Clinical characteristics and prognosis of idiopathic pulmonary hemosiderosis in pediatric patients

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Abstract

Objective: This study aimed to analyze the clinical characteristics and prognosis of pediatric idiopathic pulmonary hemosiderosis (IPH).
Methods: Pediatric IPH cases that were diagnosed at West China Second University Hospital, Sichuan University between 1996 and 2017 were reviewed. Follow-up data from 34 patients were collected.
Results: A total of 107 patients were included (42 boys and 65 girls). The median age was 6 years at diagnosis. The main manifestations of the patients were as follows: anemia (n = 100, 93.45%), cough (n = 68, 63.55%), hemoptysis (n = 61, 57%), fever (n = 23, 21.5%), and dyspnea (n = 23, 21.5%). There were relatively few pulmonary signs. The positive rates of hemosiderin-laden macrophages in sputum, gastric lavage fluid, and bronchoalveolar lavage fluid were 91.66%, 98.21%, and 100%, respectively. Seventy-nine patients were misdiagnosed. A total of 105 patients were initially treated with glucocorticoids, among whom 102 survived and three died. Among the followed up patients, two died and 32 survived, among whom 10 presented with recurrent episodes.
Conclusions: The classic triad of pediatric IPH is not always present. The rates of misdiagnosis and recurrence of IPH are high. Early recognition and adequate immunosuppressive therapy are imperative for improving prognosis of IPH.

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Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder that is responsible for recurrent episodes of diffuse alveolar hemorrhage in children.[1,2] IPH is characterized by the triad of hemoptysis, iron deficiency anemia, and pulmonary infiltrates on chest imaging. This condition was first described by Rudolf Virchow in 1864 in patients after their death.[3] The exact incidence and prevalence of IPH are largely unknown. In select pediatric populations, the incidence of IPH varies between 0.24 and 1.26 patients per million, with a mortality rate of up to 50%.[4,5]

Children with IPH appear to more frequently experience a rapid course and have a worse prognosis than adults. Death may quickly occur with acute, massive, pulmonary hemorrhage or may occur over longer periods as the result of continued respiratory insufficiency and heart failure.[5,6] Historically, patients with IPH had an average survival of 2.5 years after diagnosis. Currently, 86% of patients with IPH may survive beyond 5 years.[3] At present, several pediatric IPH cases have been reported in the literature,[7,8] but few cohorts have been described. There is limited knowledge on the physiopathology, and there is a lack of consensus regarding care for IPH.[9] Therefore, we conducted a retrospective review to investigate the clinical characteristics and prognosis of IPH in children.

Methods

Subjects

Complete data from children with confirmed IPH who were hospitalized at West China Second University Hospital, Sichuan University between January 1996 and January 2017 were reviewed. Patients with IPH were defined as follows: (1) the triad of iron deficiency anemia, respiratory symptoms (including dyspnea, cough and hemoptysis), and pulmonary infiltrates on chest imaging; (2) the presence of hemosiderin-laden macrophages in sputum, gastric lavage fluid, or bronchoalveolar lavage fluid; and (3) exclusion of other diseases, which are associated with diffuse alveolar hemorrhage, such as bronchiectasis, interstitial pneumonia, neoplasms, cardiovascular disease, coagulation disorders, infections, connective tissue diseases, celiac disease, and systemic vasculitis.[1] Laboratory investigations for antinuclear antibodies (ANA), anti-double-stranded DNA, antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibodies, antiphospholipid antibodies, and rheumatoid factor were negative in all patients. Because this was a retrospective study, ethical approval and consent were not required.

Data collection

"Idiopathic pulmonary hemosiderosis" and "children" were used as the keywords to collect data from hospital medical records and from the Department of Pathology. Cases with complete data were included in this study. A database was established using Microsoft Excel 2007 software, with double entry of demographic data, clinical manifestations, laboratory findings, treatments, and clinical outcomes. Long-term prognosis was assessed in March 2018 by contacting the families by telephone.

Statistical analysis

All of the data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA). Normally distributed data are presented as the mean ± standard deviation. Continuous variables were analyzed using the Student's t-test, and categorical variables were analyzed using the chi-square test or Fisher's exact test, if any expected value was below five. Data that were not normally

distributed were reported as the median. The results were considered significant when $P < 0.05$.

Results

Patients' characteristics at diagnosis

A total of 107 hospitalized children were diagnosed with IPH during the 21-year study period. There was no clustering of patients in time or site during the 21-year period. The main clinical data at diagnosis are shown in Table 1. All of the patients were sporadic patients, comprising 42 boys and 65 girls. The median age of onset of IPH was 5 years (1 month to 14.3 years). The median age of diagnosis was 6 years (4 months to 14.6 years old). The average time from onset to diagnosis was 10.46 months, with the longest time of 6 years. Seventy-six (71.03%) patients were from rural areas, while 31 (28.97%) patients were from urban areas. Nine patients had a history of allergies before the diagnosis of IPH. Among these patients, four were allergic to milk, two were allergic to penicillin, and the other three patients were allergic to shrimp, eggs, and azithromycin in one each. Among the 107 patients, one patient had concomitant Down syndrome and one had congenital esophageal atresia, and no comorbidity was found in any of the other patients.

Main clinical manifestations

The main initial manifestations of the patients included cough (n = 62, 57.94%), hemoptysis (n = 53, 49.53%), fever (n = 20, 18.69%), and dyspnea (n = 17, 15.89%). Among the patients, 15 (14.02%) manifested with cough, hemoptysis, and anemia simultaneously. A total of 28 (26.17%) patients had anemia as the only initial symptom and six (5.61%) patients had hemoptysis as the only initial symptom.

The main manifestations at diagnosis included cough (n = 68, 63.55%), hemoptysis (n = 61, 57%), fever (n = 23, 21.5%), dyspnea (n = 23, 21.5%), hepatomegaly (n = 13, 12.15%), and heart murmurs (n = 11, 10.28%). There were relatively few pulmonary signs. Only 17 (15.89%) patients had wet rales in pulmonary auscultation.

Laboratory tests at diagnosis

Hemoglobin levels ranged from 26 to 130 g/L, with an average level of 74.86 g/L. Anemia was defined by a hemoglobin level below the range considered normal for age and sex.[10] One hundred (93.45%) patients had anemia, among whom 28 were classified as mild (90 g/L to normal levels), 40 were moderate (60–90 g/L), 30 were severe (30–60 g/L), and two were critical (<30 g/L). A red blood cell morphology test was performed in 97 of the anemic patients, of whom 57 (58.8%) showed microcytic hypochromic anemia. Reticulocyte counts were recorded in 54 patients, of whom 53 (98.15%) had high reticulocyte counts.

All of the patients showed normal liver function. ANA and antinuclear cytoplasmic antibody studies were negative in all of the patients. Allergen-specific immunoglobulin E was screened in 12 patients, among whom three were allergic to milk, one to dust mite allergies, and one to animal fur. In addition to ANA, antineutrophil cytoplasmic antibodies, allergen-specific immunoglobulin E, anti-double-stranded DNA, antiglomerular basement membrane antibodies, antigliadin antibodies, antireticulin, antiphospholipid antibodies, rheumatoid factor, and cow-milk precipitins were tested. However, all of these tests were negative.

A total of 72 patients underwent an iron metabolism test, and 64 (88.9%) showed iron deficiency anemia. Serum iron tests

Table 1. Baseline clinical profiles of 107 pediatric patients with idiopathic pulmonary hemosiderosis.

Variables	n	Age at diagnosis (years)					Duration before admission (days)				
		0~ (n = 22)	3~ (n = 49)	6–14.6 (n = 36)	χ^2 value	P value	0~ (n = 17)	22~ (n = 25)	90–2160 (n = 65)	χ^2 value	P value
Male sex	42	13	15	14	5.167	0.076	11	7	24	6.094	0.047
Main symptoms and signs											
Cough	62	10	30	22	1.773	0.412	9	19	40	12.015	0.002
Hemoptysis	53	7	26	20	3.528	0.171	12	17	32	4.116	0.128
Fever	20	4	8	8	0.551	0.810	5	2	16	3.887	0.156
Dyspnea	17	6	6	5	2.611	0.298	3	4	16	0.821	0.751
Wet rales	17	3	7	7	0.547	0.784	6	6	5	9.289	0.012
Anemia	100	21	46	33	5.198	0.521	13	24	63	4.415	0.361
Iron deficiency anemia	57	12	27	18	0.229	0.892	7	13	37	0.215	0.898
Chest imaging											
Patchy density	31	9	13	9	1.387	0.556	4	6	21	0.221	0.875
Miliary changes	11	1	8	2	4.786	0.103	1	2	8	0.187	1.000
Small nodular changes	11	1	5	5	1.577	0.454	1	1	9	1.408	0.623
Interstitial changes	12	0	5	7	5.758	0.062	2	4	6	1.939	0.388
Ground-glass opacity	9	2	6	1	2.986	0.249	1	3	5	0.890	0.745

Values are mean ± standard deviation or number.

were performed in 72 patients, and a decrease in iron levels was detected in 64 patients. Transferrin saturation was decreased in 62 (91.2%) of 68 patients. Serum ferritin tests were normal in 60 of 62 tested patients. The total iron binding capacity was increased in 32 (45.07%) of 71 tested patients.

Bone marrow examinations were performed in 52 patients, among whom 46 (88.5%) showed proliferative bone marrow, two (3.8%) showed a decreased myeloid/erythroid ratio, and four (7.7%) were normal.

Chest radiographs at diagnosis

All of the patients showed abnormal chest X-rays or computed tomography scans. Among them, 71 patients were examined by chest radiograph, 48 were examined by chest computed tomography, and 12 were examined by both tests. Patchy or cloud-like density was observed in 57 patients, ground-glass opacity in 36, small nodular changes in 20, miliary changes in 13, an enlarged heart shadow in 10, and reticular interstitial changes in 21.

Hemosiderin-laden macrophages at diagnosis

Hemosiderin-laden macrophages were found in all of the patients. Sputum from 48 patients was examined for hemosiderin-laden macrophages and 44 (91.66%) patients were positive, with an average of 1.69 tests. Gastric juice from 56 patients was examined for hemosiderin-laden macrophages and 55 (98.21%) patients were positive, with an average of 1.95 tests. Thirty-five patients who had hemosiderin-laden macrophages in sputum also had positivity in gastric juice. Bronchoalveolar lavage fluid from eight patients was examined for hemosiderin-laden macrophages, and it had a positive rate of 100%. Bronchoalveolar lavage fluid was sent for culture to exclude infectious etiologies and cytological analysis, but the results were negative.

Misdiagnosis

A total of 79 (73.83%) patients were misdiagnosed. Misdiagnoses included the following: nutritional iron deficiency anemia (n = 24), bronchial pneumonia (n = 21), pulmonary tuberculosis (n = 6), hemolytic anemia (n = 4), upper respiratory tract infection (n = 4), bronchiectasis (n = 3), myocarditis (n = 1), intestinal diseases (n=1), and favism (n = 1).

Comparison of the clinical features of different ages at diagnosis and of different symptom durations

The main clinical features of IPH (except for cough and wet rales; $P = 0.002$ and $P = 0.012$, respectively) were not significantly different among the different age groups at diagnosis and among the different symptom durations (Table 1).

Treatment and prognosis

All of the 107 patients were provided symptomatic treatments before diagnosis, and 29 received blood transfusions. Two patients prematurely discontinued therapy after diagnosis. Of the 105 patients who received treatment, nine were administered 10 to 30 mg/kg/d of methylprednisolone for 3 days in the acute phase and then switched to 2 mg/kg/d of prednisone. The remaining 96 patients were administered oral prednisone at a dosage of 2 mg/kg/d for 2 weeks, one of whom received cyclosporine A in combination with prednisone. No patients received azathioprine. Of the 105 treated patients, three died from massive pulmonary hemorrhage and respiratory failure; 102 patients showed remission after the initial treatment. The patients were then

Table 2. Risk factors for recurrent idiopathic pulmonary hemosiderosis.

Variables	Healed or improved (n = 22)	Recurrent (n = 10)	P value
Age of onset of symptoms (months)	65.45 ± 43.14	66.10 ± 38.67	0.968
Age at diagnosis (months)	72.77 ± 44.22	83.30 ± 45.90	0.542
History of hemoptysis at presentation	14	4	0.267
Dyspnea	5	3	1.000
Hemoglobin (g/L)	81.09 ± 24.01	72.30 ± 24.55	0.348
Elevated bilirubin	6	7	0.049

followed up in outpatient clinics. Treatment was tapered and discontinued after 18 to 24 months if the patient had been free of recurrent events.

A total of 34 patients were successfully followed up, with a median follow-up time of 3.71 years (1.08–6.23 years). No children subsequently developed any form of autoimmune disease. Two patients died of severe hemoptysis and 32 patients survived. Twenty-two patients remained asymptomatic over 3 months after withdrawal of treatment. Ten patients experienced recurrent episodes of symptoms upon reduction or withdrawal of prednisone. Children who had recurrence of symptoms were administered oral prednisone for 1 to 2 weeks. Those who developed symptoms during tapering of steroids had their dosages increased to 2 mg/kg/d for 2 to 4 weeks, followed by an attempt to taper. The rate of elevated bilirubin levels was significantly higher in children who had recurrent IPH than in those who were healed or improved ($P = 0.049$). However, there were no significant differences in the age of onset, age at diagnosis, history of hemoptysis, dyspnea, and hemoglobin levels between the two groups (Table 2).

Discussion

There are four main etiological hypotheses of IPH described in the literature, including environmental, allergic, autoimmune, and genetic hypotheses.[6,9,11,12] In the present study, 71.03% of patients were from rural areas, which indicated that environmental factors might contribute to the pathogenesis of IPH. Previous studies have also indicated that exposure to second-hand smoke and indoor mold are causative factors in infants with IPH.[13,14] In addition to mold, IPH has also been associated with exposure to insecticides or mycotoxigenic pathogens, such as Aspergillus, Penicillium, and Trichoderma. The association between environmental factors and IPH still needs further study.

IPH is a rare clinical condition in children and generally occurs in children aged younger than 10 years,[15] especially between the ages of 1 to 7 years.[5] Some studies have also described family clustering of IPH.[16,17] In the present study, all of our patients were sporadic, with the highest incidence among 3- to 6-year-olds, similar to patients reported in previous studies.[1] Delayed diagnosis of IPH is frequently reported, with a delay period of 4 months to 10 years.[18] In the present study, the average time from onset to diagnosis was 10.46 months and the misdiagnosis rate was as high as 73.83%. The high misdiagnosis rate may have been due to an insidious onset, a variable clinical presentation, and a lack of awareness about the condition.[19]

Although the classic triad of hemoptysis, iron-deficiency anemia, and pulmonary infiltrates on chest imaging is characteristic of IPH, the clinical presentation is greatly

variable and is not always present in children with IPH.[7,20] In the present study, only 14.02% of patients simultaneously manifested cough, hemoptysis, and anemia. This group of patients also had the following characteristics. First, only 15.89% (initial manifestation) and 21.5% (at diagnosis) of the patients had dyspnea. Taytard et al.[9] reported that the most frequent clinical features in pediatric patients at diagnosis were anemia and dyspnea (64% and 68%, respectively). This discrepancy between studies may be associated with a longer course of disease in the present group. Second, only 49.53% (initial manifestation) and 61.57% (at diagnosis) of the patients had hemoptysis in the present study. Hemoptysis is rare in children because most of them are unable to expectorate.[9,21] For this reason, the absence of hemoptysis still does not exclude the diagnosis of IPH in children. Third, 57 (53.27%) patients had iron deficiency anemia as the primary manifestation, and 28 (49.12%) of these patients lacked any pulmonary signs in the present study. Iron deficiency anemia often occurs in malnourished children.[22] However, iron deficiency anemia is also a common manifestation of IPH, and this condition may precede other symptoms and signs by several months.[23,24] Bhatia S et al.[25] performed an etiological analysis of 108 patients with microcytic hypochromic anemia, among whom 15 (13.9%) patients were diagnosed with IPH. Although IPH and nutritional iron deficiency anemia are characterized by microcytic hypochromic anemia, patients with IPH have normal serum ferritin levels.[26] In the present study, 70 (65.42%) patients had moderate to severe anemia, and this was accompanied by chest imaging abnormalities. Therefore, IPH should be suspected in children with iron deficiency anemia who show no signs of improvement with iron supplementation and with bilateral lung infiltration.

Searching for hemosiderin-laden macrophages contributes to the diagnosis of IPH. Lung biopsy is the gold standard for diagnosis of IPH,[27] but this method is invasive and is not practiced in children.[21,28] In the present study, no patients received a lung biopsy. Bronchoalveolar lavage fluid analysis is a safe and confirmatory method for pulmonary hemorrhage.[29] Studies have shown that the sensitivity of finding hemosiderin-laden macrophages is 30% in gastric juice and 92% in bronchoalveolar lavage fluid.[1] In the present study, the positive rates of hemosiderin-laden macrophages in bronchoalveolar lavage and gastric lavage fluid were 100% and 98.21%, respectively. Repeated examination of gastric lavage fluid is also a reliable and simple method that can increase the positive rate.

Glucocorticoids and immunosuppressive agents are the first choice for treating IPH.[11,18,21,30] Despite the fact that three patients died of severe hemoptysis in our study, most patients responded favorably to glucocorticoids. This finding indicates that systematic glucocorticoids are the first-line therapy for treatment of acute episodes of IPH.[11,31] Immunosuppressive agents (e.g., hydroxychloroquine, azathioprine, and cyclophosphamide) may only be added to oral glucocorticoid therapy for those who have a severe initial condition.[32–37] Rare treatments, such as intravenous immunoglobulin, plasmapheresis, liposteroids, and diet modification, have also been prescribed in some case reports.[38–41]

The prognosis of IPH is influenced by several factors, including the time of diagnosis, early initiation of treatment, and the presence of comorbidities.[20] Historically, patients had an average survival of 2.5 years after diagnosis of IPH, but Saeed et al.[3] found that 86% of patients may survive beyond 5 years. Le et al.[42] followed up 15 children with IPH for an average of 17.2 years, and found that 14 patients received

long-term glucocorticoid therapy and 80% of patients led a normal life. In the present study, glucocorticoid therapy could control symptoms, but the recurrence rate was high. Many of the children continued to have recurrent pulmonary hemorrhage during the reduction or withdrawal process. In a series of 23 children with IPH,[18] low-dose oral prednisone was associated with prolonged survival and a decreased recurrence rate compared with historical controls. In patients who have recurrent episodes of pulmonary hemorrhage that limit the tapering of glucocorticoids, a combination of glucocorticoids with other immunosuppressants may be considered.

Because IPH is a rare disease, performing a randomized, controlled trial is difficult. Our study has some limitations that should be noted, namely its retrospective nature and its lack of a control group.

In conclusion, our study shows that IPH has diverse clinical manifestations. The classic triad of IPH is not always present in children. The misdiagnosis ratio is high in IPH. Chest imaging combined with repeated examinations for hemosiderin-laden macrophages in sputum, gastric lavage fluid, or bronchoalveolar lavage fluid are helpful for diagnosing IPH. Systemic glucocorticoids are the main treatment for IPH, but recurrence is frequent during the reduction or withdrawal process. Long-term, low-dose glucocorticoid therapy, or a combination with other immunosuppressive agents, may help to reduce recurrence. Early recognition of IPH and adequate immunosuppressive treatment play a crucial role in prolonging survival and improving prognosis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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