

Development of food protein–induced enterocolitis syndrome (FPIES) to egg after immunoglobulin E–mediated egg allergy



Food protein–induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE)–mediated condition characterized by repetitive vomiting 1 to 4 hours after ingestion of the particular food accompanied by additional symptoms such as lethargy, pallor, or diarrhea.¹ Atypical FPIES characterizes patients who are noted to have IgE-mediated sensitization to the FPIES-inducing food² and has been associated with an increased likelihood of persistent FPIES.³ A clinical conversion from an FPIES phenotype to an IgE-mediated phenotype to the same food has been described.³ Specifically, Caubet et al³ described their experience of 160 patients with FPIES and found that 24% had evidence of IgE sensitization to the FPIES-inducing food.³ Among the 70 patients with cow's milk–induced FPIES, 17 participants were noted to be sensitized to cow's milk, 7 of which developed IgE-mediated allergy to cow's milk based on clinical symptoms at follow-up.³ Therefore, although FPIES is a non-IgE-mediated process, current recommendations suggest considering specific IgE (sIgE) testing to the culprit food before oral food challenge (OFC), given the risk of converting to an IgE-mediated phenotype.¹ We describe a patient who developed FPIES after an IgE-mediated allergic phenotype to the same food.

At 9 months of age, a female infant with no medical conditions ingested scrambled eggs for the first time and developed hives immediately without other symptoms. The family tried scrambled egg in isolation again and within minutes of ingestion, she developed hives and an episode of immediate vomiting. She did not have delayed vomiting or diarrhea. She had never ingested egg, including baked egg, before these episodes. She was referred to an outside allergist, who performed skin prick testing (SPT) and sIgE to egg white, which demonstrated sensitization (Table 1). She was instructed to avoid all forms of egg.

At 2 years of age, repeat SPT to egg white was performed by the outside allergist and was negative (Table 1). An OFC to baked egg was recommended. She tolerated the OFC without symptoms in the 2-hour observation period so was discharged home. However, after leaving (approximately 4 hours after ingestion of baked egg), she developed profuse, repetitive vomiting for several hours to the degree that her parents described her as lethargic and pale. She subsequently developed diarrhea several hours later. The parents reported no symptoms of hives, angioedema, or respiratory distress. After discussion with their allergist, it was believed that this was likely a viral illness, and they should offer baked egg at home.

On 3 subsequent occasions after ingestion of egg-containing products (a pancake in a restaurant, cake and ice cream that all had egg of varying degrees of baking), she had recurrent, forceful, and repetitive vomiting to the point of lethargy and pallor that would last several hours as well as delayed diarrhea. She similarly did not have cutaneous or respiratory IgE-mediated symptoms. No other foods were ingested surrounding the episodes that were not otherwise regularly tolerated to suggest an IgE-mediated reaction to another food. Outside of egg, she otherwise tolerates an unrestricted diet, including all other major food allergens. These events were separated by days, occurring over several weeks when she was well without viral symptoms. This infant otherwise does not vomit regularly or having any other feeding problems. On one occasion, the patient's mother thought the vomiting may have started approximately 1 hour after ingestion, but all of the others were delayed (2–4 hours after). In all episodes, the product with egg was eaten in isolation or was ingested

with foods that are routinely tolerated. Outside of these described episodes, she has ingested 1 bite of a store-bought waffle containing egg without symptoms but, to the parents' knowledge, she has had no other ingestions of egg in any form.

She was then referred to Children's Hospital Colorado allergy clinic for a second opinion. She presented 2 months after the baked egg challenge. Repeat SPT to egg white, sIgE egg white, and ovomucoid were positive, with an elevated total IgE (Table 1). Given that no serum testing was performed 2 months earlier when her SPT to egg white was negative, whether the prior test was inaccurate or whether a rapid change in her sensitization occurred is unclear. However, her serum egg white IgE of 5.8 kU_A/L at 9 months of age and of 47.8 kU_A/L 26 months later would suggest that her serum egg white IgE was elevated at the time of baked egg challenge at 24 months of age.

Based on clinical history, this patient meets current diagnostic criteria for FPIES to baked egg.¹ Although she did not have IgE-mediated symptoms after ingestion of baked and more lightly cooked forms of egg, she has yet to ingest an age-appropriate serving of uncooked egg to conclusively determine whether she has outgrown her IgE-mediated egg allergy. Her skin and serum testing to egg white demonstrates sensitization to the degree that many would manifest IgE-mediated symptoms on ingestion.⁴ More importantly, she has a clinical history consistent with an IgE-mediated allergy to scrambled egg, which preceded the development of FPIES to egg. Therefore, possibly her IgE-mediated allergy to uncooked egg persists, so it was recommended that she continue to carry an epinephrine autoinjector and the parents were instructed on management of IgE-mediated food allergy as well as FPIES. Although an OFC would be helpful to clarify whether her IgE-mediated egg allergy persists, the family did not want to pursue this testing, given her recent symptoms after egg ingestion. The absence of an OFC to confirm her egg allergy phenotype is a limitation of our case. We conclude that this is likely a case of FPIES and IgE-mediated allergy to different forms of the same food. She has not had any further symptoms since these 3 episodes and has not had any accidental exposures to egg. Although she did have 1 bite of a waffle containing baked egg with no reaction, we speculate this is attributable to ingestion of too small an amount of egg protein to trigger symptoms.

Two recent publications similarly describe patients converting from IgE-mediated phenotype to an FPIES phenotype to the same food. Miceli Sopo et al⁵ described an infant who had symptoms of IgE-mediated egg allergy at 10 months of age, positive SPT to egg at 21 months, and then likely FPIES to both baked and scrambled egg on OFCs without IgE-mediated symptoms.⁵ The authors could not conclusively determine whether this was an IgE-mediated or FPIES reaction, however, and suggested that this infant may have a mixed process, similar to our patient.⁵ Barni et al⁶ described 2 very young infants with IgE-cow's milk allergy and high levels of sensitization,

Table 1
Summary of Allergy Testing

	May 2016	August 2017	October 2017
Skin prick testing (mean wheal diameter, mm) ^a	3	0	9
Egg white IgE (kU _A /L) ^b	5.8		47.8
Ovomucoid IgE (kU _A /L) ^b			3.89
Serum IgE (kU/L) ^c			139

^aNegative is <3 mm.

^bNormal is 0 to <0.34 kU_A/L.

^cNormal is 0 to 45 kU/L.

who then both had negative sIgE testing 2 to 3 months later and FPIES demonstrated on cow's milk OFCs, suggesting conversion of 1 phenotype to another to the same food.⁶

In addition to the conversion between allergic phenotypes seen in atypical FPIES,³ change amongst allergic phenotypes has additionally been noted in patients with eosinophilic esophagitis and atopic dermatitis, with cases demonstrating the development of IgE-mediated symptoms after removal of a food for treatment of the presenting atopic condition.^{7,8} Our case adds to the growing literature demonstrating the possibility of patients converting between allergic phenotypes as well as possible mixed processes that physicians should be aware of. Similarly, clinicians should also consider a diagnosis of FPIES in a child who demonstrates characteristic symptoms after apparent resolution of an IgE-mediated allergy to the culprit food.

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Pilot study of the CAPS (Clinical extent, Area, Pruritus, Sleep) measure for atopic dermatitis severity



As new treatments are developed, tested, and approved for atopic dermatitis (AD), valid and practical tools are needed to assess their effectiveness in clinical trials and in routine practice. Atopic dermatitis severity is usually assessed clinically in 2 different ways: physician-assessed signs of the disease and patient-reported symptoms. Commonly used outcome measures include the Eczema Area and Severity Index (EASI) for signs and Patient-Oriented Eczema Measure (POEM) for symptoms; these are recommended by the Harmonizing Measures for Eczema initiative.^{1,2} However, current measures of AD severity, particularly signs, are cumbersome and difficult to use in routine clinical practice; they are time-consuming and use complex scoring systems.

To address the need for a practical assessment of the signs and symptoms of AD in clinical trials and routine clinical practice, we have developed and pilot-tested the CAPS (Clinical extent, Area, Pruritus, Sleep) measure (eFig 1). This tool has 4 questions, each with a maximum score of 10. Two of the questions relate to clinical signs of the disease (clinician-assessed), and 2 are related to symptoms (patient-assessed). The signs subscale includes an assessment of (1) representative lesion severity and (2) body surface area. The representative lesion is defined as the worst lesion for that patient at that assessment, with involvement of the face, hands, or genitals or the presence of impetiginization increasing the score. The symptoms subscale includes assessments of pruritus and sleep, each on visual analogue scales, which have been identified as major drivers of AD morbidity and are similar to the patient-reported component of the

SCORAD (Severity Scoring of Atopic Dermatitis).^{3–5} The signs and symptoms subscales are given equal weight, with each scored out of 20 for a total score out of 40.

In a pilot study to assess internal consistency and criterion validity, we administered CAPS to a convenience sample of adult AD patients in 2 academic dermatology practices in Providence, Rhode Island. The study was approved by the Lifespan and Brown University institutional review boards. All patients met Hanifin and Rajka diagnostic criteria.⁶ The CAPS was administered at the conclusion of the clinic visit, along with an Investigator Global Assessment (IGA), EASI, POEM, and 2 quality of life instruments, the Dermatology Life Quality Index (DLQI) and SKINDEX-16.⁷ We hypothesized that CAPS would positively correlate with the other outcome measures, and that the signs and symptoms subscales would correlate with other physician-reported measures and patient-reported outcomes, respectively.

We had 25 patients in our pilot study, 10 (40%) of whom were males. The median age was 34 years (range, 20–75 years). Median scores and ranges for each assessment are presented in eTable 1. Cronbach's alphas were high for the signs (0.94) and symptoms (0.88) components and the overall score (0.93), indicating good internal consistency. Pearson correlation coefficients were all moderate to strong and statistically significant for the signs and symptoms components of CAPS and the overall instrument with the other outcome measures (Table 1).

Our study is limited by its small sample size and being conducted at tertiary care clinics in one US state only. Larger studies in more diverse settings are necessary to replicate our findings and to assess other measurement properties of CAPS, including feasibility/efficiency, responsiveness, inter- and intra-rater reliability, and interpretability. Future assessments of criterion validity would benefit from other outcome measures, including the SCORAD. We did not collect data on patient race/ethnicity, which will be important for future studies given that AD appears differently in different skin types. The original CAPS used for this pilot study did not include explicit completion instructions; these have been added to the reformatted CAPS (eFig 1B), and

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