

Case Study

FOOD ALLERGY PRESENTING AS A SURGICAL ABDOMEN IN A NEONATE

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INTRODUCTION

Food allergies, especially of the non IgE-mediated variety, can masquerade as a number of other conditions in the young child. The following case report illustrates how a neonate with cow's milk induced enteropathy was misdiagnosed initially as pyloric stenosis and subsequently as sepsis, leading to unnecessary diagnostic tests and surgery.

CASE STUDY

A six-week old baby presented with a history of severe, intractable vomiting, present intermittently since day two of life. The infant had not been breast fed, by choice, but was placed onto a cow's milk formula, which resulted in vomiting on the second day of life. A stomach wash out was performed and the condition settled. He was discharged on day three.

At home, he developed intractable vomiting and was taken back to the paediatrician where he was diagnosed with lactose intolerance and placed onto a lactose free formula, which resulted in a slight improvement of the vomiting. In his third week, the vomiting recurred and when the vomiting continued, a second opinion was sought at 6 weeks of age. On examination, he was pale, dehydrated and ill looking and was immediately admitted to hospital.

A workup for sepsis was performed but the blood test results were non-specific. The abdominal x-ray revealed some air fluid levels throughout the bowel. The classical x-ray features of upper abdominal obstruction were not demonstrated. A barium swallow was performed two days later and a diagnosis of pyloric stenosis was made. Subsequently a surgical opinion was sought and the baby was taken to theatre for repair of the pyloric stenosis. The baby was then discharged home on soya milk formula, which was better tolerated in comparison to the cow's milk based formula.

At a later date, two independent radiologists at differing centres, with no clinical history provided, reviewed the radiology studies and in both circumstances they were reported as normal.

The vomiting began again after a week of appearing well post discharge. The mother reported poor sleeping, incessant crying, arching of the back, frequent runny stools and cramping. A return to the paediatrician resulted in a diagnosis of colic and gastroesophageal reflux disease. The milk was then changed to an anti-reflux formula and a proton pump inhibitor was prescribed. Advice was given to provide regular small feeds.

This regime was adhered to for two weeks, but the baby continued to vomit and pass frequent stools. No weight gain was noted during this period. The child continued to deteriorate and presented to the third paediatrician in extremis. Clinical examination revealed a critically ill child that was pale, dehydrated, mottled and hypothermic. Additionally, there was evidence of failure to thrive with his weight being similar to his birth weight.

A preliminary diagnosis of sepsis was made and treated as such. The baby responded well to the fluid resuscitation. Initial haematological testing revealed a lymphopaenia with a thrombocytosis of $553\ 000/\text{mm}^3$. The C-reactive protein (CRP) was within normal limits. There was pre-renal picture of renal dysfunction, with an elevated creatinine of $74\ \mu\text{mol/l}$. His serum albumin was low at $30\ \text{g/dl}$. Cerebrospinal fluid (CSF) revealed 3 polymorphs/ μl . The urine dipstick revealed no abnormalities, stool microscopy demonstrated a few pus cells, but no organisms were isolated on microscopy or culture.

In view of the clinical presentation and his previous admissions into hospital, he was diagnosed as having nosocomial sepsis and treated with empiric antibiotics for three days. These were subsequently stopped when the blood and CSF cultures returned negative.

During this period he remained well until day four when his anti-reflux formula was reintroduced. Within four hours of feeding, intractable vomiting developed together with bloody diarrhoea. He was clinically shocked with signs of mottling, lethargy, and had cold peripheries with delayed capillary refill. Blood pressure was not recordable and following resuscitation he was transferred to the intensive care unit (ICU). Initial blood gas measurement

demonstrated a normal anion gap metabolic acidosis. The delta ratio suggested a hyperchloraemic metabolic acidosis (pH: 6.9; pCO₂: 15 mmHg; pO₂: 80 mmHg; HCO₃: 5.6 mmol/l; BE: minus 17 mmol/l; Na⁺: 143 mmol/l; K⁺: 3.5 mmol/l; Cl⁻: 119 mmol/l; Ca²⁺: 1.19 mmol/l) .

The differential diagnosis at this stage was:

- Inborn error of metabolism;
- Shock from gastrointestinal losses;
- Renal tubular acidosis;
- Lactic acidosis;
- Sepsis;
- Renal insufficiency.

Haematological testing included a metabolic screen, lactate, pyruvate, ammonia and organic acids as well as a screening for renal tubular acidosis. All these test results were ultimately found to be normal.

In the ICU, the baby remained on intravenous fluids with only NaHCO₃ replacement. On day seven, oral fluids sips were started and his formula was changed to an amino acid based formula, which was well tolerated with no further episodes of vomiting and diarrhoea.

By day twelve of hospitalisation, our little patient was on full feeds for his age, and he demonstrated an appropriate weight gain. A differential diagnosis of cow's milk protein enterocolitis, possibly of the food protein induced enterocolitis syndrome (FPIES) variety, was made pending the outcome of the metabolic screen. A food allergy screening ImmunoCAP RAST test (FX5) and Phadiotop test also performed at this time, were negative.

Prior to discharge, he was given an oral challenge of 10 mls anti-reflux formula and within twenty minutes it was vomited.

Consequently, all cow's milk protein was removed from his diet and the mother was advised to keep him on an amino acid formula until further review.

During this time the metabolic screen result returned as normal and the patient remained well, with appropriate growth, on the amino acid based formula.

At the four month follow up, the child was well and thriving, but waking up frequently to feed. The mother felt that the new formula was no longer satisfying him and it was decided to start him on a rice-based cereal.

Two hours after ingestion of the rice-based cereal, he was admitted to hospital with severe gastrointestinal symptoms and shock. Feeds were stopped and the mother was advised to continue the amino acid formula until age six months.

A definitive diagnosis of FPIES to multiple foods was made at this stage and the dietician was consulted to help with the weaning process.

At six months, he was weaned on to vegetables, which were well tolerated. Sweet potato was then added to his diet at seven months and he was once again admitted for diarrhoea and vomiting. Stool cultures were negative and sweet potato was removed from the diet.

Over the following month's oats, lentils, chicken and eggs were also identified as triggers of gastrointestinal symptoms and these were removed from his diet. At this point, he had not been exposed to any nuts or shellfish.

At twenty months he continues to grow well, and his milestones are appropriate for his age. He continues to see the dietician for nutritional support, and a food challenge is under consideration. The photographic sequence of this little



Four weeks of age



Seven weeks of age



Post-operative scar following surgery for pyloric stenosis

one's life is reflected below.

DISCUSSION

Food protein induced enterocolitis syndrome (FPIES) represents an interesting spectrum of non IgE-mediated food allergy disorders,¹ and can masquerade as a number of clinical entities.²

FPIES is a cell mediated, non IgE-mediated, gastrointestinal food hypersensitivity that is commonly caused by cow's milk protein or soy. It signifies the severe end in the spectrum of protein induced gastrointestinal disease in the neonatal period and infancy.^{3,4} There are, however, a number of other gastrointestinal disorders that can be attributed to food proteins allergy and the entire gastrointestinal tract can be affected.⁵⁻⁹

FPIES

Non IgE-mediated gastrointestinal food-induced allergic disorders include FPIES, food protein induced allergic proctocolitis (FPIAP), and food protein induced enteropathy (FPE). FPIES is currently the most actively studied non IgE-mediated gastrointestinal food allergic disorder.¹⁰ This disease was described in the 1940's by Rubin, who described intestinal bleeding in neonates fed on cow's milk.³ Similarly Grybowski¹¹ and Powell¹² described a condition in infants within the first six weeks of life, which presented with recurrent vomiting, bloody diarrhoea, and abdominal distension following ingestion of cow's milk. Feeding with cow's milk-based formula would cause recurrence of severe emesis within 1-3 hours, as well as elevation of the peripheral neutrophil count that would peak at six hours following food ingestion.¹¹⁻¹³

PATHOPHYSIOLOGY OF FPIES

The mechanisms through which FPIES develops are poorly defined. Although FPIES is predominantly considered to be a T-cell mediated disorder, there is little evidence



20 months old well child

to support this viewpoint. Equally, humoral responses in FPIES, are not understood.³ Symptoms have been produced with purified milk allergens that included casein, β -lactoglobulin (BLG), α -lactoglobulin (α -LG) and bovine serum albumin (BSA).^{14,15}

Symptoms resolve following a complete elimination diet. Unlike IgE-mediated cow's milk allergy, in which baked milk products are often tolerated, in FPIES denaturing the milk proteins with heat does not seem to abate symptoms. Moreover, the threshold to induce symptoms in patients with FPIES is in the gram range, but for IgE-mediated food hypersensitivity, the range is in milligrams.¹

FPIES may also be precipitated by foods, other than milk or soy, including fish, wheat, and eggs. Food allergens such as rice, oats, banana, sweet potato, green peas, beef and chicken may also trigger FPIES. Therefore, a wide variety of common foods have the potential to induce FPIES and the resolution of symptoms over time suggests that FPIES is an inappropriate adaptive immune response to foods.¹

Villous sampling suggests that villous atrophy, subsequent to milk exposure, is responsible for the malabsorption syndrome in the more "chronic" FPIES presentation. Avoidance of milk results in normalisation of the intestinal architecture, whereas reintroduction of milk leads to partial villous atrophy. Lymphocyte numbers increase in the epithelium, with a large number of them expressing T-cell intracytoplasmic antigen (TIA1), a marker of cytotoxic granules.^{16,17}

The humoral response in FPIES is poorly understood. FPIES is typically a non IgE-mediated food allergy, yet some patients have been found to have low levels of IgE against the precipitating food allergen. This is termed atypical FPIES. The presence of IgE to the triggering food by blood

or skin test is thought to be a marker for persistent FPIES.¹

CLINICAL PRESENTATION

In its acute form, FPIES can present with recurrent severe vomiting, typically 1-3 hours after ingestion of the offending food. Diarrhoea, lethargy, pallor and dehydration usually follow. In its extreme form (15-20% of cases), it may be associated with hypotension, hypothermia and abdominal distension.^{2,3}

The laboratory findings may mimic that of sepsis, with an elevated neutrophil count and thrombocytosis, but typically no increase in the CRP. Blood gas analysis may reveal a metabolic acidosis, which in combination with the clinical presentation, is often diagnosed as a metabolic disorder.^{2,3} Methaemoglobinaemia is present and may be caused by severe intestinal inflammation and reduced catalase activity resulting in increased nitrites.^{2,3}

In typical FPIES, there is a negative IgE test to the trigger foods.

Radiological assessment is rarely useful in making the diagnosis and may only assist if a surgical cause for the clinical presentation is being considered.³

Chronic FPIES can present with intermittent, chronic vomiting, watery diarrhoea (bloody, mucoid or both), lethargy, pallor, dehydration, abdominal distension, weight loss and failure to thrive.

ATYPICAL FPIES

A group of individuals with "Atypical FPIES" has been identified. These infants and children fulfil the clinical diagnostic criteria for FPIES, but develop positive specific IgEs to some trigger foods. The disorder is still considered to be essentially cell-mediated, but these individuals have a more prolonged course of FPIES. They also have

the capacity to develop anaphylaxis. A large number of individuals with FPIES also develop atopic diseases, like atopic dermatitis, atopic rhinitis and asthma.⁴

DIAGNOSIS

The diagnosis of FPIES is based upon the history and the typical repetitive clinical symptoms of FPIES after exposure to specific allergens. Complete resolution of symptoms occurs with withdrawal of the culprit food(s) and significant clinical deterioration with exposure to the same food. Laboratory and radiographic findings are not diagnostic of FPIES.

Oral food challenge (OFC) is the gold standard for diagnosis of FPIES. Infants generally do not require OFC testing, as the diagnosis can generally be made on history, together with symptom resolution following the removal of the culprit food from the diet. In circumstances where the history is unclear, a specific food trigger needs to be identified, or where the presentation of FPIES is atypical, or when development of tolerance is being investigated, a specifically designed, prolonged OFC should be performed under clinical supervision in a hospital setting.^{2,3}

CONCLUSION

The diagnosis of FPIES is often not considered in the neonatal period as the symptoms of diarrhoea, vomiting, abdominal distension, poor feeding, lethargy, apathy, and hypotension are non-specific and are usually attributed to a variety of other neonatal conditions such as sepsis or intestinal obstruction. In the absence of a definite diagnosis, the astute clinician should consider food allergy as a cause of such non-specific symptoms in the neonate and infant.

The parents of this baby have given permission to publish the photos without hiding the identity of the baby.

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