

Idiopathic Pulmonary Hemosiderosis: Clinical Profile and Follow up of 26 Children

S.K. Kabra, Sumit Bhargava, Rakesh Lodha, A. Satyavani and M. Walia

*Pediatric Pulmonology Division, Department of Pediatrics, All India Institute of Medical Sciences,
New Delhi 110 029, India.*

Correspondence to: S.K. Kabra, Additional Professor, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India. E-mail: skkabra@hotmail.com

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Objectives: To describe the clinical details and follow up of children with idiopathic pulmonary hemosiderosis. **Design:** Retrospective case series. **Setting:** Pediatric chest clinic of a tertiary care hospital. **Subjects:** Children diagnosed as suffering from idiopathic pulmonary hemosiderosis (IPH). **Methods:** Charts of patients diagnosed as IPH were reviewed for clinical features and treatment regimen. Diagnosis was based on presence of iron deficiency anemia, chest radiography and demonstration of hemosiderin laden macrophages in bronchoalveolar lavage (BAL), gastric aspirate, or sputum. Treatment consisted of oral prednisolone, hydroxychloroquine (HCQ) and inhaled corticosteroids (ICS). **Results:** The common clinical features in 26 children with IPH (mean age 75 months) included: cough, breathlessness, fever, hemoptysis and wheezing in 26 (100%), 22 (85%), 19 (73%), 15 (58%) and 14 (54%) children, respectively. Clubbing, hepatomegaly and splenomegaly was seen in 16 (62%), 15 (58%) and 10 (38%) children, respectively. Hemosiderin laden macrophages were documented in BAL and gastric aspirate in 92% and 30% patients, respectively. Symptoms did not recur in 17 patients who received prednisolone and HCQ initially. 5 patients had recurrence of symptoms and required short courses of oral prednisolone, 4 patients required frequent courses of prednisolone and were started on azathioprine. Older age, longer duration of illness, history of hemoptysis and jaundice were associated with poor response. **Conclusion:** Treatment with prednisolone and hydroxychloroquine followed by inhaled corticosteroids may improve survival in children with IPH.

Key words: Anemia, Hemosiderosis, Hydroxychloroquine, Pulmonary.

IDIOPATHIC pulmonary hemosiderosis (IPH), a rare pulmonary disorder, first described in 1931 (1), that manifests as a triad of hemoptysis, anemia and diffuse parenchymal infiltrates on chest radiograph. The incidence is estimated to be 0.24 to 1.23 cases per million in selected populations(2,3). Secondary pulmonary hemosiderosis has also been associated with cardiac disease, bleeding disorders, collagen vascular disease, systemic vasculitis and celiac disease(1,4-6).

Pulmonary hemosiderosis (PH) results from recurrent bleeding into alveolar spaces and interstitial lung tissue. If untreated, fibrosis and restrictive lung disease will develop and may lead to death(7). There is no definitive treatment. Treatment modalities include oral prednisolone and immunosuppressive treatment such as azathioprine (AZA),

cyclophosphamide (CYP) and hydroxychloroquine (HCQ).

We describe the clinical presentation, diagnosis, complications and follow up of 26 children with IPH.

Subjects and Methods

Medical charts of 26 children diagnosed to be having pulmonary hemosiderosis between 1998-2005 were collected from the records of the Pediatric Chest Clinic at a All India Institute of Medical Sciences, New Delhi.

The diagnosis of pulmonary hemosiderosis was considered in patients having cough, hemoptysis, and dyspnea; iron deficiency anemia; and infiltrates on the chest radiograph. The diagnosis was

confirmed by the detection of hemosiderin-laden macrophages in bronchoalveolar lavage fluid (BAL), sputum or gastric aspirate. Children with bleeding diathesis, vasculitis, foreign body aspiration, pulmonary tuberculosis, recurrent bronchopneumonia and vascular malformations were excluded.

Once the diagnosis was confirmed, patients were administered oral prednisolone at a dose of 2 mg/kg/day for 2 weeks if they presented during acute phase. Hydroxychloroquine (HCQ) was also started simultaneously at 3-5 mg/kg/day. In addition, a milk free diet was recommended for all patients. Steroids were gradually tapered, if possible, over a period of 4 to 6 weeks after the initial 2-week period of treatment. Inhaled corticosteroids (fluticasone 125 microgram twice a day by Metered dose inhaler and holding chamber) were started during steroid tapering after the acute phase subsided. Children having recurrence of symptoms were administered oral prednisolone for 1-2 weeks; those who developed symptoms during tapering of steroid their doses increased to 2 mg/kg/d for 2-4 weeks followed by attempt to taper. Patients with anemia were given oral elemental iron (3 mg/kg/day). Azathioprine (2-3 mg/kg/day) was prescribed if response to prednisolone was not satisfactory.

All patients on HCQ treatment were monitored for ophthalmologic complications. If a patient remained symptom free for more than 6 months on inhaled corticosteroids (ICS) and HCQ; the drugs were stopped. HCQ was stopped first followed by ICS after 3 months. Children were followed up every 4 weeks in the first 2-3 months or till they were stable. After that they were followed once in 3-6 months.

Analysis was done by using STATA 7.0 software (Stata Corp, Houston, TX). All clinical details including physical examination, laboratory values, treatment, and follow up details were entered for each patient. Patients who did not have recurrence of symptoms were classified as having good response. Patients who had recurrence of hemoptysis or anemia and responded to short courses of oral prednisolone were classified as having partial response and those who did not respond to oral prednisolone and required

azathioprine were classified as having poor response. Patients with partial and poor response were compared with patients with good response to identify risk factors.

Results

Over 8 years, a total of 4100 new patients were enrolled in Pediatric Chest Clinic of our hospital. Twenty six (0.63%) children were diagnosed as having Idiopathic pulmonary hemosiderosis (*Table I*).

Chest radiographs revealed diffuse and patchy alveolar shadows in 20 and 6 children respectively. These shadows showed significant clearance on follow up, in 11 (42%) patients. Computerized tomography scans, available in 15 patients revealed diffuse or patchy ground glass opacities. Three patients showed evidence of interstitial fibrosis. The CT scans in these three patients were done after 10, 12 and 84 months (respectively) after the onset of symptoms.

Anti nuclear antibody (ANA) and Anti nuclear cytoplasmic antibody (ANCA) studies were negative in all the patients. Specific IgE against cow milk proteins was done in 4 patients and all were negative. Spirometry could be done in 6 patients in the beginning and showed restrictive pattern in all.

Lung biopsy was performed in one patient and findings were typical of pulmonary hemosiderosis.

Details of response to therapy are summarised in *Table II*. The mean follow-up was 28 ± 27 (range 2-96) months. Two patients succumbed to the illness; one of them due to congenital heart block. Two patients were lost to follow up after 9 months of follow-up. All the patients exhibited initial response to oral prednisolone. There was remission of symptoms in all but one patient by three months. Only one fourth of the patients required oral prednisolone by end of six months. Seventeen patients did not have recurrence of symptoms (anemia, hemoptysis). Nine patients had recurrence of symptoms on follow-up between 3-54 months of follow up. Out of nine patients with recurrence of symptoms, 5 could be controlled with short course of oral prednisolone. Four patients were prescribed

TABLE I- Baseline Clinical Profile of Patients with Idiopathic Pulmonary Hemosiderosis (IPH)

Variables	Observations
Age at diagnosis	
Mean(SD) months	75.3 (46.1)
Range (months)	11-144
Age at onset of symptoms	
Mean(SD)in months	46.7 (40.00)
Range (months)	3-142
Sex M: F	11: 15
Cough	26 (100%)
Breathlessness	22 (85%)
Fever	19 (73%)
Hemoptysis	15 (58%)
Wheezing	14 (54%)
Number who had received blood transfusion	25 (96%)
Mean (S.D.) of blood transfusions per child	2.7 (2.0)
History of hospitalization	26 (100%)
Hospitalization/ child mean (S.D.)	3.5 (2.4)
Pallor	26 (100%)
Clubbing	16 (62%)
Hepatomegaly	15 (58%)
Splenomegaly	10 (38%)
Hemoglobin (g/dL) mean (SD)	6.2 (2.7)
Hemosiderin laden macrophages demonstrated in GA	7/23 (30%)
Hemosiderin laden macrophages demonstrated in BAL	22/24 (92%)
Diagnosis by	
GA positive and BAL Positive (N = 23)	5 (21%)
GA positive and BAL Negative (N = 23)	2 (9%)
GA negative and BAL Positive (N = 23)	16 (65%)
Sputum alone (N = 2)	2
BAL alone (N = 1)	1

azathioprine (2-3 mg/kg/day) as they did not show satisfactory improvement with prednisolone. One patient did not respond to azathioprine and died of sepsis. One patient who has received azathioprine for almost 18 months is doing well. Her oral steroids could be stopped. Another patient has been started on azathioprine for 2 weeks at the time of reporting. No patient developed signs of retinal toxicity due to HCQ.

Higher age at diagnosis and history of, hemoptysis or jaundice at presentation were associated with partial or poor response (*Table III*).

Discussion

Idiopathic pulmonary hemosiderosis generally occurs in children below the age of 10 years; commonly between the ages of 1-7 years (1). The classical triad of anemia, hemoptysis and pulmonary infiltrates is a distinguishing characteristic of this disease; however, any one of them could be the initial manifestation(1,8,9).

The mean gap between onset of symptoms and diagnosis was 30 months in our study. This delay in diagnosis may be due to absence of the classical

TABLE II—*Response to Treatment*

Follow-up Duration	N	Number of patients without symptoms	Number receiving daily oral prednisolone	Number receiving alternate day oral prednisolone	Number receiving HCQ	Number receiving ICS	Number receiving azathioprine
1 m	26	25(96)	24 (92)	2 (8)	26 (100)	26 (100)	0
2 m	25	24 (96)	17 (68)	6 (24)	25 (100)	25 (100)	0
3 m	24	24 (100)	4 (16)	16 (67)	22 (92)	22 (92)	1
6 m	24	22 (92)	5 (21)	1 (4)	19 (79)	19 (90)	1
9 m	21	19 (90)	5 (24)	1(5)	19 (79)	19 (90)	1
12 m	18	16 (89)	3 (17)	2 (11)	14 (78)	18 (100)	2
24 m	12	12 (100)	2 (17)	0	8 (67)	10 (83)	2
30 m	8	8 (100)	2 (25)	0	5 (62)	7 (87)	1
36 m	8	8 (100)	2 (25)	0	4 (50)	6 (60)	2
42 m	6	6 (100)	0	1 (17)	4 (67)	4 (67)	2
48 m	6	6 (100)	0	1 (17)	1 (17)	4 (67)	2
54 m	5	5 (100)	2 (40)	0	2 (40)	4 (80)	2
60 m	3	3 (100)	0	0	2 (67)	3 (100)	1
72 m	3	3 (100)	0	0	0	2 (67)	1
96 m	2	2 (100)	0	0	0	2 (100)	1

m = months; Figures in parentheses are percentages.

TABLE III—*Risk Factors for Poor Response*

Variables	Good response N = 17	Partial or poor response N = 9	p value
Age at diagnosis (months)	48 (18-87)	96 (84-139)	0.03
Age of onset of symptoms (months)	24 (8-59)	60 (20-84)	0.09
Duration of symptoms (months)	12 (7-24)	36 (5-77)	0.18
Sex M:F	7:10	4:5	0.87
History of hemoptysis at presentation	7 (41%)	8 (89%)	0.02
History of jaundice at presentation	0	7 (78%)	0.04

triad, an insidious onset and lack of awareness about the condition.

The clinical profile of our patients was similar to that reported earlier(2,3,8-10). The most consistent laboratory abnormality was anemia, present in 100% patients(8). In our patients the atypical clinical manifestations included associated complete heart block, infant presenting with severe anemia requiring repeated blood transfusions and absence of hemoptysis in one third of patients. Heart block has been described in a 24 year old male who also had celiac disease in addition to heart

block and hemosiderosis(11). Anemia as a sole manifestations of IPH has been described in children(12,13). In a series of 17 patients from University of Southern California School of Medicine, hemoptysis was present only in 65% of cases(10). Other reports also suggest absence of hemoptysis(9,14). Children presenting with anemia and recurrent respiratory problems and abnormal X-ray film may be a clue to diagnosis of IPH(15).

The gold standard for diagnosis has been considered to be lung biopsy. However, in the presence of typical finding of hemosiderin-laden

What is Already Known

- Idiopathic pulmonary hemosiderosis is a rare pulmonary disorder, most patients respond well to oral prednisolone.

What this Study Adds

- Outcome of IPH can be improved with inhaled corticosteroids and hydroxychloroquine.

macrophages on bronchoscopy or in gastric aspirate/sputum along with chronic pulmonary symptoms, an unequivocal diagnosis of IPH may be made(7,16,17). For demonstration of hemosiderin laden macrophages, gastric aspirate, broncho-alveolar lavage (BAL) or sputum can be used.

In the present study gastric aspirate had a sensitivity of 30% while BAL had a sensitivity of 92%. Doing both GA and BAL helped in identification of additional 9% patients. There are no studies to compare sensitivity of BAL and GA. BAL from involved areas has a higher diagnostic yield than the sputum examination(18).

Systemic corticosteroids are the first line treatment for acute alveolar haemorrhage state(2, 9, 10,16,18,19-21). Long-term steroid therapy may also reduce morbidity and decrease mortality. Most investigators have used other immunosuppressive agents such as HCQ and AZA in children who did not respond to corticosteroids(10, 22,23).

In our patients, we decided to use prednisolone to control the acute process and maintained them in remission with inhaled corticosteroids and HCQ. The decision to use HCQ in present study was based on case reports suggesting long term improvement in IPH(10,19,20). Use of ICS in IPH is limited to single case reports(24-26). All these reports suggest that with inhaled corticosteroids the need for oral prednisolone could be decreased in patients with IPH. Our results suggest that ICS along with HCQ may be an effective alternative treatment. However, our study is a retrospective review that does not allow us to compare one therapy to another or evaluate the efficacy of individual therapies. There is need to document beneficial effect of ICS in tapering oral prednisolone by a randomized controlled trial in future.

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