

Idiopathic Pulmonary Hemorrhage

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Introduction

Idiopathic pulmonary hemorrhage is a rare condition that affects the lower respiratory tract. It can be divided into two clinical entities depending on whether the pathophysiology and presentation are acute or chronic. Acute idiopathic pulmonary hemorrhage usually presents as diffuse alveolar hemorrhage (DAH), while the more insidious or chronic pulmonary hemorrhage often presents as idiopathic pulmonary hemosiderosis (IPH) following repeated alveolar bleeding. The terms idiopathic pulmonary hemorrhage, idiopathic pulmonary hemosiderosis, and diffuse alveolar hemorrhage are often used interchangeably. Historically, idiopathic pulmonary hemorrhage was first described by Virchow in 1864 as "brown lung induration." Ceelen in 1931 gave a more detailed description of the condition after autopsies revealed large amounts of hemosiderin in 2 children, while Waldenstrom, in 1944, made the first antemortem diagnosis.^[1]

Pulmonary hemorrhage is the extravasation of blood into the alveoli, that is, bleeding into the lower respiratory tract. It can be severe and life-threatening.^[1] In diffuse alveolar hemorrhage, the bleeding is usually of sudden onset and is widespread and not limited to a section of the lungs. In idiopathic pulmonary hemosiderosis, repeated alveolar hemorrhage causes the accumulation of hemosiderin, a by-product of hemoglobin breakdown, in the alveoli. Alveolar macrophages take up these hemosiderin molecules, usually within 36 to 72 hours, and can remain in the lungs for up to 8 weeks.^[1] Acute idiopathic pulmonary hemorrhage in infants (AIPHI) is a rare, quite distinct clinical presentation of the condition that occurs in infants and is characterized by the sudden onset of pulmonary bleeding in a previously healthy infant in the absence of other known co-morbidities including prematurity.^[2] The clinical spectrum of IPH ranges from asymptomatic cases to life-threatening acute respiratory failure.^[3] AIPHI often presents acutely with severe respiratory distress.^[2] Due to its rarity and varied presentations, IPH often causes a diagnostic pitfall for many clinicians. Unfortunately, delayed diagnosis leads to delayed treatment and, ultimately, a poor outcome.^[4]

Etiology

As the name implies, there is no known cause for IPH, and it is a diagnosis of exclusion. A diagnosis of IPH can only be made after thorough investigations have ruled out other known causes of pulmonary hemorrhages, such as vasculitis and bleeding disorders (eg, von Willebrand disease). Other causes of systemic or visceral hemorrhages, such as gastrointestinal bleeding, should also be excluded. However, possible triggers in at-risk children include lower respiratory tract infections, celiac disease, and cow's milk protein allergy, although the evidence for these is not very strong, perhaps due to the rarity of the condition.^{[1][4][5]} A possible association with Down's syndrome has been reported.^[4] Similarly, an association with the fungi, *Stachybotrys chartarum*, was reported but has now been refuted. There is no substantial evidence linking it to tobacco smoking or any other known environmental factors.^[6]

Epidemiology

IPH is a rare clinical condition that affects mainly the pediatric age group, especially in children aged below 10 years. 80% of cases are thought to occur in this age group.^{[1][5][7]} It has a bimodal age

distribution with two peaks, one in patients below 5 years and the other in patients above 11 years.[4] Adult-onset IPH usually occurs before age 30.[1] Some cases have been reported in infants, but this is not common.[2] In a 10-year retrospective study conducted in Boston, only 4 out of 154 infants presenting with pulmonary hemorrhage were diagnosed with AIPHI.[2] The incidence of IPH is about 0.24 to 1.23 cases per million globally.[4][5] There is no sex predilection for the condition in children, but it is reported to have a higher prevalence in adult men than women.[1][4] There is no known ethnic preference. Some cases of family clustering have been reported, however, no genetic basis for the disease is known so far.[7]

Pathophysiology

The pathogenesis of the disease is unknown, although some consider it to be an autoimmune condition.[4] The evidence for autoimmunity is weak but is backed by the fact that the disease responds to immunosuppressants.[8] Other hypotheses for the pathophysiology of the condition include allergy, due to its frequent association with cow's milk protein allergy, genetic, due to the rare finding of familial clustering (but without any identified genes yet), and environmental due to the now refuted claim of its association with the fungi *Stachybotrys chartarum*. [9] Recurrent episodes of intra-alveolar hemorrhage attract macrophages to the alveoli, which digest the hemosiderin (iron component) found in hemoglobin, leading to an abnormal accumulation of hemosiderin-laden macrophages. This attracts more pro-inflammatory cytokines and causes chronic inflammation and thickening of the alveolar basement membrane. Ultimately this causes interstitial lung fibrosis with a restrictive picture on spirometry.[4] In infants, the disease is poorly understood.[2]

Histopathology

Histological findings in IPH include the presence of hemosiderin-laden macrophages, fibrin deposition, pneumocyte hyperplasia (type II), features of acute inflammation, and organizing pneumonia.[3] Unlike other causes of DAH, especially vasculitis, where capillaritis (inflammation of the alveolar capillaries and disruption of the alveolar-capillary membrane) is the common histologic finding, in IPH, there is no evidence of capillaritis. Rather the alveolar membrane is thickened and its integrity undisrupted. Bland pulmonary hemorrhage is often seen.[8] In advanced cases, the lungs appear brownish due to the accumulation of hemosiderin.[8]

History and Physical

The clinical features of idiopathic pulmonary hemorrhage depend on whether it is acute or chronic. Acute pulmonary hemorrhage, as seen in DAH, presents as a sudden onset of severe dyspnea and hemoptysis, which, if not treated immediately, could be fatal.[1] In many patients, it has an unpredictable course.[8] Idiopathic pulmonary hemosiderosis, on the other hand, has a more insidious onset characterized by variable symptoms such as hemoptysis, iron deficiency anemia, cough, and dyspnea, as a result of recurrent DAH. Anemia and dyspnea are the most frequent presentations. The classical triad often described in medical texts of hemoptysis, iron-deficiency anemia, and diffuse parenchymal shadowing on chest imaging is not seen frequently in children.[4][7] Some children may present with weight loss and failure to thrive.[1] In severe cases, hypoxemic (type 1) respiratory failure may be seen, especially in infants. Hemoptysis is not common in younger children as they often swallow their sputum.[2][4] In some infants with sudden-onset pulmonary hemorrhage, there may be no respiratory distress and chest radiology findings may be absent. This is sometimes referred to as 'probable AIPHI'. [6]

In some cases of IPH, iron deficiency anemia precedes other symptoms by many months. In these patients, there is often the need for repeated blood transfusions despite iron supplementation.[4][5] Other infrequent and non-specific symptoms in IPH include recurrent chest infections, fever, chest pain, and tachypnea.[4][8] Physical examination findings also vary depending on whether it is an acute or chronic presentation. In the acute phase, the physical examination may be completely normal or include respiratory signs such as tachypnea. In the chronic phase, there may be pallor, failure to thrive, weight loss, or hepatosplenomegaly. It may also be unremarkable. If pulmonary fibrosis has set in, there may be digital clubbing and other signs of chronic hypoxia.[1]

Evaluation

The diagnosis of acute IPH is made clinically after other known causes of pulmonary and systemic or visceral hemorrhage have been excluded.[2][4] Unfortunately, delayed diagnosis and misdiagnosis are common. In about three-quarters of cases, the correct diagnosis is missed on initial presentation and can take up to a few years (even up to 10 years) to be correctly diagnosed.[7] The causes of delayed or missed diagnoses are attributed to the fact that the condition is rare and may present with unusual symptoms such as anemia in the absence of definite respiratory symptoms and signs.[9] IPH should be suspected in patients with recurrent chest infections and persistent, unexplained anemia despite iron supplementation, and bilateral lung infiltrates on chest radiographs, after exclusion of other possible causes of anemia.[4] In infants, congenital heart disease, prematurity, congenital and acquired lung diseases, and congenital or acquired coagulopathies should be excluded.[2] Gastrointestinal hemorrhage should also be excluded as the source of bleeding.[6]

Blood tests are non-specific and may show reduced hemoglobin counts and hematocrit, leucocytosis, and elevated erythrocyte sedimentation rate.[2][8] Chest x-ray findings are also non-specific and may include patchy, focal, or diffuse alveolar shadowing, often with apical and peripheral sparing. Air bronchograms may also be seen.[8] Computed tomography scans of the chest, especially high-resolution scans, show more specific changes such as ground-glass opacities, consolidations, and interstitial reticular and micronodular opacities with varying degrees of fibrosis, and can be useful in confirming the findings from chest x-ray. They are also valuable for determining the extent of the disease.[1][3][8] Pulmonary function tests, if done, may show a restrictive pattern, with varying severity.[1]

Lung biopsy is the gold standard for the diagnosis of IPH, where the hemosiderin-laden macrophages can be visualized. However, it is an invasive procedure and is often not practicable in children.[4][5][7] However, it may be required to exclude some types of vasculitis.[9] Broncho-alveolar lavage (BAL) fluid analysis is a more practical method of investigation and has a sensitivity of about 92%.[7] Sequential BAL is performed to look for increasing red blood cell count in subsequent aliquots from the same location to confirm the diagnosis of DAH. The same BAL fluid is also analyzed to rule out infectious etiology, like bacterial, fungal, viral, Pneumocystis pneumonia, and tuberculosis.[10] Gastric lavage fluid analysis can also be used in children but has a relatively low sensitivity. Its sensitivity can be improved by repeated sampling and testing.[4]

Treatment / Management

There is no universal gold-standard treatment for IPH, however, high-dose steroids are frequently used to control symptoms, with good results.[4][7] Recurrence rates are high. Immuno-suppressants such as hydroxychloroquine, azathioprine, cyclophosphamide, and 6-mercaptopurine are sometimes

used in combination with steroids for severe cases, or singly when steroids are contraindicated or not tolerated.^{[2][4][7]} In infants, steroid dosages of 2 mg/kg/day for durations ranging from 80 to 210 days have been used, with good outcomes.^{[2][7]} In older children and adults, a case report recommended a dose of less than 1 mg/kg/day, continued until alveolar infiltrates resolve, and then weaned off slowly.^[1] The combination of azathioprine and corticosteroids has been reported in some case reports to yield better outcomes.^{[1][11]} Other treatment options with unknown efficacies include intravenous immunoglobulin, plasmapheresis, liposteroids, and dietary modification (gluten-free diet in those with celiac disease and IPH has been shown to improve symptoms).^{[7](B3)}

Differential Diagnosis

The differential diagnoses of IPH include other causes of diffuse alveolar hemorrhage. These include vasculitides such as microscopic polyangiitis, pauci-immune glomerulonephritis, Wegener's granulomatosis, Churg Strauss syndrome, hypersensitivity vasculitis, systemic lupus erythematosus, rheumatoid arthritis etcetera. Other examples are Goodpasture's syndrome, antiphospholipid syndrome, and lung transplant rejection. Other non-vasculitic differential diagnoses include coagulopathies (eg, von Willebrand disease), thrombocytopenia, pulmonary embolism, lung cancers, pulmonary infarction, non-traumatic lung injury, pulmonary hemangiomas, etcetera.^[1] Restrictive lung diseases such as pulmonary fibrosis, other autoimmune diseases such as celiac disease, cow milk protein allergy, recurrent respiratory infections, and other causes of anemia in children may also be differential diagnoses.^[4]

Prognosis

The prognosis of IPH depends on factors such as the time of diagnosis, how early treatment is commenced, and the presence of co-morbidities.^{[4][7]} Prompt diagnosis and early treatment lead to a better prognosis.^{[4][11]} It has an average survival rate of 2.5 years, although one study reported 86% of patients surviving beyond 5 years.^[7] Its mortality rate is 50%, however, no mortality was recorded in the 4 infants with ALPHI in a retrospective study.^{[2][4][11]} Generally, the disease runs a more severe course with a worse outcome in children and adolescents compared to adults.^[1] Mortality is usually caused by acute respiratory failure following massive alveolar hemorrhage or complications of chronic respiratory failure and cor pulmonale following severe pulmonary fibrosis.^[1] Long-term steroid use reduces morbidity and mortality.^[1]

Complications

The immediate complication of the condition is hypoxic respiratory failure, which can lead to death, especially in children. Long-term complications include anemia, pulmonary fibrosis, and other restrictive pulmonary lung diseases. Other possible complications are secondary to the side effects of long-term corticosteroid use.

Deterrence and Patient Education

As with other respiratory illnesses, patients and their caregivers are advised to present to the hospital early, at the first occurrence of symptoms. Being an idiopathic condition, there are no specific preventive measures to avoid the condition. It is not a contagious disease.

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