ABSTRACT

Background: Idiopathic pulmonary hemosiderosis (IPH) is a rare disease, having an unknown etiology and variable outcome, characterized by recurrent episodes of hypochromic anemia, alveolar bleeding and typical radiological findings, like patchy alveolar infiltrates or ground glass attenuation. It mostly occurs during childhood and it has been reported as having a high mortality rate.

Methods: We carried out a retrospective study using the medical charts of patients diagnosed with IPH, admitted in four Tertiary Romanian Pediatric Departments between 1984 and 2007. The diagnosis was established through the evidence of recurrent pulmonary hemorrhages, associated with severe repetitive microcytic hypochromic anemia, with the detection of hemosiderin-laden macrophages in Perls reaction.

Results: Throughout a 23 years period (1984-2007), twenty patients were diagnosed with IPH. The onset of the symptoms was at a median age of 6.25 years and median age at diagnosis was 10.2 years with an average delay of 29.05 months. All patients had anemia and most of them required blood transfusions. The diagnosis was made mostly by bronchoalveolar lavage and positive hemosiderin-laden macrophages identified by Perls reaction. The clinical course was variable and with corticosteroids in monotherapy, fourteen patients continued to have recurrent bleeding, five patients received also immunosuppressive agents with a better outcome Younger age at onset and history of fever or hemoptysis at first presentation were associated with poor prognosis.

Conclusions: Anemia as the sole presenting symptom of IPH’s patients is not an uncommon finding, especially in young children. After diagnosis, immunosuppressive therapy and cortisone therapy may provide a better prognosis in patients diagnosed with IPH.

Key words: idiopathic pulmonary hemosiderosis, children
INTRODUCTION

Idiopathic pulmonary hemosiderosis (IPH) is a rare pulmonary disease of unknown etiology, characterized by recurrent alveolar bleedings subsequently with accumulation of hemosiderin in the lungs. It develops as a triad of anemia, hemoptysis and pulmonary infiltrates, like patchy alveolar infiltrates or ground glass attenuation, at clinical level. The disease was first described in 1864, by Virchow, as “brown lung induration” or “the iron lung” (1). The first intravitam diagnosis was established after 80 years, by Waldeström in 1944 (2). Since then, there have been reported multiple cases, but IPH is still a rare disorder with an estimated incidence that varies from 0.24 to 1.23 cases per million per year depending on the study (3,4). Its etiology is unknown but an immune-mediated disease is suspected (5)(6). The prognosis is severe and the mean age of survival after diagnosis is of 2.5-3 years (5,7). Death can occur suddenly after a massive pulmonary hemorrhage or by chronic restrictive pulmonary insufficiency induced by pulmonary fibrosis, in those who survive for a longer period.

With the purpose of showing some of the most significant aspects of this rare disease, clinical presentation, diagnosis and prognosis we reviewed the clinical course of 20 patients diagnosed with IPH in four Romanian Tertiary Pediatric Departments.

MATERIAL AND METHODS

We performed a retrospective study using the medical charts of patients diagnosed with IPH, admitted in four Tertiary Pediatric Departments (Cluj-Napoca, Timisoara, Craiova, Constanta) between 1984 and 2007. This is a preliminary study of IPH in Romania and for this reason, other Pediatric Departments (Bucharest, Iasi) are not included. The diagnosis was established through the evidence of severe repetitive microcytic hypochromic anemia associated with recurrent pulmonary hemorrhages, with the detection of hemosiderin-laden macrophages in the bronchoalveolar lavage fluid, sputum, gastric aspirate or pulmonary biopsy. We excluded secondary causes of pulmonary hemosiderosis, like tuberculosis, cardiac disease, bleeding disorders, vasculitis, rheumatologic diseases and glomerulonephritis. We collected the following data: age at diagnosis, sex, clinical presentation, method of diagnosis, treatment and clinical course during follow up. We reported the clinical parameters as median and range, because of the small number of cases and extreme values.

OUTCOMES

Throughout a 23 years period twenty patients were diagnosed with IPH in our study. There have been an equal number of girls and boys, supporting the data from the literature. The symptoms started at a median age of 6,25 years (range 9 months to 13 years and 11 months) and the median age at diagnosis was 10,2 years with a delay of 29,05 months (range 1 month to 118 months). (TABLE 1)

All patients had anemia, at first presentation and most of them (15 patients) a severe form that required blood transfusions. The median value of hemoglobin at diagnosis was 4,90 g/dL (range 1,9 to 9,5 g/dL). The patient with the lowest hemoglobin level came in comatous stage and succumbed short time after presentation. Even though hemoptysis is considered a necessary symptom for IPH’s diagnosis, only seven patients presented it in our study. Both syndromes (anemic and pulmonary syndromes) appeared simultaneously in these patients (35%).

Antinuclear cytoplasmic antibody (ANCA) and rheumatoid factor (RF) were determined in two patients and they were present in only one child, almost 10 years after the onset of the disease.

The diagnosis was established in our patients mostly through bronchoalveolar lavage and positive hemosiderin-laden macrophages identified by Perls reaction (9 patients) (TABLE 2, FIGURE 2). One patient presented severe hypochromic anemia without any pulmonary symptoms until death by massive hemoptysis. The family refused necropsy and the diagnosis was established on clinical grounds. The family of another patient refused all diagnostic...
TABLE 1. Data of patients diagnosed with IPH

M = male, F = female, D = deceased, A = alive, L = lost from study, Dx = diagnosis, HS-megaly = hepatosplenomegaly, BT = blood transfusions, PDN = prednisone, CP = ciclophosphamide, CQ = cloroquine, HQ = hidroxicloroquine, AZA = azathioprine, ICS = inhaled corticosteroids, M-PDN = methylprednisolone.

FIGURE 1. Chest X-Ray. Micronodular aspect in IPH, patient no. 5 from Table 1.
procedures and discharged the child without medical approval. The presence of severe microcytic anemia, hemoptysis and pulmonary infiltrates established the diagnosis in this case.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL</td>
<td>9</td>
</tr>
<tr>
<td>Sputum</td>
<td>5</td>
</tr>
<tr>
<td>Necropsy</td>
<td>2</td>
</tr>
<tr>
<td>Clinical diagnosis*</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary biopsy</td>
<td>1</td>
</tr>
<tr>
<td>Gastric washing</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 2. Method of diagnosis
*severe microcytic anemia, hemoptysis and pulmonary infiltrates

The lack of compliance from a number of patients and the reduced data, that sometimes characterizes a retrospective study, made difficult to assess exactly the follow-up duration. Nevertheless, we determined the median follow-up duration of 18.5 months.

After diagnosis, twelve patients were treated with prednisone alone, 0.9-2.3 mg/kg/day (median 1.6 mg/kg/day) for 2-3 weeks followed by small doses (5-10 mg on alternative days for 6-12 months in those who were compliant. They also received blood transfusions in order to equilibrate the hemodynamics. The clinical course was variable, sixteen patients continuing to have recurrent hemorrhages. Two of them received inhaled corticosteroids (fluticasone propionate) without hemorrhages one year later. Five patients received immunosuppressive agents (azathioprine, ciclophosphamide or chloroquine) after prednisone was unable to stop the bleeding with a better survival rate and less pulmonary hemorrhages than the other patients. Three cases had a severe hypochromic anemia, without any pulmonary symptoms and did not receive any pathogenic medication (immunosuppressives and/or corticosteroids). Necropsy established the diagnosis.

One patient matched the characteristics of Heiner’s syndrome. This patient was the youngest in our study (9 months) and had clinical evidence of allergy to cow’s milk proteins. His clinical status improved until remission of symptoms, mainly, after avoiding milk products followed by short time of immunosuppressive therapy (3 months of ciclophosphamide). In general, children diagnosed with Heiner’s syndrome or cow’s milk hypersensitivity have a typical picture of IPH, besides the unusual high serum titers of precipitins to multiple constituents of cow’s milk and positive intradermal skin tests to various cow’s milk proteins. Some patients with cow’s milk protein hypersensitivity fail to improve in any way on a milk-free diet. However there have been reported patients without multiple serum precipitins who improved on a milk-free diet (5).

In our study, nine patients developed a severe right heart failure, secondary to pulmonary fibrosis, which precipitated the death in five of them. One patient associated duodenal polyposis that postponed the IPH diagnosis for a short period of time. Two patients were infected with hepatitis B virus (HBV) after repeated blood transfusions. Nine patients died, from massive pulmonary hemorrhages within a period of 16.5 months from the diagnosis, six patients are lost from the study and five are still alive. We found a median survival rate after the onset of symptoms of 3.05 years.

Given that IPH is a rare disease, with many unknown data, we tried to identify factors of prognosis. Smaller age at onset and history of fever or hemoptysis at first presentation were associated with a decline in the survival rate (19 months, 24 months, respectively 30 months). We also observed that patients who received immunosuppressive agents associated to corticosteroids survived longer (145 months) than the patients who received only cortisone therapy (27 months).

The patient with the longest survival, 24 years from the beginning of the disease, became oxy-
gen dependent due to extensive pulmonary fibrosis. She was diagnosed by the age of 12 years old and begun intermittent cortisone treatment and for a short period of time, hydroxychloroquine. By the age of 17 years, she presented one severe hemorrhagic episode that required blood transfusion. The clinical status remained relatively stable for a large period. She gave birth to a healthy baby girl, who was breastfed for the first 5 months of life and then stopped due to right heart failure developed gradually in the past years. This is the single case registered in Romania with active IPH who carried out a pregnancy and who also has the longest survival so far.

**DISCUSSIONS**

The accurate incidence and prevalence of IPH is unknown. Our study shows one of the biggest series of cases, 20 patients in 23 years, but we gathered cases diagnosed with IPH from four different Tertiary Pediatric Departments. Other studies reported 10 cases in 30 years in a Swedish study, 5 cases in a 25 years Taiwanese study or 26 cases in a 7 years recent Indian study (3,8,10).

Like reported in the literature we also found an equal sex distribution. The median age of diagnosis was higher in our study, 10.2 years, but the symptoms started also later in life, 6.25 years. Other studies reported much smaller onset ages (from 4 years to 5 or 5.8 years) (3,8-10).

The median survival rate after the onset of symptoms is in our study 3.05 years. Related to other studies, where it varies from 2.5 years until 5 years in 86% of patients (as it is illustrated in TABLE 3) this is a mean value (4,11-13).

Almost half of the patients (45%) died 16.5 months after the diagnosis. These patients presented a median hemoglobin level lower than the ones who lived (3.8 g/dL versus 5.05 g/dL). In most of these cases, severe microcytic anemia was the sole symptom and it was rectified under blood transfusions, but relapsed. The relapsing anemia was the main characteristic of our IPH patient’s. Anemia as the sole presenting symptom is not an uncommon finding, especially in young children, as many reports testify and we are supporting this allegation (14-16).

We also find that females, survived longer (37.5 months vs. 33 months, males). This could suggest an autoimmune basis of the disease (4). Nevertheless our single case with immunological abnormalities was a male. The patient presented permanent positive acute phase reactants and intermittent, renal modifications (isolated proteinuria) but negative anti-glomerular basement membrane antibodies) and flowcytometric alteration, like granulocytosis, associated to absolute or relative lymphocytopenia, with the decrease of all lymphocytic subsets, but mostly CD4+.

It is reported that cases which survive longer than 10 years, like our patient did, could develop some form of autoimmune disease (17, 18). One marker in this direction could be the measurement of ANCA in all patients with pulmonary hemorrhagic syndromes, serving also as a warning of poor prognosis (9,19). The biological aspects of this patient might point towards the group of small vessel vasculitis (20-22). There have been reports of isolated pauci-immune pulmonary capillaritis that were diagnosed in childhood as IPH (23) and this is a possibility that cannot be ruled out, but until future data, the diagnosis of IPH is the correct one.

**TABLE 3.** The average survival rate - a literature review

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>History of fever</th>
<th>History of hemoptysis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good prognosis (median survival in months)</td>
<td>F (37,5)</td>
<td>Over 7 years (68)</td>
<td>No (38)</td>
<td>No (37)</td>
<td>IS±P (145)</td>
</tr>
<tr>
<td>Poor prognosis (median survival in months)</td>
<td>M (33)</td>
<td>0.3 years (19); 4-7 years (38)</td>
<td>Yes (24)</td>
<td>Yes (30)</td>
<td>P (27)</td>
</tr>
</tbody>
</table>

**TABLE 4.** Factors of prognosis

F = female; M = male; IS = immunosuppressive; P = prednisone
Also, our study shows that patients who received immunosuppressive agents next to corticosteroids survived longer (145 months) than the patients who received only cortisone therapy (27 months). This point of view supports similar conclusion by other authors (8,10,11,24-26). Although reports indicate that corticosteroids might cause substantial improvements in recovery of symptoms and early prognosis, their effect on long-term prognosis is not known (27,28).

CONCLUSION

IPH is a rare pulmonary disease with unknown etiology and severe prognosis.

Severe microcytic anemia was the main clinical feature in our patients, especially in young children; rarely, both syndromes (anemic and pulmonary syndromes) appeared simultaneously. A thorough evaluation of severe microcytic anemia with no other cause may conclude to an earlier diagnosis of IPH with a better prognosis for these patients.

The diagnosis of IPH was made after a variable period (1 month to 118 months), due to imitativeness of anemia; the gold diagnosis test was the evidence of hemosiderin-laden macrophages identified by Perls reaction.

Our study shows that after diagnose of IPH is made, follow-up therapy with immunosuppressive and cortisone can provide with a higher survival rate, hence a better prognosis. However, this retrospective review does not allow us to compare one therapy to another.

In addition, based on our experience, we consider of utmost importance to evaluate and establish the development towards immune disorders in long survivors of IPH.

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