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Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome

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Diagnostic tests are lacking in food protein-induced enterocolitis (FPIES), a non-immunoglobulin E, presumably T cell-mediated food allergy disorder. FPIES typically presents in infancy with profuse vomiting and diarrhea 2 to 4 hours after ingestion of the allergen, combined with a left-shift in peripheral blood leukocytes, occasionally causing profound dehydration, hypotension, and lethargy.¹ Chronic exposure results in failure to thrive and hypoalbuminemia.¹ FPIES is elicited commonly by milk and soy protein,¹ oat, rice, and other foods.² Oral food challenge (OFC) is performed to follow tolerance development in FPIES, but protracted emesis and dehydration necessitate fluid resuscitation in up to 50% of reactive challenges. Therefore, OFC to confirm the diagnosis of FPIES can be associated with high risk.

The atopy patch test (APT) has been suggested as a promising diagnostic test for FPIES³ based on the potential involvement of allergen-specific T lymphocytes, which have been cloned from APT biopsy specimens,⁴ in FPIES pathophysiology.⁵ Furthermore, it was recently shown that cutaneous exposure to food antigens can reprogram gut-homing effector T cells in lymph nodes to express skin-homing receptors, eliciting skin lesions on cutaneous food allergen contact.⁶ We performed APT in children with FPIES before OFC performed to monitor tolerance development. All these children had a history of reaction suggestive of “typical” FPIES as proposed by Sicherer et al¹ (acute onset of severe, repetitive emesis within 1–4 hours of ingestion) to at least 1 of the following foods: milk, soy, oat, or rice. The study was approved by the Institutional Review Board. Informed consent was obtained from parents and assent from children when appropriate. A standard APT panel of cow milk, soybean, rice, and oat was performed on each patient within a week before OFC as described previously.³ Briefly, a thick paste of nonfat dried milk powder or soy, rice, or oat flour in normal saline was applied into Finn Chambers placed on the back with Scanpore tape (Allerderm Laboratories, Inc., Petaluma, California). Vanicream (Pharmaceutical Specialties Inc, Rochester, Minnesota) was used as a negative control. Patches were removed after 48 hours; reactions were blindly scored by a study physician at 72 hours. Erythema alone was considered “irritation” (negative); positive reactions included erythema with infiltration (+), or with few papules (++), several papules (+++), and vesicles (+++).⁷

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Inpatient OFCs were performed by administering food in 3 equal doses over a 45-min interval with a peripheral intravenous line in place. The total amount of challenge food was calculated as (0.15–) 0.6 g food protein (or 17.6 mL liquid milk, 20.3 mL liquid soy milk, 9 g infant rice cereal, or 4.5 g infant oat cereal) per kilogram body weight. Positive challenges comprised symptoms and laboratory findings as described previously.⁸

We performed 38 nonblinded challenges in 25 subjects (15 males, 10 females) at median age of 3.3 years (range, 1.5–16.8 years) (Table 1). Their most recent FPIES reaction had occurred a median of 24.5 months (range, 14.5–79 months) before the OFC. Of the 38 OFCs, 16 (42%) were positive and included vomiting and sometimes other symptoms (Table 1), within a median of 2.5 hours (range, 2–6.2 hours) from the start of the challenge to a total dose in all the patients; only 2 subjects had a positive APT. Among the 23 negative OFCs, 2 subjects had a positive APT. The median age was comparable between those with a positive and negative OFC. The APT had sensitivity of 11.8%, specificity 85.7%, positive predictive value 40%, and negative predictive value 54.5%. A total of 102 tests were done as part of the APT panel to foods other than the offending food; 5 were positive. In 3, food was tolerated; in 2, food had not yet been introduced.

The discrepancy compared with the report by Fogg et al (sensitivity of 100%, specificity 71%, positive predictive value 75%, negative predictive value 100%)³ may be attributable to the fact that we considered only palpable infiltration as a positive reaction, as recommended by the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network.⁷ The median age in the study by Fogg et al³ was younger, and the median time since the most recent reaction was shorter (12 months, range 4–29 months), which could represent a group of children with more “active” disease. However, their reaction rate was not significantly higher than ours (48.5% vs 42%). It is possible that the activation capacity of responsible T cells diminishes over time resulting in a negative APT. However, this was not the case in the gut mucosa during a positive OFC.

In conclusion, APTs to common food allergens have poor utility in the follow-up prediction of outgrowing FPIES in children.

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Table 1

Characteristics of the study population and test results according to the trigger food^a

	Age at symptoms (mo)	Initial symptoms	Age at last reaction (mo)	Age at testing (mo)	OFC symptoms ^b	APT	SPT/sIgE ^c	Other foods reported as causing FPIES	Atopic dermatitis
Milk (<i>n</i> = 12)	0.25–14	V 12, L 4, D 3	0.5–51	18–109	V 8, D 1, HT 1, none 4	Pos 1, Neg 11	Pos 1/Pos 1	Soy 4, beef 2, rice 2, none 5	Present 6, absent 6
Soy (<i>n</i> = 14)	1–18	V 13, D 6, L 5, S 2, n/a 1	1–161	17–201	V 5, L 1, none 9	Pos 2, Neg 12	Pos 1/Pos 1	Milk 6, beef 1, rice 1, none 7	Present 6, absent 8
Oat (<i>n</i> = 4)	4–7.5	V 4, D 2, L 2	4–12	24–56	V 2, none 2	Pos 1, Neg 3	Pos 0/Pos 0	Milk 2, rice 2, Sweet potato 1, wheat 1, none 1	Present 2, absent 2
Rice (<i>n</i> = 8)	4–7	V 8, D3, L4, S 1	3–17	17–79	V 1, none 7	Pos 0, Neg 7	Pos 0/Pos 0	Milk 2, wheat 1, oat 1, sweet potato 1, rice 1, none 4	Present 4, absent 4

Abbreviations: D, diarrhea; HT, hypotension; L, lethargy; S, shock; V, vomiting; n/a, not applicable (never ingested the food but avoided due to FPIES to other foods).

Results are expressed as a range for the ages shown, otherwise as number of patients.

^aFor APT, only palpable infiltration including edema and eczema was considered as a positive (Pos) test.

^bMedian increase in peripheral blood polymorphonuclear cells in positive oral food challenges was 4,000/mm³, range 1,600–13,200/mm³.

^cPositive SPT is defined as wheal diameter at least 3 mm and positive specific IgE as >0.35 kU/L (UniCAP, ThermoFischer Scientific, Portage, Michigan).