

LETTERS TO THE EDITOR

Serum thymus and activation-regulated chemokine level as a potential biomarker for food protein-induced enterocolitis syndrome

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy in infants characterized by repetitive vomiting and diarrhea occurring within 1–4 hours of ingesting the offending food.¹ Diagnosis of FPIES is difficult because patients present with non-specific symptoms such as vomiting and diarrhea, and useful diagnostic biomarkers are lacking.¹ We report on three infants who had FPIES with a transient increase in serum thymus and activation-regulated chemokine (TARC) levels 1 day after ingesting the offending food. Serum TARC levels were quantified by a chemiluminescent enzyme immunoassay using an HISCL[®] system (Sysmex, Hyogo, Japan). In two of these cases, no increase in the serum TARC level was observed following the oral food challenge (OFC), which yielded a negative result. We suggest that a transient elevation in serum TARC levels 1 day after ingesting an offending food may be a useful diagnostic marker in some cases of FPIES.

Case 1: The patient was a 7-month-old girl without any previously described atopic disease who had a negative family history of atopy. She was born at term via vaginal delivery and was breast-fed from birth. At 7 months of age, she ingested miso soup containing tofu (15 g) with rice porridge. After 3 hours, she presented with repetitive vomiting and diarrhea and became lethargic, necessitating intravenous fluid therapy but lacking any skin or respiratory symptoms. After 10 days, she ingested the same soup and again reacted in a similar way. At this point, the total IgE level was 19 IU/mL, and CAP-fluoroenzyme immunoassay (CAP-FEIA) to soybean was undetectable. After these episodes, she was suspected of having soybean FPIES and directed to eliminate soy products. After the elimination of soy products, she showed no symptoms for 4 weeks. She was diagnosed with soybean FPIES after presenting with lethargy with repetitive vomiting 4 hours after an OFC with tofu (15 g). An elevation in the serum TARC level was observed 1 day after the ingestion of the offending food in the OFC. Serum TARC levels returned to the normal range after 2 days (Figure 1A). The OFC was repeated when she was 18 months old, and neither the symptoms nor the serum TARC level elevation was observed (Figure 1B).

Case 2: The patient was an 11-month-old boy without any previously described atopic disease who had a negative family history of atopy. He was born at term via vaginal delivery. Although he received breastmilk exclusively, he was started on milk formula at 5 months

because of poor weight gain. Four hours after the ingestion of 10 mL of milk formula, he presented with vomiting, necessitating intravenous fluid therapy. He was advised to be fed extensively hydrolyzed casein formula instead of milk formula due to the suspicion of FPIES. After ingesting this formula, he showed no symptoms for 6 months. At 11 months, he was diagnosed with cow's milk FPIES after presenting with lethargy and repetitive vomiting 3 hours after OFC with yogurt (180 g). At this point, the total IgE was 39 IU/mL, and CAP-FEIA to cow's milk, α -lactalbumin, β -lactoglobulin, and casein was undetectable. An elevation in the serum TARC level was observed 1 day after the ingestion of the offending food in the OFC. The serum TARC levels returned to the normal range after 2 weeks (Figure 1A). An OFC with cow's milk (60 mL) was performed when he was 18 months old, and neither vomiting nor an elevation in TARC levels was observed (Figure 1B).

Case 3: The patient was a 7-month-old girl without any previously described atopic disease who had a negative family history of atopy. She was born at term via vaginal delivery and was breast-fed from birth. At 7 months of age, 3 hours after ingesting two teaspoons of tofu, she presented with repetitive vomiting without skin or respiratory symptoms and required intravenous fluid therapy. She went home after her symptoms disappeared and then inadvertently ingested biscuits with soy on the same day. She again reacted in a similar way. At this point, the total IgE was 20 IU/mL, and the CAP-FEIA to soy was undetectable. She was suspected of having soybean FPIES and was directed to eliminate soy products. After the elimination of soy products, she showed no symptoms for 2 weeks. We did not perform an OFC because her parents refused the procedure. Although her serum TARC level was not elevated immediately after vomiting, it was elevated on the following day. After 2 weeks, the serum TARC levels had returned to a normal range (Figure 1A).

Although FPIES is a relatively rare disease, diagnostic criteria have been proposed,¹ and the number of FPIES cases has increased in recent years. This disease lowers patients' quality of life, and patients may undergo extensive workups due to diagnostic difficulty.^{2,3} Therefore, new and more convenient biomarkers for diagnosing FPIES are urgently needed. Based on previous research investigating biomarkers of FPIES, increase in the serum levels of C-reactive protein (CRP), neutrophils, IL-4, and tumor necrosis factor- α (TNF- α) can be

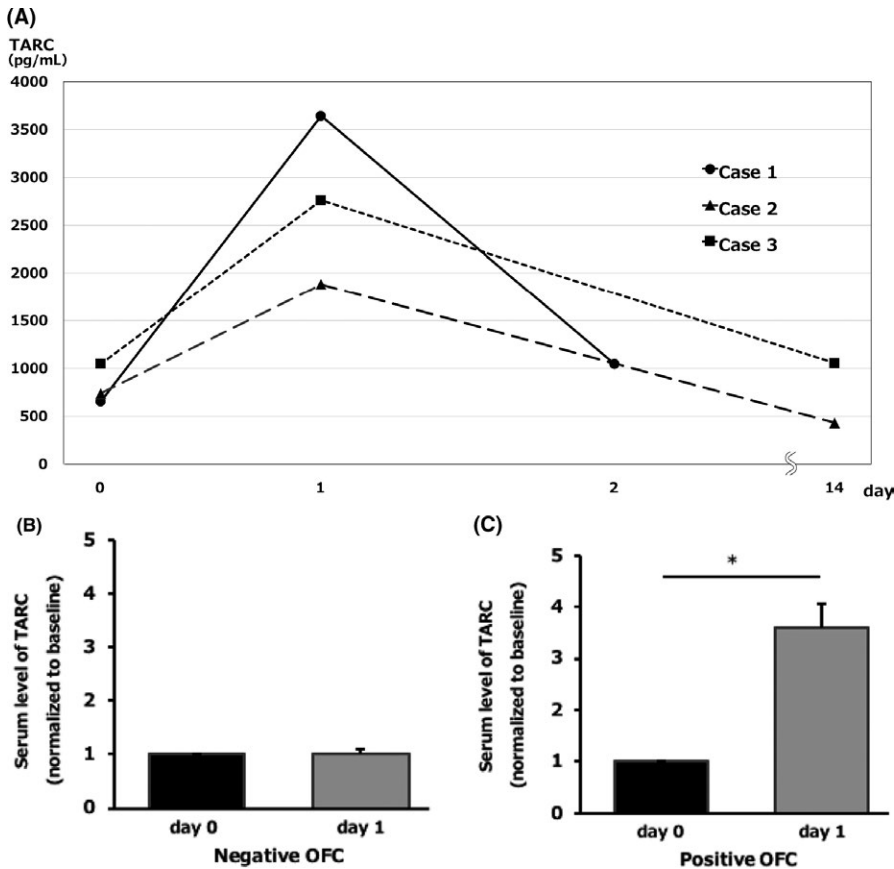


FIGURE 1 Changes in serum TARC levels in children with FPIES. A, Individual serum TARC levels in patients with repetitive vomiting. B, C, Serum TARC levels in children with negative OFC (B) and positive OFC (C). Mean + SEM. $n = 3$ (positive OFC) and $n = 2$ (negative OFC), where n is the number of cases. Statistical significance was assessed using a ratio paired t test, $*P < 0.05$. FPIES, food protein-induced enterocolitis syndrome; OFC, oral food challenge; TARC, thymus and activation-regulated chemokine

observed.^{1,4,5} Although we measured the serum levels of CRP, neutrophils, procalcitonin, and TARC before and after OFC, these markers did not significantly increase, except for TARC. TARC is a chemokine that causes Th2 cells expressing chemokine receptor type 4 to migrate to the site of inflammation.⁶ Recent investigations have demonstrated that serum TARC levels are high in atopic dermatitis,⁶ pediatric asthma,⁷ and FPIES,⁸ but none of the diseases described above, except for FPIES, were observed in our three patients. Furthermore, the changes in serum TARC levels before and after the OFC have not been previously validated. This is the first to report an increase in serum TARC levels after repeated vomiting in FPIES patients. We observed that the TARC levels were elevated on the following day but not immediately. A previous report showed that TARC is generated by human eosinophils stimulated by TNF- α plus IL-4. Detectable levels of TARC were noted at 20 hours (TARC was undetectable for the first 3 hours).⁹ The TARC elevation in FPIES may also require approximately 10 hours due to a similar mechanism. Moreover, a study previously reported that TARC is induced in intestinal epithelial cells in a mouse allergy model.¹⁰ The changes in serum TARC levels might be related to allergic reactions in intestinal epithelial cells. In these three cases, the serum TARC level was significantly elevated 1 day after ingesting an offending food (Figure 1C). In contrast, no elevation was observed when the OFC did not cause gastrointestinal symptoms (Figure 1B). We statistically compared the second serum TARC level measurement to baseline levels (before ingesting the offending food in Case 1 and Case 2, and 3 hours later in Case 3). Although we could

not determine whether this transient elevation was specific to FPIES as we had no control cases, it is possible that screening for a transient elevation in serum TARC levels may be useful for diagnosing some cases of FPIES. If serum TARC elevation is useful for the diagnosis of FPIES, this measurement may reduce the need for extensive workups in patients presenting with repetitive vomiting and suspected of infectious gastroenteritis, sepsis, etc. Furthermore, this delayed transient serum TARC elevation may suggest potential delayed accumulation of T cells which is not relevant for an isolated acute FPIES reaction but may be relevant for chronic FPIES.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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Insights into tree nut and sesame consumption from a cohort of 80 peanut-allergic children

To the Editor

Peanut allergy is increasing in prevalence in the United States according to reports¹ and has become a global concern. Sensitization to tree nuts is common with reported rates of up to 86% for multi-nut sensitization with increasing age.^{2,3} In addition, peanut allergy has been associated with an increased risk of sesame sensitization and allergy.⁴ Patients' attitudes toward tree nut and sesame consumption can be variable following a diagnosis of peanut allergy and have not previously been examined.

Tree nut consumption can be nutritionally beneficial and is reportedly associated with better adiposity measures (lower BMI and waist circumference), and cardiovascular (lower systolic blood pressure) and metabolic syndrome health risk factors (lower insulin resistance, higher high-density lipoprotein cholesterol).⁵ A previous European study has reported that consumption of food products by

peanut-allergic patients, including those with precautionary allergen labeling (PAL), is modulated by factors related to anxiety such as label reading and knowledge of threshold and concomitant tree nut allergy.⁶

We performed a prospective evaluation of a cohort of 80 peanut-allergic children, presenting in our tertiary pediatric allergy clinic for follow-up, with the aim to investigate the patients' approach to tree nut and sesame consumption (complete avoidance, selected eating or free eating) and the reasons underlying this approach. IRB approval was obtained for this study.

Eighty children with known peanut allergy (diagnosed by an allergist based on a clinical history of allergic reaction and positive specific IgE or SPT to peanut) presenting consecutively to our food allergy clinic, over a period of 6 months (February-July 2018), were asked to participate in this study. Seventy-eight agreed to participate and two declined. Skin prick testing (SPT) to tree nuts and sesame (in addition to peanut SPT) was performed to assess sensitization to these foods. Sensitization was defined as a wheal of 3 mm or higher to the food tested, compared with the negative control. Patients or caregivers (if the child was unable to provide the relevant

Abbreviations: IRB, Institutional Review Board; PAL, precautionary allergen labeling; SPT, skin prick tests.

IRB approval number and statement: The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) reviewed and approved the research protocol (# H-40400).