CASE REPORT
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A Report of Two Patients with Food Protein-induced Enterocolitis Mimicking Bartter Syndrome

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ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES), is a non-IgE mediated food allergy presenting in infants younger than 12 months. Diagnostic delay may occur due to overlapping clinical symptoms with several conditions. Here, we present two cases of FPIES, mistakenly diagnosed and treated as Bartter syndrome. This study aims to emphasize the several features of this syndrome that may mimic other diagnoses and sometimes leading to near-death events due to delay in the diagnosis and improper treatment. The first patient was a 30-month-old boy with multiple episodes of profuse vomiting and diarrhea within 1 hour after breastfeeding, beginning from the first month of life progressing to hypokalemia and metabolic alkalosis at the age of 5 months leading to the diagnosis of Bartter syndrome. The second patient had a history of unremitting diarrhea which had been started soon after his first breastfeeding followed by biliary vomiting on the 7th day of life. He was treated in another hospital for neonatal sepsis, however, without an appropriate response to treatment. To conclude, despite the current belief on the rarity of FPIES, it is a more prevalent disease than expected with various non-specific manifestations imitating other conditions which may result in diagnostic delay and sometimes fatalities. To shed light on the importance of the physicians' awareness of this syndrome, these two cases are presented here as examples of FPIES imitating other disorders.

Keywords: Bartter syndrome; Failure to thrive; Food hypersensitivity

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy presenting in infants younger than 12 months and may appear as a life-threatening condition. Despite the current belief on the rarity of FPIES, a prevalence of 3 per 1000 has been reported recently based on a prospective birth cohort report.[1]

Previously, FPIES had been suggested as a disease of formula-fed infants but recently there are increasing reports indicating the occurrence of the disease in exclusively breast-fed infants.[2]

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Clinical features may be acute or chronic and include profuse vomiting and diarrhea within 1 to 4 hours following food ingestion, pallor, lethargy, floppiness, hypotension, and hypothermia.[3,4] In chronic undiagnosed cases malabsorption syndromes, anemia, and diarrhea even without metabolic disturbances and severe dehydrations may occur failing to thrive.[3] Diagnostic delay may occur due to overlapping clinical symptoms with several conditions. In addition, the lack of definitive diagnostic tests and also unawareness of many primary and secondary care physicians are other causes for delay in diagnosis.

Cow's milk, soy, and solid foods are the most common inciting foods, respectively. Elimination diets and the resolution of symptoms by removal of the causative food and reappearance of the symptoms again after the reestablishment of culprit food, are the cornerstone of food allergy diagnosis. Patients with FPIES induced by cow's milk may well tolerate extensively hydrolyzed milk. However, in some of them with refractory symptoms or signs, the amino-acid-based formula may become essential.[5]

Here, we present two cases of FPIES, mistakenly diagnosed and treated as Bartter syndrome. This study aims to emphasize the features of this syndrome that mimic those of other diseases, so misdiagnosis may lead to even fatal events due to diagnostic delay. Thus, the role of timely proper diagnosis and the physicians' awareness of such a disease is essential to the future outcome of these patients.

Case 1

A 30-month-old boy was admitted with a diagnosis of Bartter syndrome. The patient was born full-term with a weight of 4 kg and a height of 52 cm. He experienced multiple episodes of profuse vomiting and diarrhea within 1 hour after breastfeeding in his first month of life. At the age of 5 months, an episode of severe vomiting and diarrhea led to severe dehydration with metabolic alkalosis accompanied by hypokalemia. Lab data and a prenatal history of polyhydramnios suggested Bartter syndrome clinically. Table-1 demonstrates the laboratory data of the patient at the time of admission. However, Bartter syndrome was ruled out after thorough investigations despite low serum potassium levels (due to the low urinary potassium and chloride concentrations) and the lack of adequate clinical response to treatment. Because of the predominant gastrointestinal symptoms, other differential diagnoses including FPIES were suggested to be ruled out.

Tissue specimen obtained by colorectal biopsy was indicative of marked eosinophilic infiltration (>20/HPF) suggesting proctocolitis. Empirical treatment including azathioprine, prednisolone, and omeprazole was started by a gastroenterologist with no clinical improvement. After allergy consultation, FPIES was suggested (based on the International consensus guideline with one major and more than three minor criteria and also lack of appropriate therapeutic response to other possible differential diagnoses including Barter syndrome).[6]

Because of the severity and long duration (30 months) of symptoms in this patient, the possibility of solid food FPIES was suggested for him which may occur in combination with cow's milk/soy protein in one-third of the patients.[7]

Therefore, a six-food elimination diet was started which was accompanied by significant improvement. Both vomiting and diarrhea stopped soon after the initiation of the diet. Hypokalemia resolved, and growth and development became normal. The patient was well in the next six months of follow-up.

Case 2

A full-term male with unremarkable prenatal history was born from consanguineous parents with a normal birth weight of 4060 grams and a height of 49 centimeters. Unremitting diarrhea was started soon after his first breastfeeding on the first day of life followed by biliary vomiting after a week. He was treated in another hospital for neonatal sepsis, however, without an appropriate response to treatment. Therefore, the hydrolyzed formula was started for him. But again his condition was aggravated after ingestion of this formula at the age of 19 days. He was referred to our center at the age of one month with dehydration, hypotension, lethargy, and pallor while he had lost 1500 grams during these 30 days. Bartter syndrome, infectious diseases, cystic fibrosis, primary immunodeficiency syndromes, renal tubular acidosis, and even surgical conditions were all suggested as probable causes and were ruled out after thorough investigations. Among these, Bartter syndrome was at the top of the diagnoses due to severe and rebellious hypokalemia detected in the patient. However, it was excluded due to the low levels of potassium and

chloride in the patient's urine. Abdominopelvic ultrasound revealed bilateral nephrocalcinosis which was explained by the patient's severe dehydration due to intractable vomiting and never detected again in subsequent investigations.

Increased quantitative C-reactive protein (CRP) (90 mg/L), hypokalemia (K=1.8 mEq/L), and metabolic acidosis were prominent lab findings (Table 1).

After performing allergy consultation, chronic FPIES with intermittent acute attacks, based on International Consensus Guideline with one major and more than three minor criteria[6] was considered and an extensively hydrolyzed formula (Neutramigen-Enfamil) was started which again aggravated his clinical condition (leading to severe diarrhea, intermittent vomiting, lethargy, and shock). He was admitted to PICU with severe respiratory distress where he experienced a cardiopulmonary arrest, although he was successfully resuscitated. After a week of mechanically assisted ventilation, oral feeding with amino-acid-based formula (Neocate -Nutricia) was started. Within an hour of his first oral intake of the formula, diarrhea returned which resulted in severe hypovolemia, respiratory distress due to profuse vomiting, and unconsciousness. At this time, we concluded that any types of formulas, even hypoallergenic ones, could significantly deteriorate the patient's condition. Meanwhile, his mother tried apple juice for him via nasogastric tube and realized that he could tolerate it without any symptoms.

Due to the lack of evidence for dietary substitutions, as well as the patient's age and his severe reactions to different types of hypoallergenic formulas, we made an individualized diet plan based on our own experience for the patient including brown rice milk and cooked grape juice with Quebec meat juice being added gradually to his diet. Surprisingly, gastrointestinal symptoms did not recur this time and his hypokalemia improved. He was discharged from the hospital at the age of 105 days weighing 2750 grams. Potato, cooked rice, broccoli, date, pumpkin, carrot, and sunflower seeds were gradually added to his diet. He is two years old now, while still on milk and dairy avoidance. However, he can tolerate egg, wheat, nuts, soy, and fish with a normal pattern of growth and development. Figure 1 illustrates the patient's conditions before and after the diagnosis and treatment, respectively.

Informed written consent was taken from both patients' caregivers.

Table 1. Lab data of the two patients presenting with Food protein-induced enterocolitis syndrome (FPIES) mimicking Bartter syndrome

Lab data (Normal Range)	Case 1	Case 2
WBC(6-17)x10^3/mL	8.2	7.6
Neutrophil (31%)	68.2%	62.6%
Lymphocyte (61%)	24.6%	31.3%
Hb (12)g/dL	11.1	10.4
ESR (0-10) mm/hr	28	29
CRP (<6) mg/dL	104	71
ABG PH (7.35-7.45)	7.53	7.29
PCO2 (32-48) mmHg	32.2	38
HCO3 (20-28) mEq/L	27.4	18.9
Serum CL (97-107) mmol/L	102	111
BUN (5-18) mg/dL	20	20
Cr (0.3-0.7) mg/dL	0.8	0,6
Na (130-145) mEq/L	127	129
K (4.1-5.3) mEq/L	2.2	1.8
Ca (8.8-10.8) mg/dL	11	7.9
P (4-6.5) mg/dL	2.6	3.7
Mg (1.6-2.4) mg/dL	2.6	4

WBC: White blood cell; Hb: Hemoglobin; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ABG: Arterial blood gas; PCO2: Partial pressure of carbon dioxide; HCO3: Bicarbonate; Cl: Chlorine; BUN: Blood urea nitrogen; Cr: Creatinine; Na: Natrium; K: Kalium; Ca: Calcium; P: Phosphorus; Mg: Magnesium.

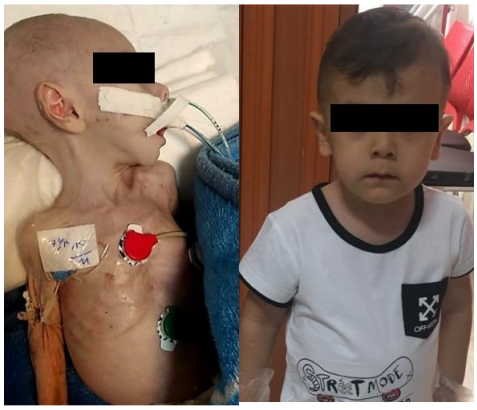

Figure 1. Patient number 2 before diagnosis and treatment at 3 months of age (left picture) and the same patient after diagnosis and treatment at two years of age (right picture).

DISCUSSION

Here we present 2 patients with severe, chronic, intermittent vomiting and diarrhea within 2 hours after feeding on early days of life leading to severe failure to thrive and protracted hypokalemia who were eventually diagnosed as FPIES.

FPIES is typically characterized by several confounding and sometimes fatal clinical manifestations and lack of laboratory diagnostic tools which make the diagnosis difficult and cause extensive unnecessary investigations. Therefore, misdiagnosis commonly occurs in these patients.[7,8] Our first patient in whom the diagnosis was deferred until 30 months of age is a good example of this misdiagnosis.

FPIES may present with acute or chronic phenotypes. Chronic FPIES commonly presents with chronic or intermittent vomiting, diarrhea, failure to thrive, anemia from chronic blood loss, hypoalbuminemia, dehydration, and shock, which were all detected in both of our patients. Thus, diagnosis of FPIES was considered in our patients based on the classic history and fulfilling criteria of the International Consensus Guideline of 2017.[6,9] Of note, oral food challenges (OFCs) may not be needed if the diagnosis is clear. OFCs become essential when any types of uncertainty exist such as inconclusive history, atypical timing of symptoms, or symptom persistence despite appropriate avoidance of the triggering foods.

FPIES is a clinical diagnosis based upon the exclusion of other causes. Therefore, several differential diagnoses should be ruled out before establishing the diagnosis. Increased TNF-α and decreased TGF-β may play role in inducing intestinal inflammation in FPIES which may lead to increased intestinal permeability and hypokalemia in these infants.[10] However, we explained metabolic alkalosis which is not a usual feature of FPIES by intractable vomiting in the second patient which in conjunction with hypokalemia and severe failure to thrive led to misdiagnosis of Bartter syndrome. As far as we know this is the first time that electrolyte disturbances were dominated in the clinical picture of the disease and Bartter syndrome had been erroneously proposed because of this condition.

Bartter syndrome is a renal tubular disorder caused by defective salt reabsorption at the thick ascending part of the loop of Henle, resulting in salt wasting, hypokalemia, and metabolic alkalosis. Most cases of Bartter syndrome are characterized by their early age of onset, failure to thrive, growth retardation, vomiting, and diarrhea. There is usually a history of maternal polyhydramnios and premature labor.[11] Hypercalciuria and nephrocalcinosis may also be seen in some of these patients.[12] This is why these two patients were first diagnosed with Bartter syndrome. Both of them had many manifestations in common with this syndrome, of which the most important were diarrhea, vomiting in both of the patients and failure to thrive, hypokalemia, and alkalosis in the first one.

Another laboratory finding which has been considered helpful in the diagnosis of the patients with FPIES is CRP which was increased in both of our patients.[13] Blood neutrophilia at the time of food challenge was seen in both patients. Tissue eosinophilia was detected in a tissue sample obtained

from colonoscopy in our first patient which was also indicative of FPIES. Breastfeeding is commonly thought to be protective for FPIES, However, both of the patients were breastfed at the onset of symptoms. Since food allergens may pass through breast milk, infants may become sensitized to various food allergens. There are also other reports of cases occurring in breast-fed infants.[2] In many infants with FPIES, extensively hydrolysate formula has reportedly been tolerated. However, this type of formula is not tolerated in 20% of the affected infants, and therefore, amino-acid-based formulas are recommended in these situations.[8,11]

We faced a serious diagnostic dilemma about the second patient. Having metabolic alkalosis, instead of acidosis which is often expected in patients with FPIES, was explained by his refractory vomiting leading to the excessive loss of hydrogen ions and also dehydration which occurred immediately after each feeding. To our great surprise, feeding the second patient with amino-acid based formula again led to the deterioration of the patient's condition and after making several trials to start different types of formulas, we realized that he could not tolerate any kinds of hypoallergenic formulas, even amino acid-based ones, which was in contrast with many previous reports. Shapiro et al. reported a similar case who initially experienced an increased frequency of guaiac-positive stools with mucus after introducing an amino-acid-based formula. So, they stopped feeding the child and reintroduced the same formula with slowly increasing doses over a two-week period, which was well tolerated then.[14] However, our patient could not tolerate even very small amounts of different types of extensively hydrolyzed and amino-acid based formulas (Elecare and Neocate), so that every time such an effort was associated with severe clinical deterioration due to diarrhea, vomiting, and dehydration which continued hours to days even after stopping the formula. Since two of these challenges induced near-fatal reactions in the baby, necessitating emergency intubation and cardiopulmonary resuscitation, resumption of feeding even with amino-acid-based formula seemed illogical and hazardous. We explained severe multiple food allergies in our second patient by relating it to multiple sensitizations resulting from his previous breastfeeding and also the severity of the condition, as in 32% of the patients with FPIES triggered by cow's milk or soy in a study, solid food FPIES developed later due to the severity of the condition.[7] Due to the patients' critical clinical conditions, the unfavorable clinical response to the amino acid-based formula, the possibility of a large number of foods contributing to the patient's food allergies, as well as the lack of published evidence-based experiences regarding food alternatives in severe delayed-type food allergies including FPIES, we planned a six-food elimination diet for the first patient, and a strict individualized diet for the second one, which led to the resolution of the clinical symptoms as well as hypokalemia in both patients and also significant weight gain in the second one.

These two cases present some unique features. First, although Powell criteria appear conspicuous and clear in the diagnosis of FPIES, patients may even experience near-fatal complications before the establishment of the correct diagnosis because of the similarities with other disorders. Hypokalemia was detected in both patients, but Bartter syndrome was considered as the underlying cause of this electrolyte disturbance, and therefore FPIES was ignored as the real cause. Second, both patients were breastfed at the onset of the symptoms, indicating an increasing prevalence of the disease in breastfed infants compared to the previous reports.[15] Third, although FPIES is a non-IgE-mediated food allergy that responds well to extensively hydrolyzed formula, these two patients did not show any favorable response to these formulas and even to aminoacid-based formulas in the second patient after several unsuccessful attempts.

To conclude, due to the probable fatal clinical course, and the similarity of symptoms to many other diagnoses including Bartter syndrome, primary care physicians should be more aware of FPIES and consider it in the differential diagnosis of any acute or sub-acute gastroenteritis with or without electrolyte abnormalities. Therefore, a high index of suspicion is required not only for the timely diagnosis of FPIES but also to avoid mortalities and possible morbidities including the financial and psychological burden on the family and health system.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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