

Heiner Syndrome and Milk Hypersensitivity

Subjects: **Nutrition & Dietetics**

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Infants affected by Heiner syndrome (HS) display chronic upper or lower respiratory tract infections, including otitis media or pneumonia. Clinically, gastrointestinal signs and symptoms, anemia, recurrent fever and failure to thrive can be also present. Chest X-rays can show patchy infiltrates miming pneumonia. Clinical manifestations usually disappear after a milk-free diet. The pathogenetic mechanism underlying HS remains unexplained, but the formation of immune complexes and the cell-mediated reaction have been proposed. Patients usually outgrow this hypersensitivity within a few years.

allergy

anemia

cow's milk

children

immunology

non-IgE-mediated food allergy

pneumonia

pulmonary hemosiderosis

pulmonary infiltrates

1. Introduction

Heiner syndrome (HS) is a rare food-induced hypersensitivity disease characterized by chronic respiratory symptoms with X-ray (XR) infiltrates, and the resolution of signs and symptoms after the removal of milk proteins. Other clinical manifestations include poor growth, gastrointestinal signs and symptoms, iron deficiency anemia and pulmonary hemosiderosis (PH). Precipitins to cow's milk (CM) were also considered a useful aid in recognizing hypersensitivity to CM ^[1]. The literature concerning HS is restricted to a few case reports or series, although the disease has always been described at infant or pediatric age ^[2]. The definition of the disease is lacking and the diagnosis is often delayed, since its presentation is uncommon with dissimilar manifestations.

2. Age at Onset

The clinical onset of the disease has been described typically by the age of 1 month to 48 months, but it can develop even during the first 5 days of life, as reported by Torres et al. ^[3]. However, it can also appear later (the oldest patient was 5 years old) ^[4]. Nevertheless, there was a frequent delay in diagnosing this disease, due to its various modes of presentation and lack of standardized diagnostic criteria. The past medical history of affected children was always unremarkable. A family history of allergic disorders was often present. Differently from immediate-onset IgE-mediated CM allergy, HS did not display signs and symptoms before several days or weeks after CM consumption.

3. Etiology

Although HS is more likely to be induced by homogenized CM, the disease also may occur in some infants fed with CM-derived formula. Furthermore, it has been speculated that it can be related to non-IgE-mediated allergy to food proteins differently from CM at an older age (e.g., soy, egg, pork, wheat and peanut) [5][6]. In this context, a single case of PH hemosiderosis due to buckwheat has also been reported [7].

4. Clinical Characteristics

Respiratory features of the disease included persistent cough, dyspnea, tachypnea, wheezing, occasional sputum production and rales. The peculiarity of pneumonia in these case series was the refractoriness of antibiotic treatments. Of note, in most cases, the additional administration of anti-inflammatory drugs probably might have resolved hypersensitivity pneumonia or idiopathic PH (IPH). The most commonly described systemic clinical manifestations were intermittent fever, progressive anorexia and FTT. Inflammatory markers were usually found to be high. Eosinophilia and severe iron deficiency anemia were frequently described at blood count examination. Gastrointestinal manifestations were reported in about half of the patients and included frequent vomiting or diarrhea. Rarely, lymph node hypertrophy with hepatomegaly, splenomegaly and hypertrophied tonsils or adenoids were labeled [8]. Noticeably, lymphonodular hyperplasia in biopsy was found in a child with HS-manifesting hematochezia [9].

Clinically, the disease can be complicated with cardiopulmonary involvement, such as alveolar hypoventilation, massive acute PH, pulmonary hypertension and *cor pulmonale*, or nephrological ones, such as crescentic glomerulonephritis [10][11]. These characteristics contributed drastically to morbidity and emerged in situations of overdue diagnosis and management. In particular, a delayed manifestation of the disease is episodic hemoptysis, which may represent a PH with repeated episodes of intra-alveolar bleeding, hemosiderin deposition in alveolar macrophages, followed by the development of pulmonary fibrosis and severe anemia [10]. PH may occur as a primary disease of the lung (also called IPH) or secondary to cardiac diseases, bleeding disorders, collagen-vascular diseases or systemic vasculitis. IPH, if not treated, leads to progressive pulmonary fibrosis and may be lethal [12].

5. Pathogenesis and Immunological Implications

The exact mechanism that triggers HS is not fully understood. Feasibly, the formation of immune complexes is strongly suspected (Gell and Coombs type III reaction) and the cell-mediated reaction (Gell and Coombs type IV reaction) may contribute to the development of this challenging disease.

Some cases showed positive skin tests [13][8], high serum total IgE levels [8], high milk-specific IgE antibodies [11][5] or circulating immune complexes [13]. A significant increase of histamine and ECP in BAL several hours after a milk OFC was reported [3]. In one case report, deposits of immunoglobulins, complement, fibrin and milk protein antigens diffusely scattered were described on immunofluorescence studies of lung tissue biopsies [2]. It is probable that a cause concurring to HS is the aspiration of milk, in particular among patients with an uncoordinated

swallowing mechanism, tracheal/esophageal anomaly or gastroesophageal reflux. However, in the paper of Boat et al., this condition was ruled out [8]. Concerning the data on delayed immunity, in some cases a delayed skin test response to intradermal test [13][8] or a lymphocyte response [10] was reported. Other authors postulated that milk antigens might trigger an immune complex reaction resulting in multiorgan abnormalities, such as pulmonary, gastrointestinal and renal ones. In fact, pulmonary and gastrointestinal signs and symptoms were frequently associated [14] and granular immuno-deposits have been demonstrated along the glomerular basement membrane in a child with crescentic glomerulonephritis and PH [11].

Most studies, mainly the oldest ones, characteristically found high titers of precipitins (likely immunoglobulins of class G) against bovine milk proteins in the patients' sera, by using the Ouchterlony double-immunodiffusion technique [4][15][8][14]. However, it is not sufficiently explicable why some children develop precipitating antibodies to ingested protein and other children do not. Moreover, it is not known if these precipitins play a causative role in the disease. Children with precipitins usually have an increased incidence of recurrent respiratory tract diseases, anemia and hepatosplenomegalia. However, precipitating IgG antibodies to milk are not pathognomonic of the disease, since they have been found among around 1% of healthy children in the absence of clinical manifestations [4], and in 4% to 6% of children with chronic disorders, including celiac disease, cystic fibrosis, IgA deficiency, Down's syndrome, Wiskott–Aldrich syndrome and Hurler's syndrome [8]. Additionally, methods used for detecting precipitins are obsolete and reports on them are timeworn. Therefore, the role of these antibodies should be critically considered.

In other more recent reports, high values of specific IgG to milk proteins were found using an immunoenzymatic technique [5]. In one case report [16] CM IgG4 was found to be elevated. Even in these cases, the role of this specific CM IgG is not clear.

6. Pulmonary Modifications and Immunofluorescence Studies

Chest roentgenograms displayed variable patchy and transient infiltrates, frequently associated with areas of atelectasis, consolidation, reticular opacities, pleural thickening or hilar lymphadenopathy. The lung biopsy obtained in patients who had hemoptysis showed an abnormal accumulation of hemosiderin in the lungs, which resulted in alveolar hemorrhage or PH [2]. Among patients with anemia and hemoptysis, PH was verified by the demonstration of iron-laden macrophages by using Prussian Blue staining of bronchial aspirates or morning gastric washes [10].

7. Diagnostic Criteria

As described in detail above, in order to better stratify the level of evidence for the diagnosis, we are herein proposing the first structured diagnostic approach for the diagnosis of HS to the best of our knowledge. We auspicate that this approach may allow clinicians to stratify patients with a clinical history consistent with the

suspicion of HS in probable (criteria A + B) or convincing (criteria A + B + C) HS ([Figure 1](#)). According to our criteria, only 6 out of 61 patients had a convincing clinical diagnosis of HS, in 25 patients the clinical diagnosis was probable and in the others the HS diagnosis was doubtful ([Table 1](#)). Due to the heterogeneity in the methodologies applied for laboratory tests and missing reporting/lack of data, we decided to exclude laboratory parameters from the diagnostic criteria. We suggest in the future that milk-specific IgG tests with current diagnostic methods (i.e., immunoenzymatic), in the case of suspected HS, could be studied. Nevertheless, further points remain questionable in our proposed diagnostic approach. First, some cases of occurrence of signs and symptoms during exclusive maternal breastfeeding were reported (e.g., in three out of seven cases in Heiner et al. [\[13\]](#), leading to the question of whether or not minimal quantities of CM passing in breast milk are capable of inducing a clinical response through an IgG-mediated mechanism in the infant). As a second observation, one case of resolution of signs and symptoms without dietary restriction has been described (one out of seven patients from Heiner et al.). Again, a real, controlled OFC of milk was reported only in 6 cases [\[13\]\[8\]\[14\]](#) and a recurrence of clinical manifestations was reported in a further 6 cases (although without details on exact timing of the symptoms' onset) based only on clinical history [\[15\]\[17\]\[8\]\[11\]\[5\]\[18\]](#), for a total of 12 cases. Moreover, in some cases [\[11\]\[5\]](#) pharmacological therapy was associated to the CM elimination diet, making it difficult to differentiate the effect of each single treatment. Spontaneous resolution of signs and symptoms also occurred in some cases of HS [\[1\]](#). Furthermore, some studies did not report on the follow-up and specifically on the outcome of any CM reintroduction. In conclusion, even if in a few cases a convincing diagnosis can be made using specific criteria, certainty is lacking due to the incomplete clinical and imaging monitoring of the OFC and the lack of control cases.

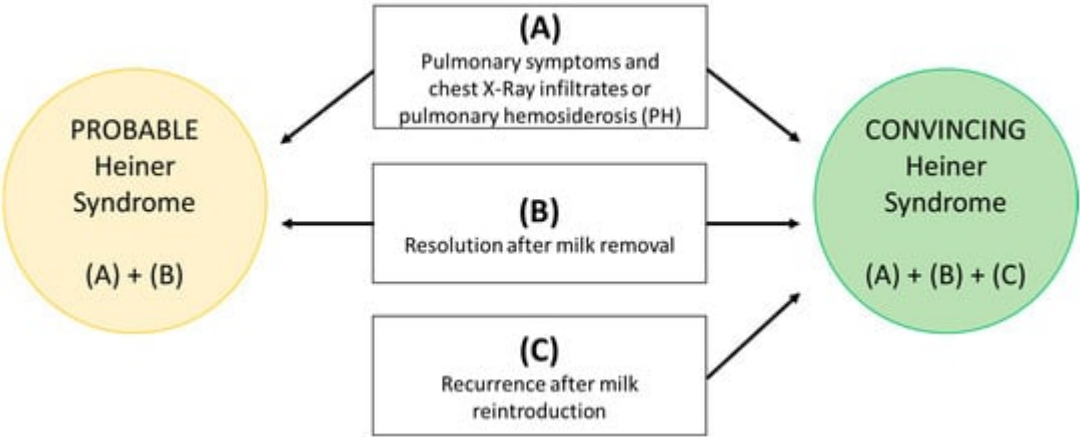


Figure 1. Proposed approach for Heiner syndrome diagnosis.

Table 1. Characteristics of the included studies of Heiner syndrome.

Authors, Year	Country	n. Cases	Age at Onset (Months)	Signs/Symptoms	Lung Radiologic Infiltrates	Pulmonary Hemosiderosis	Hemosiderosis Diagnosis	Milk Precipitins	Delayed Hypersensitivity	Allergic Sensitization to Milk [sIgE and/or skin prick test (SPT)]	Improvement Upon Milk Avoidance	Recurrence Upon Milk Reintroduction	
1	Heiner, 1960	USA	7	1–17	chronic cough (7/7); wheezing (7/7); chronic rhinitis (7/7); frequent fever (7/7); frequent earache (6/7); diarrhea (6/7); vomiting (5/7); hemoptysis (4/7)	yes, recurrent	yes (5/7)	gastric or bronchial aspirates (4/7); pulmonary needle biopsy (1/7)	yes	intradermal test (ID) late response pos (4/7)	ID +ve (7/7)	yes (6/6)	yes (2/6)
2	Holland, 1962	USA	22	4–12	respiratory disease; failure to thrive (FTT); anemia; splenomegaly; hepatomegaly	non specified (NS)	NS	NS	yes	NS	NS	yes (22/24 on milk-free diet)	NS
3	Chang, 1969	USA	1	9	FTT ; anemia; chronic recurrent lung disease	yes	NS	NS	yes	NS	NS	yes	doubtful, based on clinical history (CH)
4	Archer, 1971	England	1	13	iron-deficiency anemia; lethargy; pallor; bloody vomit; severe cardiac failure; hemoptysis	yes	yes	needle biopsy	no	NS	SPT –ve	yes	doubtful, based on CH
5	Boat, 1975	USA	6	7–48	idiopathic chronic or recurrent pulmonary disease; upper respiratory symptoms; FTT (3/6); frequent regurgitation and watery stools (1/6). SOF (1/6): Iron deficiency (5/6); Anemia (4/6); Eosinophilia (4/6); right	yes (6/6)	yes (5/6)	gastric washing or bronchoalveolar lavage (BAL)	yes (6/6)	4 ID delayed response	total IgE –ve (6/6); SPT +ve (5/6)	yes (5/6); 1/6 loss of data	yes (1/6)

Authors, Year	Country	n. Cases	Age at Onset (Months)	Signs/Symptoms	Lung Radiologic Infiltrates	Pulmonary Hemosiderosis	Hemosiderosis Diagnosis	Milk Precipitins	Delayed Hypersensitivity	Allergic Sensitization to Milk [slgE and/or skin prick test (SPT)]	Improvement Upon Milk Avoidance	Recurrence Upon Milk Reintroduction
				ventricular hypertrophy (3/6); adenoid hypertrophy (3/6)								
6 Stafford, 1977	USA	7	8–48	wheezing (5/9); chronic rhinitis (3/9); large adenoids/tonsils (4/9); anemia (4/9); gastrointestinal symptoms (4/9); eosinophilia (6/9)	yes (7/9)	yes (3/9)	gastric washing and BAL	yes (9/9)	lymphocyte response (3/3)	SPT +ve (6/9), slgE +ve (5/8)	NS	NS
7 Fossati, 1992	Italy	1	7 years	anemia; respiratory symptoms	yes	yes	NS	yes	NS	NS	yes	NS
8 Torres, 1996	Spain	1	0 (5 days)	vomiting with blood; respiratory failure; restrictive miocardiopathy; anemia; eosinophilia	yes (chest X-Ray, CXR)	yes	BAL	NS	NS	neg	yes	symptoms not reported
9 Moissidis, 2005	USA	8	4–29	cough (7/9); wheezing (3/9); dyspnea (1/9); hemoptysis (2/9); nasal congestion (3/9); recurrent otitis media (OM) (3/9); recurrent fever (4/9); gastrointestinal symptoms (5/9); in 7/8; hematochezia (1/9); FTT (2/9); eosinophilia in 5/8	yes (9/9)	yes (1/9)	NS	yes (6/6)	NS	slgE (1/3), SPT (1/2)	yes (8/9)	positive challenge (3/3)
10 Sigua, 2013	USA	1	12	persistent cough; progressive anorexia;	yes (CXR)	no	BAL	yes	NS	slgE –ve	yes	doubtful, based on CH

Characteristic pulmonary hemorrhage attacks cannot be enlightened by modest bronchial asthma. The lack of chronic inhalant exposure and BAL examination can rule out hypersensitivity pneumonitis. Bronchopulmonary aspergillosis is unlikely if skin reactivity to *Aspergillus* antigens is negative or precipitating serum antibodies to *A. fumigatus* are absent. No hemorrhagic focus nor foreign bodies can be found on bronchoscopy. In particular, DD should consider IPH, that includes the classic triad hemoptysis, radiologic lung infiltrate and iron deficiency anemia, having a more severe course and prognosis [19]. Moreover, IPH occurs in older children, and it is rarely associated with gastrointestinal symptoms [20] (Table 2).

Table 2. Differential diagnosis between Heiner syndrome (HS) and idiopathic pulmonary hemosiderosis (IPH).

	HS	IPH
Age	infants or young children	older children/adults
Hemosiderosis	often	always
GI symptoms	often	rarely
Precipitins	yes	no
Response to diet	yes	no
Prognosis	good	variable

Authors, Year	Country	n. Cases	Age at Onset (Months)	Signs/Symptoms	Lung Radiologic Infiltrates	Pulmonary Hemosiderosis	Hemosiderosis Diagnosis	Milk Precipitins	Delayed Hypersensitivity	Allergic Sensitization to Milk [slgE and/or skin prick test (SPT)]	Improvement Upon Milk Avoidance	Recurrence Upon Milk Reintroduction
				intermittent fever; weight loss; iron deficiency anemia								
11 Yavuz, 2014	Turkey	[13][15][17][3][14][5]	3	respiratory distress; hemoptysis; recurrent bronchitis; FTT; iron deficiency anemia; eosinophilia; increased inflammatory index;	yes (CXR, CT)	yes	BAL	NS	NS	slgE +ve	yes	doubtful, based on CH
12 Mourad, 2015	USA	1	17	severe anemia; respiratory distress	yes (CXR)	yes	BAL	IgG	NS	slgE +ve	yes	doubtful, based on CH
13 Alsukhon, 2017	USA	1	2	FTT; recurrent diarrhea; persistent cough; tachypnea; high inflammatory markers	yes (CXR)	NS	NS	IgG4	NS	slgE –ve	yes	NS
14 Ojuawo, 2019	Nigeria	1	4	FTT; cough; dyspnea; wheeze; rhinitis; gastrointestinal symptoms; anemia	yes (CXR)	NS	NS	NS	NS	NS	yes	NS doubtful, based on CH
15 [46] 2019	Turkey	1	6	massive hemoptysis; hematemesis; deep anemia	yes (CXR, CT)	yes	gastric washing	NS	NS	NS	yes	NS
16 Liu, 2020	China	1	4	respiratory failure; hematochezia; diarrhea; elevated WBC	yes (CXR, CT)	no	sputum or fasting gastric fluid	NS	NS	–ve	yes	NS

When signs of oral intolerance remain and the milk therapy for acute anemia in more severe cases of HS, other immunomodulatory treatments may be helpful, such as hydroxychloroquine, azathioprine or cyclophosphamide. On the contrary, antibiotic therapy seems not to be useful.

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and C-reactive protein													

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Abbreviations: BAL, bronchoalveolar lavage; CH, clinical history; CT, computerized tomography; CXR, chest X-Ray; ID, intradermal test; NS, non-specified; SPT, skin prick test; -ve, negative; +ve, positive.

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