A formula-fed infant with profound dehydration, cerebral venous sinus thrombosis, and intracranial hemorrhage

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ABSTRACT

Background: *Chronic food protein–induced enterocolitis syndrome (FPIES) is a cell-mediated gastrointestinal food hypersensitivity described almost exclusively in infants fed cow's milk or soy formula. A timely diagnosis is challenging due to a number of factors, including broad differential diagnoses, absence of specific biomarkers, and delayed symptom onset.*

Objective: *This report aimed to highlight how the severity of presentation can further impede a timely diagnosis in chronic FPIES.*

Methods: *A case of presumed chronic FPIES to soy with previously unreported complications of intracranial hemorrhage and cerebral venous sinus thrombosis was described.*

Results: *We reported a case of a female infant fed a soy formula who presented during the third week of life with intermittent and progressive emesis, diarrhea, and lethargy, which culminated in severe dehydration, with early hospital course complications of seizures, intracranial hemorrhage, and cerebral venous sinus thrombosis. Although not recognized until weeks into the hospital course, many of the presenting symptoms and laboratory abnormalities were characteristic of chronic FPIES. An ultimate consideration of FPIES led to transition to amino acid–based formula and gradual resolution of gastrointestinal symptoms. Close outpatient follow-up was essential in facilitating subsequent age-appropriate solid food introduction.*

Conclusion: *The severity of presentation in FPIES can represent an additional barrier to a timely diagnosis. Early consideration of this entity in the differential diagnosis of patients with typical FPIES features, regardless of the additional presence of atypical and severe complications, may help with more timely recognition and intervention. In addition, there is an increased need for close follow-up as an outpatient in severe FPIES cases.*

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Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE, cell-mediated gastrointestinal food hypersensitivity, which typically manifests in infancy.[1,2] FPIES has an acute form, with profuse, repetitive emesis, and lethargy starting 1–4 hours after ingestion of the trigger food, and a chronic form characterized by intermittent and progressive emesis and watery diarrhea with frequent ingestion. The chronic form is described almost exclusively in infants ages < 4 months who are fed cow's milk (CM) or soy formula, although rare cases through breast milk are reported.[3] Here, we reported a case of presumed chronic FPIES, in which the severity of presentation hindered a timely diagnosis.

CLINICAL PRESENTATION

A female infant, the product of a full-term, healthy, surrogacy pregnancy, was initially thriving on soy formula. During the third week of life, she developed intermittent and worsening emesis, watery diarrhea, and lethargy. At presentation to the emergency department on day of life 20, she was severely dehydrated, with a 22% weight loss from birth. Laboratory abnormalities included anion gap metabolic acidosis, elevated lactate, hyperammonemia, neutrophilia, bandemia, thrombocytosis, elevated inflammatory markers, and transaminitis (Table 1). Findings on abdominal and head ultrasounds were within normal limits. Evaluations for infection (blood, urine, and cerebral spinal fluid (CSF) cultures; respiratory and stool pathogen polymerase chain reaction (PCR) panels) and inborn errors of metabolism (plasma amino acids, pyruvate, acylcarnitine profile, and urine organic acids) were initiated, and, ultimately, unrevealing. Fluid resuscitation and empiric antibiotics were started

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Table 1 **Abnormal laboratory findings on clinical presentation in a case of chronic FPIES***

Serum Study	Value	Age-Specific Reference Range
Absolute neutrophil count, $\times 10^3/\mu L$	33.2 (↑)	1.0–8.5
Bands, %	16 (↑)	0–6
Eosinophil count, $\times 10 \times 10^3/\mu L$	0; HD 2: 0.89 (↑); HD 33 (peak): 3.21 (↑); HD 40 : 0.45 (↑)	<0.3
Leukocyte count, $\times 10^3/\mu L$	58.2 (↑)	4.0–19.5
Platelet count, $\times 10^3/\mu L$	782 (↑)	150-150
C-reactive protein, mg/dL	2.6 (↑)	<1.0
Procalcitonin, ng/mL	13.16 (↑)	<0.08
Lactate (venous), mmol/L	5.3 (↑)	0.5–2.2
pH (venous)	6.99 (↓)	7.31–7.41
Bicarbonate, mEq/L	<10 (↓)	19–24
Albumin, g/dL	2.3; HD 2: 2.1 (↓)	2.2–4.8
Alanine aminotransferase, U/L	184 (↑)	13–45
Ammonia, μmol/L	156 (↑)	21–50

FPIES = Food protein–induced enterocolitis syndrome; ↑ = abnormally high; HD = hospital day; ↓ = abnormally low.
**Values are those from the emergency department presentation unless otherwise noted.*

and she was admitted to the pediatric intensive care unit. On hospital day (HD) 1, she developed new-onset seizures, which were treated with benzodiazepines. A computed tomography of the head revealed a large intraparenchymal hemorrhage, with early hydrocephalus and midline shift, which required emergent placement of an external ventricular drain. The clinical course was further complicated by sinus venous thrombosis identified on magnetic resonance imaging on HD 7; this was managed with hyperhydration and heparin infusion.

CLINICAL OUTCOME

With intravenous hydration and initiation of parenteral nutrition, she gradually improved. Due to emesis after restarting soy formula, the patient transitioned to a hypoallergenic, extensively hydrolyzed casein-based formula on HD 14. On HD 27, with continued intermittent emesis and abdominal distension, providers suspected chronic FPIES to soy and CM as the causes for both initial and ongoing gastrointestinal symptoms, respectively. Significant eosinophilia noted at this time was also attributed to chronic FPIES. The patient was transitioned to AAF on HD 27 with gradual resolution of gastrointestinal symptoms. She was discharged home at 12 weeks of life on AAF and with strict avoidance of soy and CM. After the hospital discharge, whole exome sequencing revealed a heterozygous likely pathogenic variant of the *FGA* gene (encoding fibrinogen α chain), also carried by her father who was asymptomatic.

At the follow up at 6 months of age, she was thriving on AAF. She had a moderate eczematous rash, but the examination was otherwise within normal limits. At this time, she had only tried one solid food, carrot, which resulted in emesis. After discussion with the family, skin-prick testing was done primarily as a way to guide the initial introduction of solid foods given the family's hesitation and fear of a new food allergic reaction to any new food in light of her medical history. Skin-prick testing showed sensitization to CM, peanut, and egg (Table 2). Serologic testing was deferred due to difficult vascular access. To facilitate the initial solid food introduction, she underwent a series of inpatient oral food challenge (OFC) to cauliflower, white potato, and corn, all of which were well tolerated. As of the most recent visit with us, at 8 months of age, she continued to eat these foods at home and was otherwise doing well, without any neurologic sequelae from the complications during her hospitalization.

DISCUSSION AND CONCLUSION

We described a case of presumed chronic FPIES with previously unreported complications of intracranial hemorrhage and sinus venous thrombosis. Although not recognized until weeks into the hospital course, many of her presenting symptoms and laboratory abnormalities were characteristic of chronic FPIES. Profound dehydration, lethargy, hypotension, hypoalbuminemia, neutrophilia, thrombocytosis, elevated lactate, and metabolic acidosis are well described consequences of chronic FPIES.[2,4] Although less common, elevated C-reactive protein and hypereosinophilia were also reported.[5,6]

For our patient, the diagnosis of FPIES was not considered until 1 month into the hospital admission. The severity of presentation with previously unreported complications contributed to the delayed diagnosis. The diagnosis of chronic FPIES is based on a typical clinical presentation, with symptom improvement within several days of trigger food withdrawal. Our patient's diagnosis remains presumptive without confirmatory OFC.[1] Patients with FPIES frequently have protracted symptoms and an extensive workup before a diagnosis is

Table 2 **Skin-prick testing results at the outpatient follow-up in a case of chronic FPIES**

	Wheal/flare, mm
Saline solution	0/0
Histamine	**7/17**
Soy	0/0
Egg white	**4/17**
Milk	**4/13**
Peanut	**3/0**
Cauliflower	0/0
Potato	0/0
Corn	0/0
Broccoli	0/0
Carrot	0/0
Spinach	0/0
Apple	0/0
Pear	0/0
Almond	0/0
Coconut	0/0
Fresh quinoa	0/0

FPIES = Food protein–induced enterocolitis syndrome.

reached.[2,7,8] A timely diagnosis is challenging due to broad differential diagnoses, absence of specific biomarkers, and delayed symptom onset.[1,2,7,8]

On discharge, our patient continued avoidance of soy and CM. Co-reactivity to soy and CM is reported among 30–40% of cases in the United States, and is more common among infants who present within the first month of life.[8] Although most infants with CM-FPIES tolerate extensively hydrolyzed formula (eHF), 10–20% require AAF.[8] Infants with CM or soy-FPIES have a higher risk for FPIES to solids and benefit from guidance in solid food introductions.[1] Furthermore, recently, it was shown that children with FPIES to CM in particular are at risk for poor weight gain.[9] In our patient, the ability to offer OFC helped to prevent a delay in age-appropriate food introduction.

The patient's complications of intracranial hemorrhage and sinus venous thrombosis are atypical for FPIES, and we suspected that the heterozygous likely pathogenic variant of the *FGA* gene, encoding fibrinogen A, may have predisposed her to these complications. Deficient quantity or function of fibrinogen A, which contributes to appropriate clotting, may be asymptomatic or may manifest in hemorrhages that vary from mild to life threatening.[10] Her father who is asymptomatic carries the same variant, and incomplete penetrance in some autosomal dominant *FGA* mutations may be at least partially responsible for differential expression in the parent and the child.[10] In this case, we suspect that severe dehydration from chronic FPIES, which led to electrolyte imbalances, cerebral edema, and damage to nearby blood vessels, in combination with an underlying inability to mount a normal clotting response, may ultimately be responsible for this unusual presentation.

The plan of care is to work with the family to continue new food introductions, including, ideally, home introduction of those with negative skin-prick testing, and, potentially, OFC to peanut and egg, pending further discussion with the family. The sensitization to CM highlights the interesting possibility of atypical CM-FPIES, although it may represent clinically insignificant IgE sensitization in the setting of her moderate eczema. Regardless, we recommend continued avoidance until after 2 years of age, at which point, we plan to perform OFC to soy and CM under close supervision and with secure intravenous access.

In summary, we presented a rare case of severe chronic FPIES due to soy, with previously unreported complications of intracranial hemorrhage and sinus venous thrombosis for whom FPIES was not considered until 1 month into admission. Although an underlying clotting disorder likely predisposed this patient to these atypical complications, and FPIES should not be the top differential diagnosis in such presentations, the profound dehydration in this case serves as a reminder of the potential severity of presentation in FPIES, which can represent a barrier to a timely diagnosis and an increased need for close follow-up as an outpatient.

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