

Soybean Allergy in Cow Milk-Tolerant Infants

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ABSTRACT

Seven infants aged 2 to 6 months presented with vomiting, diarrhea, apathy, and shocklike state up to 2 hours after ingesting 100 to 200 mL of soy-based formula. The reasons for the administration of soy-based formula were atopic family history, atopic dermatitis, constipation, acute gastroenteritis, and Jewish dietary (Kashrut) laws; in only one patient was soy-based formula given because of cow milk allergy. Three of the patients had a similar reaction on repeated inadvertent exposure to soy-based formula. Five infants tolerated humanized milk formula without any adverse events. In one infant an allergic reaction to humanized milk formula (generalized urticaria and vomiting) developed at age 8 months, up to which time he had been exclusively breast fed. Only one infant had a positive skin test to soybean. The two cow milk-allergic infants had a positive skin test to cow milk. Five infants underwent oral soybean challenges at age 12 to 24 months, all of which were negative. We conclude that soybean allergy may appear in cow milk-tolerant infants in the first months of life. These infants, including the two infants with IgE-mediated cow milk allergy, presented with gastrointestinal symptoms only, which is compatible with food-induced enterocolitis. (*Pediatr Asthma Allergy Immunol* 1998;12[4]:253–258.)

INTRODUCTION

SOY PROTEIN FORMULAS are used in infants for various conditions, such as cow milk allergy, disaccharidases deficiency, and gastroenteritis.^(1,2) Their possible administration to prevent the development of atopy is controversial.^(3–7) Adverse reactions to soy-based formulas may include enterocolitis and chronic enteropathy, which can occur in young infants with and without cow milk allergy or intolerance.^(8,9) Immediate hypersensitivity and anaphylaxis after soy protein ingestion are uncommon: most of these patients are cow milk-allergic infants with positive skin prick tests to soybean and mainly cutaneous symptoms.^(10–16)

We describe seven infants with allergic reaction to soy-based formula. The clinical pattern of the gastrointestinal symptoms, without involvement of other organs, and the absence of concurrent cow milk allergy in five of the seven patients are emphasized.

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PATIENTS AND METHODS

Seven infants were referred to the Allergy Clinic of Schneider Children's Medical Center of Israel for evaluation of food allergy, especially soybean. The patients were referred by the inpatient department to which they had been admitted for one or more episodes of vomiting, diarrhea, and shocklike state following ingestion of soy-based formula. Each patient underwent a complete clinical and nutritional history, including the details of the acute episode leading to hospitalization and the work-up done at the inpatient department, physical examination, and immediate hypersensitivity skin prick tests to common food allergens with saline and histamine as negative and positive controls, respectively (Center Laboratories, Port Washington, NY). The skin test was considered positive if the mean wheal diameter was 3 mm or greater than the negative control. Patients who continued to be followed at the Allergy Clinic underwent open oral soybean challenge, as described previously,⁽¹⁷⁾ after at least 9 months of soybean elimination from their diet.

RESULTS

The patient characteristics and the reasons for soy-based formula administration are summarized in Table 1. The patients were all healthy infants in their first months of life. Six had been breast fed for 3 to 8 months, and five had a history of exposure to small amounts of soy-based formula prior to the time of the reaction (data not shown).

Three patients (Nos. 1,6,7) had atopic dermatitis, and two of them (Nos. 6 and 7) had other food allergies (sesame and peanut). Patient 6 showed an immediate reaction to soy-based formula, which was first given to him at the age of 2.5 months because of atopic dermatitis. He continued to be breast fed with supplementation by casein hydrolysate formula. At the age of 8 months he was given humanized milk formula, which was followed by immediate urticaria angioedema and vomiting, indicative of IgE-mediated cow milk allergy. Only in patient 7 was cow milk allergy (a perioral rash following humanized milk formula ingestion) the indication for soy-based formula administration. Patient 1 tolerated humanized milk formula without any adverse events, as did the remaining, nonatopic infants (Nos. 2–5). The reasons for soy-based formula administration in these patients were acute gastroenteritis, atopic family history, constipation, and Kashrut laws; soy-based formula was preferred because the family adhered to Jewish dietary (Kashrut) laws, which prohibit the mixing of dairy foods with meat. Three infants who were inadvertently exposed to soy-based formula 1 to 4 months after the first exposure exhibited the same clinical reaction.

TABLE 1. CHARACTERISTICS OF INFANTS WITH ALLERGIC REACTION TO SOY-BASED FORMULA

<i>Patient</i>	<i>Sex</i>	<i>Age at presentation (months)</i>	<i>Atopic features</i>	<i>Cow milk allergy</i>	<i>Reasons for soy-based formula administration</i>
1	F	5	Atopic dermatitis	No	Acute gastroenteritis
2	F	5	None	No	Atopic family history
3	M	3, 4*	None	No	Kashrut laws Accidental reexposure*
4	M	2, 5*	None	No	Constipation Accidental reexposure*
5	M	2,6*	None	No	Kashrut laws Accidental reexposure*
6	M	2½	Atopic dermatitis Sesame allergy	Yes [†]	Atopic dermatitis
7	F	3	Atopic dermatitis Peanut allergy	Yes [‡]	Cow milk allergy

*Second episode

[†]Diagnosed at age 8 months; urticaria and vomiting.

[‡]Perioral rash.

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TABLE 2. CLINICAL PRESENTATION OF INFANTS WITH ALLERGIC REACTION TO SOY-BASED FORMULA

<i>Patient</i>	<i>Time after ingestion (hrs)</i>	<i>Vomiting</i>	<i>Diarrhea</i>	<i>Apathy</i>	<i>Cyanosis/pallor</i>
1	1	+	+	+	—
2	2	+	—	+	+
3	1	+	+	+	—
4	2	+	+	+	—
5	1	+	+	+	+
6	1 1/2	+	+	+	+
7	1	+	+	—	—

*Bloody.

The clinical presentation of the patients is described in Table 2. In all cases, symptoms developed up to 2 hours after the ingestion of 100 to 200 mL of soy-based formula (of the three kinds available in Israel). All patients had recurrent vomiting, six had diarrhea (bloody in two), and six had changes in consciousness (described as apathy) of whom three also had pallor and acrocyanosis indicating poor peripheral perfusion. All patients were admitted for intravenous fluid replacement, and four of them (Nos. 3–6) also underwent sepsis work-up because of their young age. Results of the work-up were negative (data not shown).

The allergic evaluation of the patients is presented in Table 3. The two cow milk-allergic infants (Nos. 6 and 7) had positive skin prick tests to cow milk. Only one infant (No. 1) had positive prick skin test to soybean. Five patients underwent open oral soybean challenges after 9 to 18 months of elimination of soybean from their diet. All challenges were negative, and no adverse events were reported after their consumption of soy-based formula or foods containing soybean at home.

DISCUSSION

Dietary proteins can cause severe type I, or IgE-mediated allergic reactions.^(8,18) In such cases, gastrointestinal involvement can appear as IgE-mediated reaction, often accompanying other systemic manifestations of immediate food hypersensitivity. Other clinical presentations of food allergy are enterocolitis and chronic enteropathy with malabsorption.⁽⁸⁾ The clinical pattern of the reaction to soy-bean formula of the seven infants described here is compatible with food-induced enterocolitis: protracted vomiting, diarrhea (bloody in two infants), and changes in consciousness with poor peripheral perfusion within 2 hours' exposure, without cutaneous or respiratory symptoms. All the patients required hospitalization for intravenous fluid replacement, and four also underwent sepsis work-up. Three infants had atopic dermatitis (two

TABLE 3. EVALUATION OF INFANTS WITH ALLERGIC REACTION TO SOY-BASED FORMULA

<i>Patient</i>	<i>Skin tests</i>		<i>Oral soybean challenge</i>	
	<i>Cow milk</i>	<i>Soybean</i>	<i>Result</i>	<i>Age (mos)</i>
1	Neg	Pos	Neg	19
2	Neg	Neg	Neg	15
3	Neg	Neg	Not done	
4	Neg	Neg	Not done	
5	Neg	Neg	Neg	24
6	Pos	Neg	Neg	20
7	Pos	Neg	Neg	12

of whom had other IgE-mediated food allergies to sesame and peanut), but only one patient had a positive skin prick test to soybean, indicating the presence of specific IgE antibodies against soybean; nevertheless, her clinical reaction did not differ from that of the other six infants.

Immediate hypersensitivity reaction and anaphylaxis caused by soybean ingestion have been reported in the literature.⁽¹⁰⁻¹⁶⁾ Most patients were children with atopic dermatitis and evidence of the presence of specific IgE antibodies against soybean; symptoms were mainly cutaneous. Unfortunately, no well-validated animal model is available for the study of food allergy, although one study recently demonstrated that rats bred and raised on a soy protein-free diet for one generation exhibit a continuous expression of antisoy protein antibodies.⁽¹⁹⁾

Food-induced enterocolitis has been described in small infants after milk ingestion and also after soybean ingestion.^(8,9) These patients have negative skin prick tests and negative *in vitro* tests for specific IgE antibodies against milk and/or soybean. The pathophysiology of food-induced enterocolitis is not clear, although it is considered to be immune mediated.⁽²⁰⁾ Previous investigations suggest a localized IgE-mediated mechanism and histamine release,^(21,22) or a localized release of eosinophilic cationic protein.⁽²³⁾ Recently, Heyman et al.⁽²⁴⁾ reported that peripheral blood mononuclear cells (PBMC) from infants with cow milk allergy with only gastrointestinal symptoms secreted much greater amounts of tumor necrosis factor α (TNF- α) after stimulation *in vitro* with cow milk proteins than PBMC from nonallergic or cured infants. A high level of TNF- α secretion directly altered the intestinal epithelium barrier capacity.⁽²⁴⁾

In contrast to IgE-mediated food hypersensitivity, which can persist for years,⁽²⁵⁾ food-induced enterocolitis is usually limited to the first months of life. This was true also for our patients: five had negative oral soybean challenges at ages 12 to 24 months and were able to continue consuming soybean at home without any adverse events.

It is noteworthy that IgE-mediated cow milk allergy was the indication for the administration of soy-based formula in only one patient (No. 7). Another patient (No. 6) was diagnosed as having IgE-mediated cow milk allergy at the age of 8 months (i.e., 5.5 months after the episode of soy-induced enterocolitis). Concomitant IgE-mediated soybean allergy has recently been reported in 14% of children with cow milk allergy.⁽²⁶⁾ Whittington and Gibson⁽²⁷⁾ described four patients with soy protein intolerance who also had cow milk intolerance.⁽²⁷⁾ By contrast, five of our seven infants tolerated humanized milk formula without any adverse effects. The two cow milk-allergic infants had IgE-mediated reaction to cow milk-based formula with cutaneous symptoms, as did the two patients with sesame and peanut allergy. Thus, the clinical pattern of enterocolitis was unique to soybean, and it was reproduced in three patients after their inadvertent repeated exposure to soy-based formula.

Other indications for soy-based formula administration in our patients were acute gastroenteritis, atopic dermatitis, constipation, and atopic family history. In two cases, soy-based formula was given because of the families' adherence to the Kashrut laws which forbid the mixing of dairy and meat products (at the same meal). Many orthodox Jewish parents prefer to feed their children the nondairy, non-meat-containing (*parve*) soy-based formula to avoid accidentally disobeying this structure. This characteristic is apparently unique to our patient population and explains the three episodes of inadvertent exposure to soy-based formula.

Soy-based formula is used in children with gastroenteritis.⁽²⁾ Constipation is not considered an indication, although pediatricians sometimes tend to switch from humanized milk to soy-based formula to ease parental concerns. The use of soy-based formula to prevent atopy is controversial. Some studies have shown that soy formula given for the first 6 months of life significantly reduces the prevalence of atopic disease in high-risk infants,⁽³⁻⁵⁾ but others have failed to show any preventive effect with regard to either their onset or prevalence.^(6,7)

In summary, soybean allergy may appear in cow milk-tolerant infants and it presents as enterocolitis. The underlying immune mechanism may be mediated by locally appearing IgE antibodies or by non-IgE-mediated reaction, involving secretion of cytokines that affect gastrointestinal function.

Pediatricians should be aware of the clinical entity of soybean allergy, which is sometimes sufficiently severe to necessitate hospitalization for intravenous fluid replacement and sepsis work-up.

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