantage of avoiding the adverse effects (i.e poor growth, cushingoid features, cataracts) of long-term corticosteroids.

References
