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Multiple food allergy presenting as Heiner syndrome in a Nigerian infant – Case report

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Abstract

Background: Heiner syndrome (HS) is a rare non-IgE mediated hypersensitivity to cow's milk or multiple food allergy characterized by chronic respiratory symptoms with chest X-ray infiltrates and resolution of these symptoms on dietary elimination of cow's milk.
Case report: We present the case of a 9- month-old male with history of cough, fever, difficult breathing and wheezing who was initially managed for bronchopneumonia with no improvement of symptoms. With subsequent review, the history of allergy to cow's milk, eggs, and crayfish with positive maternal history of food allergy was obtained. Elimination of offending foods led to symptom resolution and a re-challenge led to reappearance of symptoms.
Conclusion: This case report highlights the need for a high index of suspicion of HS in children with respiratory symptoms and a positive history of food allergy.

Keywords: Heiner syndrome, cow's milk protein allergy, multiple food allergy, pneumonia, breast milk substitutes.

Introduction

Heiner syndrome (HS) is a rare non-IgE mediated hypersensitivity to cow's milk or multiple food allergy characterized by chronic respiratory symptoms with chest X-ray infiltrates and resolution of these symptoms on dietary elimination of cow's milk.[1,2] Heiner Syndrome was first described by Heiner in 1962 in seven infants with precipitin antibodies to cow's milk antigen with pulomonary infiltrates.[3] Global prevalence of HS is unknown, however, approximately 5% of infants with cow's milk protein allergy have evidence of pulmonary infiltrates.[4] It commonly occurs between the ages of one month to 48 months but has been reported in neonates as early as 5 days of age and as late as 5 years of age.[1] The immune-pathogenesis of HS is poorly understood, however, it has been postulated to involve immune complex and cell-mediated immune reactions to cow's milk proteins causing alveolar vasculitis.[5] Affected individuals typically present with respiratory symptoms but may also have gastrointestinal symptoms, poor growth, iron deficiency anaemia, and pulmonary hemosiderosis.[1,6] This wide variability of presentations and its ability to mimic more common diseases makes diagnosis of HS difficult.[1,7-9] The diagnosis of HS, therefore requires a high index of suspicion and adequate knowledge of its various manifestations. Published literature on HS is limited to few case reports or series with only one case report published from South-west Nigeria.[1,7,10] We therefore report the first case of HS diagnosed in Calabar, Cross River State, South-south, Nigeria.

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Case report

A 9-month-old male was brought to the Children Emergency Unit with a 5-day history of cough and a one-day history of fever and difficulty breathing. Cough was gradual in onset, non-paroxysmal, and not worse at any time of the day. Fever was low grade and continuous, while difficult breathing was gradual in onset, progressively worsened and not associated

with wheeze or other noisy breathing.

He had a history of recurrent cough and catarrh treated with over-the-counter medications without complete resolution of symptoms. Patient had no history of haemoptysis. There was history of rash whenever he ingests cow's milk products. Delivery was at term with a birthweight of 3.2kg and without any neonatal complications. He was exclusively breastfed for 4 months, thereafter breast milk substitute (BMS) was introduced. Two weeks after commencement of BMS, he developed urticaria and persistent vomiting after milk feeds. A different brand of BMS was introduced with no relief of symptoms. BMS was therefore withdrawn, with resolution of symptoms, and he was fed soy-bean milk. His mother is asthmatic while his maternal aunt has allergy to shrimps.

Patient's weight was 10.5Kg (between 0 and +1 z score) and length was 78cm (on the +1 z score) using the World Health Organization growth chart. Temperature was 38.9°C, acyanosed with SpO_2 of 98% in room air, not clinically pale. Respiratory system examination revealed mild tachypnoea, nasal flaring, intercostal retractions, as well as expiratory rhonchi and crepitations in the right lung zones. Examination of the cardiovascular, digestive, and nervous systems were unremarkable.

Laboratory investigations revealed a total white cell count of 12 x 109/L; relative eosinophilia of 0.96 x 109 /L (8%), neutrophils 4500 cells/mcL(40%), lymphocytes 6000 lymphs/mcL(50%) and Packed cell volume of 37%. His blood film for malaria parasite was normal and blood culture did not isolate any organism. Results of other investigations done including serum electrolytes, urea and creatinine were within normal limits. Chest radiograph showed bilateral infiltrates (Figure 1).

The initial working diagnosis was acute bronchial asthma with bronchopneumonia. He was treated with nebulized Salbutamol at 0.15mg/kg given three sessions within one hour, intravenous Hydrocortisone 100mg stat dose followed by oral Prednisolone given at a dose of 1mg/kg/day for three days, and intravenous antibiotics (IV Crystalline Penicillin 0.2mu/kg 6 hourly and IV Genticin 5mg/kg/day for 48 hours) were prescribed. Patient was discharged home on Azithromycin suspension at 10mg/kg/day for five days. The respiratory distress resolved, however, cough persisted. Following a review by the Paediatric Pulmonologist, food allergy was suspected, and he was referred to the Paediatric Gastroenterology clinic. A gastroenterology review revealed additional history of urticaria and persistent vomiting following ingestion of cow's milk, eggs, yoghurt, and crayfish. The Cow's Milk-related Symptom Score (CoMiSS) was determined, and he had a score of 15, which was in keeping with cow's milk allergy. A diagnosis of multiple food allergy presenting as Heiner syndrome was made based on the clinical history and findings on the chest radiograph. Facilities for estimating titres of cow's milk-specific IgE, specific IgE for eggs precipitating antibodies were however not available to further support the diagnosis.

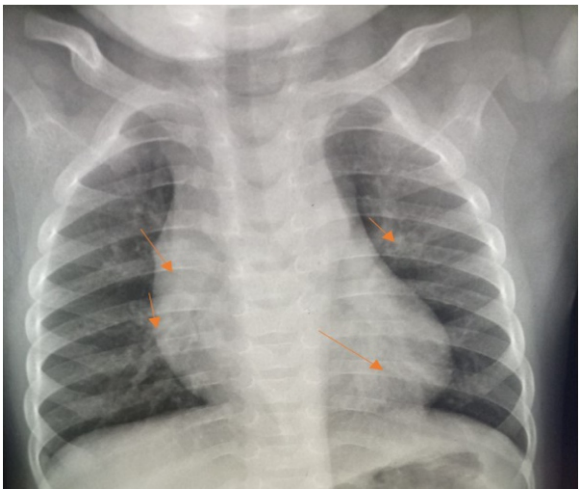

Figure 1: Chest radiograph showing bilateral pulmonary infiltrates.

An elimination diet with strict elimination of dairy products, eggs, and other triggering foods was commenced while corticosteroids was withdrawn. Elimination diet was done with taking out of one food item out per time. By his first follow-up visit two weeks later, the cough had completely resolved, and he remained symptom free on subsequent clinic visits at one and 3 months, still off cow's milk and eggs. At 15 months of age, he was admitted into the ward for open oral food challenge (OFC). Reintroduction of eggs induced urticaria within an hour of the first dose while a second OFC with cow's milk a week after induced anaphylaxis. Cow's milk reaction had the worse outcome and hence it re-challenge last. The OFC was therefore discontinued. He remains symptom free on the elimination diet at the age of 24 months.

Discussion

Heiner syndrome (HS) is primarily induced by cow's milk proteins; however, it has been postulated that it could also be due to non-IgE mediated food allergies

to proteins other than cow's milk including eggs, wheat, and peanuts.[1] It has been suggested that IgE-mediated food allergies to foods other than milk may also induce HS.[11] However, there is no evidence for involvement of milk specific IgE in HS.[5] Our patient had a mixed allergy to multiple foods, this was evidenced by sudden onset skin rash (possibly IgE-mediated) on introducing cow's milk formula during infancy, and eggs and later development of vomiting and respiratory symptoms (non—IgE mediated).

The onset of symptoms in HS usually occurs before the age of one year as was the case with our patient who presented at 9 months of age.[2] Affected individuals typically present with chronic or recurrent lower respiratory symptoms such as cough, wheezing, and dyspnoea.[1,2,5] This is often associated with upper respiratory symptoms, gastrointestinal symptoms, failure to thrive (FTT) and anaemia.[1,2,5,6] Our patient however did not manifest with failure to thrive or have anaemia, this may have been due to patient receiving proper nutritional counselling and intervention during each visit to the hospital. Systemic manifestations include fever, and progressive anorexia.[1] In severe cases patients may develop pulmonary hemosiderosis with haemoptysis.[1,2] Untreated pulmonary hemosiderosis may lead to pulmonary fibrosis.[11] Other complications include alveolar hypoventilation, acute pulmonary haemorrhage, pulmonary hypertension, cor pulmonale and crescentic glomerulonephritis.[1] These, however, did not occur in our index patient. Our patient presented with fever and lower respiratory tract symptoms and had a history of recurrent cough, as well as gastrointestinal symptoms on ingestion of cow's milk.

The wide variety of clinical manifestations, its similarity to more common respiratory diseases and lack of standard diagnostic criteria makes diagnosis of HS difficult.[1,2,8] This frequently leads to a delay in diagnosis; hence a high index of suspicion is required.[2,8] Our patient was initially thought to have had bronchopneumonia and bronchial asthma due to a similar presentation with these respiratory diseases. However, there was no laboratory evidence of these infections, and his symptoms did not completely resolve on appropriate treatment for these conditions.

HS is primarily a clinical diagnosis with no specific confirmatory tests.[2,8,11] However, several laboratory investigations can aid diagnosis. Most patients have high titres of precipitatin IgG antibodies to cow's milk.[11] These antibodies are neither pathognomonic nor sensitive for HS as they can be found among 1% of healthy children and 4% to 6% of children with other chronic diseases such as coeliac disease.[1] The pathogenetic role of these precipitins is unknown.[1] Varying degrees of peripheral eosinophilia and iron deficiency anaemia may also be found in some patients.[2] Our patient had no evidence of anaemia. Some cases show positive skin tests, high serum total IgE or circulating immune complexes.[1] Skin prick test and specific IgE levels to allergens may be negative in some patients with HS.[1,11] Chest X-rays may display patchy and transient infiltrates while patients with pulmonary hemosiderosis have iron laden macrophages on examination of bronchoalveolar lavage, gastric washings, or open lung biopsy specimens.[1,2,7] The diagnosis of HS is confirmed by complete resolution of clinical and radiological features after dietary elimination of cow's milk and recurrence of these features after reintroduction of cow's milk into the diet or an oral food challenge.[1,8,9,11,12] The diagnosis of HS was made in our patient due to his clinical history and findings on chest radiograph, and this was strengthened by complete resolution of respiratory symptoms on dietary elimination of cow's milk.

Dietary elimination of offending food is the mainstay of management for HS.[11] Recovery after elimination of cow's milk or other food implicated is usually immediate with clinical improvement within days and radiological improvement in weeks.[1,2,7] Early reintroduction of cow's milk can lead to recurrence of symptoms.[2] During the period of elimination, infants may be fed substitutes such as extensively hydrolysed protein formula, soy-based formula or synthesized free amino acid formula.[1] Recovery without exclusion of the culprit food has also been reported.[1] Patients usually outgrow the hypersensitivity in HS and may tolerate cow's milk within a few years.[1] There is no defined time frame for reintroduction of dietary cow's milk.[11] However, an oral food challenge can be tried after elimination of dietary cow's milk to ascertain if it is safe to reintroduce cow's milk into the diet.[11] In some cases, additional treatments such as bronchodilators, antihistamines, systemic or inhaled steroids may be required.[1] Oral corticosteroids are the first line therapy in acute attacks while in more severe cases immunomodulatory agents such as hydroxychloroquine or cyclophosphamide may be used.[1] Our patient initially received systemic steroids and bronchodilators as part of management of bronchial asthma with subsequent improvement in

symptoms. However, the cough persisted despite adequate pharmacotherapy. Following a review by the paediatric gastroenterologist, cows' milk, and eggs were eliminated from the patient's diet with complete resolution of symptoms.

The challenges in management of our patient in a resource poor setting included limited access to investigations such as assessing serum levels of total IgE and specific IgE for cow's milk, eggs, peanuts, and soybean. Skin prick test could also not be done. These investigations are not readily available and where available are not within the financial reach of most patients who must pay out of pocket for health care services. Hydrolysed formulas which can serve as alternatives to whole cow's milk are also not available.

Conclusion

We presented the first case of Heiner's Syndrome diagnosed and managed in Calabar, Nigeria. Early diagnosis in this case was made possible by a high index of suspicion and collaborative clinical care by the pulmonologist and gastroenterologist. However, general access to these specialists is limited in Nigeria so there is the need for increased awareness of HS and other food allergies among medical practitioners. We propose that HS should be considered in the differential diagnosis of young children with chronic respiratory symptoms who do not respond to standard pharmacotherapy and have a positive history of food allergy. Early dietary restriction of cow's milk and other offending foods in these patients could facilitate diagnosis, lead to resolution of symptoms, and prevent the long-term morbidity associated with HS.

Ethical consideration

The patient image and data were fully anonymised. The patient's mother provided informed written consent to publish this case.

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