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Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome

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ABSTRACT

Objectives: To determine tolerance rates to cow's milk and soy and to suggest guidelines for follow-up oral food challenges (FU-OFCs) in infantile food protein-induced enterocolitis syndrome (FPIES).

Methods: The authors analysed the data of 23 patients with infantile FPIES who underwent two or more FU-OFCs and were followed up until over 2 years of age. The first FU-OFCs were performed at 6 months of age, and patients were randomly allocated to cow's milk (n = 11) or soy (n = 12) challenge starting groups. Second and third FU-OFCs were performed at 2-month intervals in a crossed and switched-over manner.

Results: Tolerance rates to cow's milk and soy were 27.3% and 75.0% at 6 months of age, 41.7% and 90.9% at 8 months and 63.6% and 91.7% at 10 months, respectively. Patients outgrew cow's milk and soy intolerance at age 20 and 14 months.

Conclusions: In infantile FPIES, the first FU-OFC should be performed with soy at 6–8 months of age and cow's milk FU-OFC should be conducted at over 12 months of age. Infants with FPIES were observed to outgrow food sensitivities during the first 2 years of life.

Food allergies are most prevalent in the first 2 years of life, affecting 6–8% of infants.¹ These allergies can be either IgE mediated or non-IgE mediated. Non-IgE mediated food allergies include food protein-induced enterocolitis syndrome (FPIES), coeliac disease, food-induced proctocolitis, food-induced enteropathy, and allergic eosinophilic gastroenteritis in a subset of patients.² FPIES is a very rare and infrequently described disorder.³

Infantile FPIES manifests as profuse vomiting and/or diarrhoea in neonates or young infants before 2 months of age, and is most commonly caused by cow's milk and/or soy protein.^{4–5} FPIES is typically negative in traditional food specific IgE tests.^{2–6–7} Although atopy patch testing is under careful study in the diagnostic evaluation of FPIES,⁸ oral food challenge (OFC) remains the diagnostic standard in this disorder.⁹ An initial positive OFC is needed to confirm a diagnosis of FPIES and a follow-up oral food challenge (FU-OFC) is necessary to evaluate food tolerance in patients previously diagnosed with FPIES.

However, it has not been clearly determined when the first FU-OFC should be performed in infantile FPIES, with which food protein (eg, cow's milk or soy) or how much protein should be administered. Clinical circumstances may increase parental anxieties due to the possibility of adverse reactions, the delayed introduction of a weaning diet, the high costs of special formula, and the expected social isolation due to the requirements of

What is already known on this topic

- ▶ It has not been determined when the first follow-up oral food challenge (FU-OFC) should be performed in infantile food protein-induced enterocolitis syndrome (FPIES).
- ▶ It has not been determined whether cow's milk or soy protein or how much should be administered in the first FU-OFC in infantile FPIES.
- ▶ It has not been clearly determined when patients with infantile FPIES outgrow their food sensitivities.

What this study adds

- ▶ Infants with food protein-induced enterocolitis syndrome (FPIES) lose intolerance more readily to soy than to cow's milk. Patients with infantile FPIES outgrow food sensitivities during the first 2 years of life.
- ▶ We suggest that first follow-up oral food challenge (FU-OFC) should be performed with soy at 6–8 months of age under careful medical supervision.
- ▶ We suggest that that cow's milk FU-OFC should be conducted when the child is more than 12 months of age.

special diets. In addition, reactions to accidental exposure to food proteins may occur.⁹ Moreover, OFCs also have serious associated risks because adverse reactions may lead to shock.^{2–5–7}

In the present study, we observed tolerance rates to cow's milk and soy during a prospective long-term follow-up study using open standardised FU-OFCs, with a view to suggesting guidelines for FU-OFC and dietary management in infantile FPIES.

METHODS

Data collection

We analysed the data of 23 patients with infantile FPIES (seven female, 16 male) who had been diagnosed (aged 36 (SD 14) days, range 13–58) using a standardised OFC and prospectively followed up until over 2 years of age, and who had undergone two or more FU-OFCs between June 2003 and April 2007. Patients were recruited from the in-patients unit at the Dongsan Medical Center, Keimyung University School of Medicine. All parents were informed that venous access

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might be required during the study and that repeated challenges might cause adverse reactions such as hypotension. Therefore general consent was obtained prior to administering OFC, and all study procedures were approved by the Keimyung University Institutional Review Board.

FPIES diagnosis

When a neonate or young infant on a cow's milk or soy formula, or mixed fed (cow's milk or a soy formula with breast feeding) was admitted with vomiting and/or diarrhoea, initial clinical findings of a failure to gain weight, metabolic acidosis, serum hypoalbuminaemia and methaemoglobinaemia were regarded as indexes of suspicion for FPIES.¹⁰ In this situation, we performed a single standardised OFC based on the guidelines suggested by other studies.^{2 3 5 7} Patients were given an OFC consisting of 0.15 g of cow's milk protein per kilogram of body weight (one spoon of formula mixed with 20 ml of water). After the OFC, five parameters not present at baseline were examined. These five parameters included three clinical symptoms (vomiting, lethargy and diarrhoea) and two laboratory findings (an increase to >3500 cells/mm³ in a peripheral blood absolute neutrophil count and the presence of >5 cells/high power field in faecal leukocytes or occult blood positive). A positive challenge after an initial OFC was defined as the presence of two of these five criteria, on the basis of previous suggestions.^{2 3 5 7} After diagnosis, protein hydrolysate (HA, Maeil Dairy Industry Co., Seoul, Korea) was fed to the infant. During the study period, no patient was found to have been on soy formula at the onset of symptoms. Once a diagnosis of cow's milk protein-induced enterocolitis had been made, soy protein was not challenged or substituted for fear of adverse reactions. However, we assumed that about 50% of these patients were reactive to both cow's milk and soy, based on the findings of previous studies⁹ on this subject. Food specific IgE antibodies to cow's milk and soy were evaluated using the UniCAP system at initial diagnosis in all 23 patients with FPIES, but all findings were negative.

Follow-up diet management and FU-OFC

According to the previous observations of one of the authors (JBH),¹¹ on accidental or formal challenge in FPIES, patients lack tolerance to cow's milk or soy at 2–4 months of age, whereas 30–70% of patients tolerate cow's milk or soy at 6 months. In addition, it has been recommended that the introduction of food proteins to infants with cow's milk or soy induced FPIES be delayed until after 6–7 months of age.^{2 3} Hence, in the present study, no solid food was introduced to patients until the first FU-OFC. In the event, we decided to perform a standardised first FU-OFC at 6 months of age using cow's milk or soy formula. Taking age, sex and other clinical features on initial admission into consideration, patients were randomly

allocated to two groups, that is, a cow's milk challenge starting group ($n = 11$, group I) and a soy challenge starting group ($n = 12$, group II). Second and third FU-OFCs were performed with a 2-month interval from the age of 8 months using cow's milk or soy in a crossed and switched-over manner. Third FU-OFCs were performed only in patients who responded positively to the first or second FU-OFCs. After the third FU-OFC, patients positive by cow's milk or soy challenge were scheduled for the fourth and further FU-OFCs when in generally good condition and more than 12 months of age.

Clinical features of two groups

Table 1 shows the clinical features on admission of the two randomly allocated groups of patients. There were no significant statistical differences between groups.

FU-OFC details

FU-OFCs were performed at an out-patient clinic with an intravenous line inserted. Extremely low cow's milk or soy protein dosages were used because later phase adverse reactions observed in FU-OFC can be more severe after the resolution of chronic symptoms on protein hydrolysate.⁹ Hence, patients were given a single open OFC, which consisted of 0.03–0.05 g of cow's milk protein or soy protein per kilogram of body weight (one spoon of formula mixed with 20 ml of water). The diagnostic parameters used were the three clinical symptoms (ie, vomiting, lethargy and diarrhoea) not present at baseline. A positive challenge after FU-OFC was defined as the presence of two of these three criteria, according to the suggestions of one of the authors (JBH).⁷

Solid food challenge

In patients who tolerated cow's milk or soy formula by FU-OFC, we undertook serial challenges using low allergenic and age-appropriate solid foods (ie, fruits and vegetables, rice, beef, chicken, potato, wheat, fish, eggs, etc) in the following manner: (i) if a patient had a positive result to cow's milk or soy challenge at FU-OFC, no solid food was introduced and exclusive protein hydrolysate feeding was continued until the next FU-OFC; (ii) if a patient had a negative result to cow's milk or soy challenge at FU-OFC, solid foods were administered serially under careful observation. Challenges with small amounts of solid foods were performed early in the morning at home. If any adverse reaction occurred, the physician in charge was called and intravenous fluid therapy was initiated either at an emergency centre or in an out-patient clinic. If specific solid food intolerance was observed, challenge with this solid food was postponed until the patient was more than 2 years of age.

Statistical methods

The χ^2 test and t test were used to analyse clinical features on initial admission between the two groups and tolerance rates, and statistical significance was accepted for p values <0.05 . Data are presented as means (SD).

RESULTS

FU-OFC tests

In total 72 FU-OFC cow's milk or soy tests were performed in 23 patients with FPIES and 27 (37.5%) positive challenges were observed. After FU-OFC, projectile vomiting was observed at 1.1–4.4 h and lethargy at 1.2–4.7 h for all positive challenges. Cyanosis was observed at 1.1–4.4 h after OFC in six (22.2%)

Table 1 Clinical features on admission of the two groups of patients

Clinical features*	Group I ($n = 11$)	Group II ($n = 12$)
Age, days	35 (12), 13–44	37 (18), 15–58
Sex, F:M	3:8	4:8
Daily weight gain,† g/day	–4.2 (11.8)	–3.8 (13.5)
Serum albumin level, g/dl	3.2 (0.8)	3.3 (0.7)
Serum bicarbonate level, mEq/l	16.1 (7.6)	15.5 (6.5)
Methaemoglobinaemia, $\geq 15\%$	1	2

* $p > 0.05$ between two groups by χ^2 test and t test.

†Body weight on admission (g)–birth weight (g)/age (day)

Values are mean (SD), range.

Table 2 Results of follow-up oral food challenge* testing in infantile food protein-induced enterocolitis syndrome

Challenge	Group I (n = 11) (%)			Group II (n = 12) (%)		
	First cow's milk	Second soy	Third cow's milk	First soy	Second cow's milk	Third soy
Positive	8 (72.7)	1 (9.1)	4 (36.4)	3 (25.0)	7 (58.3)	1 (8.3)
Negative	3 (27.3)	10 (90.9)	7† (63.6)	9 (75.0)	5 (41.7)	11‡ (91.7)

*The first follow-up oral food challenges (FU-OFCs) using cow's milk and soy (0.03–0.05 g protein/kg) were performed at 6 months of age and after this, the second or third FU-OFCs were performed every 2 months in a crossed and switched-over manner.

†Included three challenge negative patients in the first cow's milk protein challenge in group I.

‡Included nine challenge negative patients in the first soy protein challenge in group II.

patients and hypotension at 1–4 h in three (11.1%). Diarrhoea was observed at 6–16 h after OFC in nine (33.3%) infants. No mucocutaneous or respiratory manifestation was observed in any of those with a positive challenge. During the food reintroduction period, no false negative challenge occurred among 45 negative cow's milk or soy challenges.

Cow's milk and soy tolerance rates

Based on the results of the initial three FU-OFCs performed, tolerance rates to cow's milk and soy were 27.3% and 75.0% at 6 months ($p = 0.022$), 41.7% and 90.9% at 8 months ($p = 0.013$), and 63.6% and 91.7% ($p = 0.104$) at 10 months (table 2). After the third FU-OFCs, cow's milk intolerance was observed in 11 of 23 patients with FPIES; when the fourth FU-OFC with cow's milk was performed at 14–16 months in these 11 patients, eight (72.7%) were found to be tolerant. The fifth FU-OFC with cow's milk was performed at 18–20 months in the three remaining intolerant patients, and all were then tolerant. On the other hand, after the third FU-OFC tests, soy intolerance was observed in two (8.7%) of the 23 patients with FPIES, and these were also intolerant to cow's milk. When fourth FU-OFCs with soy were performed in these two patients at 12–14 months of age, both were tolerant. Mean ages for outgrowing reactivity to cow's milk and soy among the 23 patients were 12.0 (SD 4.4) (range 6–20) months and 7.8 (SD 2.1) (range 6–14) months, respectively.

Solid food FPIES and atopic dermatitis

Solid food FPIES was observed in two (8.7%) of the 23 patients with FPIES (rice, beef and egg in one over 11 months of age, and fish and shellfish in another over 12 months of age); these two patients were also intolerant to cow's milk. Profuse projectile vomiting and lethargy were observed at 1–4 h after OFC. After 2 years of age, intolerant solid foods were serially challenged, and both of these patients were then tolerant with no gastrointestinal or mucocutaneous symptoms. Atopic dermatitis was not observed in any of the 23 patients with FPIES over 2 years of follow-up.

DISCUSSION

The duration of susceptibility to food protein in FPIES has not yet been determined. The present study reveals that neonatal or young patients with infantile FPIES lose intolerance more readily to soy than to cow's milk. In the present study, soy challenges at 6–8 months of age showed a 75–90% tolerance rate. However, the cow's milk tolerance rate was 27.3% in patients with infantile FPIES challenged at age 6 months, 63.6% at 10 months and 72.7% at 14–16 months. Powell⁵ performed FU-OFC with cow's milk in infantile FPIES at a mean age of 5.5 months, and found that only 22.2% were tolerant at this age, which is compatible with the observations in the present

study. Moreover, patients with infantile FPIES were observed to outgrow food sensitivities during the first 2 years of life.

The identification of tolerances to major foods using FU-OFC in infantile FPIES reduces parent inconvenience and the social isolation resulting from strict dietary management. We suggest that the first FU-OFC should be performed in infantile FPIES with soy at 6–8 months of age (when the tolerance rate is 75–90%) under careful medical supervision, and that cow's milk challenge should be performed after 12 months of age (when the tolerance rate is 70% or higher). As regards "typical" FPIES, Sicherer *et al*² reported that it occurs below 9 months of age, and that sensitivity to cow's milk is lost in 60% and to soy in 25% of patients 2 years after presentation. In addition, they suggested that FU-OFC should be performed in FPIES every 18–24 months (depending on clinical severity) to determine tolerance.^{2–9} However, these observations and this suggestion are inconsistent with our observations in neonates or young infants with classical FPIES.

Recently, delayed onset FPIES was reported to have a symptom onset at over 6–12 months of age and to be associated with persistent hypersensitivity beyond 2–3 years of age,^{2–8,12} which is quite different from that observed in classical FPIES. In some FPIES cases, patients have been reported to have detectable IgE levels to the causative protein, either at presentation or during follow-up,² even though typically in FPIES patients are negative for food specific IgE antibodies. The presence of food specific IgE has been suggested to be a poor prognostic sign for outgrowing cow's milk allergy.¹³ In the present study, food specific IgE antibodies to cow's milk and soy were evaluated using the Uni-CAP system at initial diagnosis, but all findings were negative. Moreover, whereas atopic dermatitis has been reported to be more common in patients with solid food FPIES than in patients with infantile FPIES,³ it was not observed in any of our patients over a 2-year follow-up period. The clinical spectrum of FPIES has been expanded to include more triggers, a greater age at presentation, and the possibility of persistent hypersensitivity beyond infancy.⁹

Although infantile FPIES has been reported to carry a risk of reaction to solid foods as high as 32%,³ solid food FPIES only developed in 8.7% of patients with infantile FPIES in the present study. Patients with solid food FPIES, according to Nowak-Węgrzyn *et al*,³ were less than 6 months of age at first reaction, and the greatest age at onset was 7 months. In the present study, solid food challenges were performed when patients were tolerant to cow's milk or soy. Thus, the majority of patients in our study population were challenged with solid foods at 6–12 months of age. We assume that the comparative delayed introduction of solid foods to patients in the present study versus the study by Nowak-Węgrzyn *et al*,³ explains why a lower incidence of solid food FPIES was encountered during the present study. Gut maturation during the first years of life may

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explain why the majority of children with food allergies outgrow them by 2–3 years of age,¹⁴ and it is evident from our findings that food tolerance also increases rapidly with age.

The present study also reveals that patients with infantile FPIES outgrow food sensitivities by 24 months of age. Nowak-Węgrzyn *et al*³ reported that most patients with FPIES outgrew cow's milk or soy sensitivity by 28 months of age, and Gryboski⁴ also found that almost all patients could ingest cow's milk at 3 years of age. Moreover, in infantile cow's milk sensitive enteropathy, the reintroduction of a normal diet is nearly always possible between 1 and 2 years of age.¹⁵ These findings are compatible with the observations of the present study.

Challenged protein dosages differ in related studies,^{2,3,7} although cow's milk or soy at 0.15–0.3 g protein/kg body weight is generally recommended.⁹ However, in the present study, only 0.03–0.05 g of cow's milk or soy protein per kilogram of body weight was found to be sufficient to induce symptoms. Moreover, from the results obtained during the present study using a single open challenge, a positive challenge can induce conditions severe enough to cause identifiable adverse reactions, even including hypotension and cyanosis. In addition, no false negative challenge was encountered among the 45 negative challenges. Several FPIES studies have used open challenges, which are less prone to bias.⁸ On the other hand, in the present study, intravenous fluid resuscitation was sufficient to counter adverse reactions in positively challenged patients and no other medication was infused.

The present study reveals that patients with infantile FPIES lose intolerance more readily to soy than to cow's milk and that they outgrow food sensitivities during the first 2 years of life. Future clinical studies are required to differentiate the clinical subtypes of FPIES and to develop laboratory tests that avoid or assist OFC and FU-OFC.

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