

Systemic reaction to an extensively hydrolyzed formula in an infant with cow's milk anaphylaxis

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ABSTRACT

Background: Cow's milk allergy is the most common cause of food allergy in young children. Ingestion of milk products in children with a milk protein allergy can lead to anaphylaxis and must be avoided. Some guidelines suggest the use of an extensively hydrolyzed formula (EHF) in these cases; however, rare allergic reactions can still occur. Here, we presented a 3-month-old boy who developed anaphylaxis to a cow's milk formula. Subsequently, he developed a rare systemic reaction to soy and to an EHF.

Case: The patient had an unremarkable medical history and presented with signs and symptoms consistent with anaphylaxis after being fed cow's milk formula for the first time. Symptoms included immediate vomiting, wheezing, stridor, angioedema of eyelids and lips. Although intramuscular epinephrine was given, the patient continued to clinically deteriorate, becoming more lethargic and necessitating admission to the pediatric intensive care unit. Subsequently, a trial of soy formula ingestion reproduced the symptoms and an EHF was given. However, immediately after taking an EHF, he developed facial angioedema and diffuse urticarial lesions.

Conclusion: In most patients with a cow's milk allergy, an extensively based formula can be tolerated safely due to a hydrolyzed protein chain. However, medical providers must be vigilant when switching formula because a rare systemic allergic reaction to EHF can still occur.

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Cow's milk protein allergy (CMPA) is the most common cause of food allergy in young children.¹ The estimated prevalence of cow's milk allergies ranges from ~2% to 3% in the first year of life and in ~60% of those with immunoglobulin E (IgE) mediated reactions.^{2,3} Most children will outgrow this allergy after the first years of childhood, but it is estimated that 15% of children will carry this sensitivity into the second decade of life and that 35% of these children will have allergic reactions to other foods.³ Children with a systemic reaction to cow's milk should be given a hypoallergenic formula, such as an extensively hydrolyzed formula (EHF) or amino acid formula (AAF). By

definition, they must be tolerated by 90% of children with CMPA, with a 95% confidence interval.⁴ These hypoallergenic formulas are either partially hydrolyzed, extensively hydrolyzed (short peptides < 1500 Da), or given as an amino acid-based formula.

The pathophysiologic mechanisms of CMPA include IgE-mediated, mixed-IgE-non IgE, and non-IgE-mediated reactions. IgE-mediated milk reactions are known to be the third most common cause of food-induced anaphylaxis.⁵ The related mortality from anaphylaxis in children is ~1% and accounts for 0.2% of all pediatric intensive care admissions in the United States.⁵ IgE reactions are characterized by acute onset, usually minutes to hours after the exposure of an allergen, with various presentations. Common symptoms include skin and/or mucosal (urticarial rash, angioedema, flushing), respiratory symptoms (*i.e.*, wheezing, shortness of breath, stridor), abdominal symptoms (*i.e.*, nausea, vomiting, abdominal pain), and cardiovascular instability (*i.e.*, low blood pressure, tachycardia).⁶ In children with a severe IgE-mediated reaction to cow's milk, a trial of an EHF is sometimes considered. In rare cases in which they develop an allergic reaction to an EHF, an Amino acid (AA) formula is then given. Although the intolerance rates of EHF in children with Cow's Milk Allergy (CMA) can be ~10%, an immediate systemic reaction is rare.⁷

CASE REPORT

Our patient was a 3-month old, full-term boy with an unremarkable medical history. He presented with

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anaphylaxis after being fed cow's milk formula for the first time. He was exclusively breast-fed since birth, but an initial trial of regular cow's milk formula led to a severe allergic reaction. Thirty minutes after being fed regular formula for the first time, the patient had one episode of vomiting, followed by wheezing, stridor, and bilateral eyelid and lip swelling. The emergency medical service was called, and he was treated with intramuscular epinephrine on route to the emergency department. In the emergency department, vital signs were stable (blood pressure, 83/63 mm Hg; heart rate, 153 beats/minute; respiratory rate, 48 breaths/minute; and oxygen saturation, 100%). Results of his physical examination were remarkable for diffuse urticarial rash and bilateral eyelid swelling. Subsequently, he was treated with oral prednisolone, diphenhydramine, and ranitidine, and was given a normal saline solution bolus.

After a period of observation, the patient was noted to still be lethargic and diaphoretic, and was admitted to the pediatric intensive care unit for anaphylaxis monitoring. Results of laboratory evaluations were as follows: total IgE value, 23 kU/L; IgE level to cow's milk, 1.64 kU/L; soybean IgE level < 0.1 kU/L; α -lactalbumin, 1.73 kU/L; β -lactoglobulin level, 3.73 kU/L; and casein level, 2.58 kU/L. An oral challenge with soy milk was attempted, but the patient developed acute right eyelid edema and urticarial rash. He was then trialed on an EHF but, unfortunately, developed immediate angioedema and urticaria. His condition was suggestive of a type 1 hypersensitivity phenomena, which required further management in the intensive care unit. Eventually, an amino acid-based formula was given and was well tolerated, without any further reactions. He was discharged with an epinephrine autoinjector and amino acid-based formula, and was followed up as an outpatient by the allergy team.

Our patient presented with signs and symptoms consistent with anaphylaxis, and was appropriately treated with intramuscular epinephrine, which is the single most effective treatment for anaphylaxis.⁶ Oral steroids and antihistamines were given as adjuvant therapy in the management of the anaphylactic symptoms.⁶ Although food protein-induced enterocolitis syndrome can present in a similar manner to anaphylaxis, our patient had an immediate reaction (<2 hours of exposure) and had IgE to milk protein confirmed on laboratory work.

The criterion standard for the diagnosis of IgE-mediated food allergies is a placebo-blinded oral challenge. However, this can be time consuming, costly, and even dangerous because a potentially known allergen is being administered. When the presentation is consistent with a severe allergic reaction or anaphylaxis, the diagnosis can be confirmed with a positive IgE test result in the blood or a skin-prick test.⁸ In our case, the

etiology was confirmed *via* an IgE test to milk and its components. However, an oral trial with soy and an EHF proved unsuccessful.

DISCUSSION

The most common allergens in milk protein involved in IgE-mediated reactions include the caseins (α s1-, α s2-, β - and κ -caseins) and the whey proteins (α -lactalbumin and β -lactoglobulin), which constitute 80% and 20% of reactions, respectively. Other minor allergens include albumin, lactoferrin, and immunoglobulins. The major allergens involved in soy allergy are β -conglycinin and glycinin, and they account for ~30% and 40% of the total seed proteins, respectively.² The German Multi-Center Allergy Study⁹ revealed that IgE sensitization to soy in infancy occurs primarily *via* ingestion and is relatively uncommon. The best next step in the management of any IgE-mediated allergy, including CMA, is avoidance of the allergen that causes the reaction.⁸ However, children need special nutrient and caloric requirements to grow and develop adequately. Elimination diets represent risks for malnutrition and nutritional deficiencies in children, which can result in irreversible and profound effects in developing children.⁸

The American Academy of Pediatrics (AAP) currently recommends exclusive breast-feeding for ~6 months, with continuation of breast-feeding for ≥ 1 year, as mutually desired by mother and infant.¹⁰ Although breast-feeding has been shown to be a protective factor against development of atopic conditions, such as atopic dermatitis and recurrent early wheezing in infancy, many barriers still remain.^{10,11} In 2018, the U.S. Centers for Disease Control and Prevention report¹² on breast-feeding showed that 60.6% of mothers were breast-feeding by 6 months and only 34.1% at 12 months, and exclusive breast-feeding was reported among only 25.5% of mothers by 6 months. In our case, the mother's decision to start formula supplementation was driven by the need to start working, which is a common reason in today's society.

The AAP¹⁴ generally recommends cow's milk formula supplementation when breast-feeding is not possible and soy as an option in full-term infants. Some indications of when a soy formula is preferred over a cow's milk formula includes galactosemia, hereditary lactase deficiency, and preference for a vegetarian diet.¹³ The decision to trial soy for our patient was based on a negative specific IgE result and, although most evidence indicates that there is only a cross-reactivity of 8-15% between cow's milk and soy protein, the risk for anaphylaxis or severe allergic reactions is low.¹⁴ The European Society for Pediatric Gastroenterology, Hepatology and Nutrition indicates that soy could be used in IgE-mediated reactions after 6 months of age.¹⁵ Despite the low likelihood of IgE-mediated reactions, our patient

Table 1 Summary of cases of systemic allergic reactions to EHF in patients with CMA

Study, Year	Type of Study	Patient Characteristic	Systemic Reaction
Horino <i>et al.</i> , ²⁴ 2020	Case report: reaction to casein based EHF	1 Patient: IgE-mediated CMPA	Anaphylaxis
Chauveau <i>et al.</i> , ¹⁶ 2016	Case reports: reaction to whey protein EHF Pepti Junior (Picot, Torcé, France)	2 Patients; confirmed IgE-mediated CMPA	1 with generalized urticaria; 1 with anaphylaxis
Antunes <i>et al.</i> , ²⁵ 2009	Case reports	6 Patients; confirmed IgE-mediated CMPA	1 urticaria alone; 1 with urticaria and angioedema alone; 4 with anaphylaxis
Sotto <i>et al.</i> , ²⁶ 1999	Case reports: reaction to EHF 1985–1998	4 Patients: confirmed IgE-mediated CMPA and skin-prick test	4 with anaphylaxis
Sampson <i>et al.</i> , ²⁷ 1992	Prospective randomized double-blind, placebo controlled food challenges to cow’s milk, EHF, and AAF	1 Patient; confirmed IgE-mediated CMPA	Skin rash, respiratory symptoms, and vomiting
Businco <i>et al.</i> , ²⁸ 1989	Case reports: reaction to whey EHF (Alfa-Ré, Nestlé (a lactose free extensively hydrolysed formula for GI impaired infants and young children with CMPA and/or food intolerance))	3 Patients: confirmed IgE and skin-prick test to CMPA	1 with asthma and urticaria; 1 with angioedema and urticaria; 1 with angioedema and asthma

EHF = Extensively hydrolyzed formula; CMA = cow’s milk allergy; IgE = immunoglobulin E; CMPA = cow’s milk protein allergy (CMPA); AAF = amino acid formula.

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developed an immediate systemic reaction with soy formula challenge.

EHF has been found to be a safe option in cow’s milk allergy. The AAP¹⁴ recommends EHF in children in the setting of cow’s milk allergy.¹³ Although EHF has been deemed safe in large studies, up to 2–18% of children will develop an allergic reaction to extensively hydrolyzed formula (EHF); still, only a few cases of systemic IgE-mediated reactions have been reported.^{16–18} As per Chauveau *et al.*,¹⁶ immediate hypersensitivity to residual cow’s milk protein in eHF has been nonexistent for the past 20 years. Historically, it has been known to exist, and limited cases have been documented in the literature (Table 1).

After our patient developed a systemic reaction to an EHF, we decided to try an AAF. This has been recommended by the World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA) Guidelines,¹⁹ British Society for Allergy and Clinical Immunology (BSACI) guidelines,²⁰ and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPHGAN) guidelines²¹ as a

possible first-line formula in patients with severe allergic reactions to milk or an inability to tolerate EHF. A physician-supervised challenge to EHF has also been recommended as an alternative to an AA formula in the setting of a severe allergic reaction to milk.¹⁸ To date, there are no current guidelines in the United States that address the use of amino acid (AA)-based formulas, and the cost and palatability of these formulas are still factors to consider in our patients.¹⁸ Our patient tolerated an AA formula without further reactions and was discharged home with an epinephrine autoinjector, with the recommendation to continue feeding breast milk and to use the AA formula for supplementation.

Our patient’s mother limited ingestion of milk products due to a history of lactose intolerance. She was encouraged to limit milk product ingestion due to a risk of a possible severe reaction during breast-feeding.¹⁵ Contrary to what was previously known, there is evidence that the early introduction of highly allergenic foods such as peanuts (Learning Early About Peanut Allergy (LEAP) study) allows tolerance and

decreases the risk of allergic reaction in infants.²² It is interesting to note, that because our patient's mother had avoided all milk products during her pregnancy, it is reasonable to theorize that our patient never developed a tolerance to milk products due to a lack of exposure. However, this will need to be further evaluated in future studies. Some studies have already found that regular exposure to cow's milk starting in the first month of life might prevent IgE-mediated CMA but larger prospective studies are also needed to yield larger-scale recommendations.²³

Breast-feeding is still the best source of nutrition for the infant, and continued efforts are needed to ensure and support this practice. In patients with CMA, the available guidelines need further recommendations addressing systemic IgE-mediated reactions in infants. Soy milk in children with CMA, even in the setting of IgE-mediated reactions, needs to be used with caution due to cross-reactivity concerns. Furthermore, EHF's are not devoid of adverse reactions and special attention should be undertaken for children with systemic allergic reactions to cow's milk. We concluded that the use of an AAF should be considered in a patient at high risk when breast milk is not available.

CONCLUSION

We are in the age of precision medicine in which the diagnosis, treatment, and management of patients with food allergy should be individualized. Board-certified allergists are in a unique position to appropriately care for these patients by using their expertise. Diagnostic tools, such as skin testing and oral food challenges, should be done by specialists when feasible. Furthermore, allergy specialists are increasing their usage of current technology, such as telemedicine, mobile health (mHealth), and remote patient monitoring to appropriately care for these patients.

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