

(IBD), were excluded by grossly normal colonoscopies. Celiac disease was excluded based on serologic testing.

In patients presenting with PPD, one must consider the following in the differential diagnosis: maldigestion due to bile acid malabsorption, celiac disease, IBD, irritable bowel syndrome with diarrhea, systemic mastocytosis, and mastocytic enterocolitis. Bile acid malabsorption was excluded based on the absence of obstructive jaundice, and IBD was excluded by colonoscopy. Systemic mastocytosis and celiac disease were excluded by non-elevated mast cell biomarkers (Table 1). Irritable bowel syndrome with diarrhea does not usually present with diarrhea exclusively after eating, and affected patients do not consistently respond to antihistamines.^{3–5} These patients cannot be classified as having mast cell activation syndrome (MCAS)² using accepted criteria because none exhibited elevated tryptase levels during their symptomatic periods before initiation of treatment. Furthermore, although gastrointestinal symptoms in MCAS may include diarrhea or abdominal pain, these symptoms often occur spontaneously in MCAS and not exclusively after eating as observed in our patients. In addition, these patients exhibited mild cutaneous symptoms (urticaria, flushing) and not anaphylactic manifestations characteristic of MCAS. Our patients cannot be classified as having mastocytic enterocolitis, a pathologic finding described by Jakate et al⁶ in patients presenting with chronic diarrhea in whom diarrhea was not characterized as being postprandial nor responsive to antihistamines.

The beneficial responses in these patients to H₁- and H₂-receptor blockers suggest that histamine released by gastrointestinal mast cells is a key mediator of PPD. Histamine has known effects on bowel motility, and all 4 histamine receptors have been detected in gastrointestinal tissues.^{7,8} In human studies, H₁-, H₂-, and histamine₄ (H₄)-receptor stimulation was demonstrated to increase gastrointestinal motility.^{9,10} The physiologic role of mast cells in the gastrointestinal tract has not been clearly defined. In our patient population, the exact mechanism by which gut mast cells are stimulated in response to food ingestion is unclear. It is possible, although unproven, that gut peristalsis in response to food ingestion could activate mast cells. The favorable response in these patients to antihistamines would suggest that H₁-receptor and H₂-receptor stimulation by histamine mediates PPD. It is unknown whether other mast cell mediators or H₄-receptors also mediate elicitation of PPD in patients with this syndrome.

This case report describes a previously unrecognized clinical entity of idiopathic PPD responsive to antihistamines. Antihistamine-responsive PPD is not uncommon in patients with concurrent chronic idiopathic urticaria and dermatographia and can be distinguished from MCAS. This syndrome should also be considered in the differential diagnosis of patients presenting with general food intolerance after excluding food allergy and other gastrointestinal disorders. Future studies are necessary to identify the prevalence and natural history of this syndrome and to evaluate optimal treatment regimens.

Yasmin Hassoun, MD

Margo Rockwell Stevenson, MD

David I. Bernstein, MD

Division of Immunology, Allergy, and Rheumatology

University of Cincinnati College of Medicine

Cincinnati, Ohio

BERNSTDD@ucmail.uc.edu

References

1. Arasaradnam RP, Brown S, Forbes A, et al. Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology, 3rd edition. *Gut*. 2018;67:1380–1399.
2. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract*. 2019;7:1125–1133.e1.
3. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology*. 2002;123:2108–2131.
4. Magen E, Chikovani T. Possible therapeutic role of IgE blockade in irritable bowel syndrome. *World J Gastroenterol*. 2016;22:9451–9456.
5. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. *N Engl J Med*. 2017;376:2566–2578.
6. Jakate S, Demeo M, John R, Tobin M, Keshavarzian A. Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. *Arch Pathol Lab Med*. 2006;130:362–367.
7. Nakamura E, Kataoka T, Furutani K, et al. Lack of histamine alters gastric mucosal morphology: comparison of histidine decarboxylase-deficient and mast cell-deficient mice. *Am J Physiol Gastrointest Liver Physiol*. 2004;287:G1053–G1061.
8. Fargeas MJ, Fioramonti J, Bueno L. Involvement of different receptors in the central and peripheral effects of histamine on intestinal motility in the rat. *J Pharm Pharmacol*. 1989;41:534–540.
9. Breunig E, Michel K, Zeller F, Seidl S, Weyhern CW, Schemann M. Histamine excites neurones in the human submucous plexus through activation of H1, H2, H3 and H4 receptors. *J Physiol*. 2007;583:731–742.
10. Buhner S, Schemann M. Mast cell-nerve axis with a focus on the human gut. *Biochim Biophys Acta*. 2012;1822:85–92.

Successful vaccination with tetanus and diphtheria and acellular pertussis vaccine after adverse reaction to diphtheria and tetanus toxoids and acellular pertussis vaccine or diphtheria and tetanus vaccine in pediatric patients



Diphtheria, tetanus, and pertussis vaccination is an integral component of the pediatric immunization schedule, with diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine administered to patients as a primary series at 2, 4, and 6 months of age and booster doses at 15 to 18 months and 4 to 6 years of age. A single tetanus and diphtheria and acellular pertussis (Tdap) vaccine dose is recommended at 11 to 12 years old. Per the Centers for Disease Control and Prevention, contraindications to DTaP and Tdap vaccination include anaphylaxis after a previous dose or to a

vaccine component and encephalopathy within 7 days of administration.¹ Anaphylactic reactions to vaccines are rare, occurring at a rate of approximately 1 per 1 million doses administered.² Currently, there is limited information regarding the outcome of diphtheria and tetanus (DT) vaccine in patients with a history of adverse events after prior immunization. We describe 3 patients who developed symptoms consistent with IgE-mediated reactions after DT or DTaP vaccination.

Patient 1 received DT vaccine and placement of a purified protein derivative test at 4 years of age. DT immunization had been tolerated previously. Within 10 minutes of vaccine

Table 1
Results of Skin Prick and Intradermal Testing With Challenge

Variable	Patient 1	Patient 2	Patient 3
Year (patient age, y) at testing or challenge	2009 (12)	2017 (14)	2017 (11)
Skin prick testing, wheal/flare			
Saline	0 mm/0 mm	3 mm/0 mm	0 mm/0 mm
Histamine	5 × 7 mm/flare not recorded	7 mm/flare not recorded	5 mm/0 mm
DTaP 1:10 dilution	Not done	3 mm/0 mm	0 mm/0 mm
Tdap 1:10 dilution	Not done	3 mm/0 mm	0 mm/0 mm
DTaP full strength	Not done	0 mm/0 mm	0 mm/0 mm
DT full strength	0 mm/0 mm	Not done	Not done
Intradermal testing, wheal/flare			
Saline	0 mm/0 mm	0 mm/0 mm	0 mm/0 mm
DTaP 1:100 dilution	Not done	5 mm/flare not recorded	8 mm/flare not recorded
Tdap 1:100 dilution	Not done	0 mm/flare not recorded	0 mm/0 mm
DT (full strength)	4 × 4-mm wheal ^a	Not done	Not done
Challenged with			
Tdap (full strength)	Tdap vaccine, full strength, 2 doses, 10%/90%	Tdap vaccine, full strength, 3 doses, administered for 1 hour: 0.1 mL, 0.15 mL, 0.25 mL	Tdap vaccine, full strength, 1 dose
Adverse reaction	None	None	None

Abbreviations: DT, diphtheria and tetanus; DTaP, diphtheria and tetanus toxoids and acellular pertussis; Tdap, tetanus and diphtheria and acellular pertussis.

^aA 4 × 4-mm wheal and 10 × 10-mm flare that then decreased to a wheal of 2 × 2 mm 25 minutes later (likely irritant reaction).

administration, the patient developed generalized hives, pruritus, and facial swelling, which resolved in 2 to 3 days after treatment with diphenhydramine. Before booster vaccination at 12 years of age, skin prick tests (SPTs) and intradermal tests (IDTs) were performed to full-strength DT. The SPT results (wheal/flare) were as follows: saline, 0 mm/0 mm; histamine, 5 × 7 mm/flare not documented; and full-strength DT, 0 mm/0 mm. The IDT results were interpreted as negative because initial wheal and flare faded and were thought to be an irritant reaction. Of note, IDTs should be performed only at a dilution of 1:100 because higher concentrations can produce irritant reactions.³ The patient tolerated cautious challenge to full-strength Tdap vaccine in 2 divided doses (Table 1).

Patient 2 received DTaP (vaccine 4) and *Haemophilus influenzae* type b vaccines together at 18 months. He previously tolerated 3 doses of DTaP. Within 5 minutes, he developed urticaria followed in 10 minutes by difficulty breathing. He improved and was discharged several hours after treatment with diphenhydramine, oral corticosteroid, and nebulized albuterol. At 14 years of age, he presented for allergy evaluation. The SPT results were as follows (wheal/flare): saline, 3 mm/0 mm; histamine, 7 mm/not recorded; 1:10 DTaP, 3 mm/0 mm; full-strength DTaP, 0 mm/0 mm; and 1:10 Tdap, 3 mm/0 mm. The IDT results were as follows: saline, 0 mm/0 mm; 1:100 DTaP, 5 mm/not recorded; and 1:100 Tdap, 0 mm/not recorded. The patient subsequently tolerated administration of full-strength Tdap vaccine in 3 incremental doses during 1 hour in 20-minute intervals without adverse reaction (Table 1).

Patient 3 received DTaP (vaccine 5) and measles-mumps-rubella vaccines together at 5 years of age. Within 60 minutes, he developed urticaria, severe abdominal pain, emesis, respiratory distress, and lethargy. Symptoms resolved within minutes after administration of intramuscular epinephrine. He had previously tolerated measles-mumps-rubella vaccination and 4 doses of DTaP vaccine. At 11 years of age, he presented for allergy evaluation. The SPT results were as follows (wheal/flare): saline, 0 mm/0 mm; histamine, 5 mm/0 mm; 1:10 DTaP and 1:10 Tdap, 0 mm/0 mm; and full-strength DTaP, 0 mm/0 mm. The IDT results were as follows: 1:100 DTaP, 8 mm/not recorded; and Tdap, 0 mm/0 mm. He subsequently tolerated a single dose of Tdap vaccine without adverse reaction (Table 1).

In contrast to mild local reactions and fever, anaphylactic reactions to vaccines are rare. According to the Adverse Reactions to Vaccines Practice Parameter 2012 update, evaluation for

anaphylactic reactions should include skin testing with the vaccine as well as its components.²

Rarely, hypersensitivity to the microbial component itself in tetanus and diphtheria toxoids has been implicated.⁴

There are reports of anaphylaxis to natural rubber latex within the syringe or stopper of some vaccines. Some DTaP and Tdap vaccine packaging contains natural rubber latex.² We were unable to obtain the name of the manufacturer and lot number of the original vaccines administered to the 3 patients.

All 3 patients previously tolerated either DT or DTaP vaccination before their reaction, suggesting that some degree of sensitization to the vaccines could have occurred before the reactions, prompting future testing and challenge. Skin test results were difficult to interpret because of the lack of complete results recording and uneven responses to positive and negative controls but may have shown some reactivity to DTaP vaccination in patients 2 and 3. If so, the reactivity to DTaP and not Tdap vaccination may have been attributable to the larger amount of diphtheria and pertussis antigen in the former.

DTaP and Tdap vaccines contain trace amounts of residual casein in the medium, raising concern for potential allergic reaction, including anaphylaxis. However, most patients with cow's milk allergy tolerate DTaP and Tdap immunizations, supporting cautious administration rather than withholding of the vaccines.⁵ Despite a history of emesis and blood in stools associated with cow's milk ingestion and the presence of IgE to milk (specific IgE, 24.30 kIU_A/L; 18 months of age), patient 3 tolerated immunization to Tdap without difficulty.

This series demonstrates the negative predictive value of SPTs and IDTs in allowing for subsequent Tdap challenge for patients with previous adverse reaction to DT or DTaP vaccines.

IgG levels to the immunizing agents in a vaccine may be measured to determine whether a patient is adequately protected.² In this circumstance, Tdap immunization is recommended as is subsequent tetanus and diphtheria toxoids vaccination every 10 years and as indicated for wound management.¹ DT titers were not measured as part of the evaluation of our patients who were lost to follow-up.

The amount of time that elapsed between doses or why patients 1 and 2 were administered Tdap in graded doses vs a single dose for patient 3 is not documented. We speculate that this variability may have been related to clinical judgment during the procedures.

There may be some effect on tolerance mechanism by Tdap administration many years after initial reaction to DT or DTaP that allowed for successful challenge years later.

Reactions have been described to DTaP and DT, but there are limited case reports of subsequent skin testing followed by successful Tdap administration. Following the Practice Parameter Update protocol, we were able to safely perform skin testing and Tdap immunization for 3 patients with IgE-mediated reactions to DTaP or DT.

Acknowledgment

We thank Magee DeFelice, MD, Division Chief of Allergy & Immunology, Nemours Alfred I. duPont Hospital for Children, for scientific and editorial assistance throughout this project.

Neha Sirohi Campbell, MD^{*,†}
Denise Diprimio Kalman, DO^{*}

^{*}Division of Allergy & Immunology
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware

[†]Thomas Jefferson University Hospital
Philadelphia, Pennsylvania
neha.sirohi.drexel@gmail.com

References

1. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018;67(2):1.
2. Kelso JM, Greenhaw MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25–43.
3. Wood RA, Setse R, Halsey N. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007;120:478–481.
4. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol*. 2018;141(2):463–472.
5. Kattan JD, Konstantinou GN, Cox AL, et al. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. *J Allergy Clin Immunol*. 2011;128(1):215–218.

Slow graded reintroduction of oxcarbazepine for delayed maculopapular eruption



Antiepileptic drugs (AEDs) are known to be associated with delayed T-cell-mediated hypersensitivity reactions that range from maculopapular eruptions to severe cutaneous and systemic reactions. Approximately 2% to 16% of patients taking AEDs will develop a rash.^{1,2} Conditions that require AEDs are often difficult to treat and may require multiple medication trials before the optimal treatment is determined. Complicating the matter, prior and concurrent use of multiple AEDs heightens the risk of developing a drug hypersensitivity reaction (DHR). Antiepileptic drugs are frequent culprits of the most concerning form of DHRs: severe cutaneous adverse reactions.² When a reaction occurs, it is especially difficult to find an alternative because of cross-reactivity among aromatic amine AEDs, including carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and lamotrigine.¹

Pharmacogenetic studies have identified HLA-B*15:02 as a risk factor for carbamazepine- and oxcarbazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in certain Asian populations.³ Moon et al⁴ reported higher frequency of HLA-B*40:02 and HLA-DRB1*04:03 in Korean patients with oxcarbazepine-induced maculopapular eruptions. In European populations, HLA-A*31:01 is a risk factor for cutaneous hypersensitivity reactions to carbamazepine and oxcarbazepine, including maculopapular eruptions, drug eruption with eosinophilia and systemic symptoms (DRESS), and SJS/TEN.^{5,6} Risk stratification to guide future management, such as strict avoidance, direct rechallenge, or graded reintroduction, is based on history, but patch testing and HLA genotyping may also aid in cross-reactivity and guide future management.

A 16-year-old girl of European decent with paroxysmal kinesigenic dyskinesia presented to the outpatient allergy clinic for evaluation of multiple drug reactions. Paroxysmal kinesigenic dyskinesia is a condition with involuntary muscle spasms usually triggered by sudden movements or changes in position⁷ that interfered with the patient's daily activities and had been refractory

to several AEDs, including lamotrigine, tetrabenazine, and levetiracetam. The patient began a trial of oxcarbazepine, which provided life-changing symptom control. Approximately 1 week after starting the trial, she developed a pruritic, maculopapular eruption on the medial thighs and popliteal and antecubital fossae without associated systemic symptoms. Photographs provided by the family revealed small maculopapular patches. Oxcarbazepine therapy was stopped and eruption subsided in 3 to 4 days without intervention. No laboratory studies were available. At the time of presentation, she was not taking medications for paroxysmal kinesigenic dyskinesia and had made lifestyle adaptations to minimize interference with daily activities. There was no evidence of skin lesions or residual markings at the time of presentation. A similar eruption had occurred several weeks after starting lamotrigine treatment and self-resolved several days after she stopped taking the medication. She had no other occurrences of a similar rash.

Patch testing was performed using previously published and nonirritating concentrations of 10% and 30% oxcarbazepine and the potentially cross-reactive drugs carbamazepine, phenobarbital, phenytoin, and lamotrigine, all formulated from commercially available products.⁸ All test results were negative at 48 hours, 96 hours, and 1 week. Pharmacogenetic testing revealed the presence of HLA-A*02:01, HLA-A*11:01, HLA-B*15:01, HLA-B*35:01, HLA-DRB1*11:03, and HLA-DRB1*12:01, none of which are consistent with known risk alleles for carbamazepine, oxcarbazepine, lamotrigine, or other AED cutaneous hypersensitivity reactions. The benign nature of the eruption, negative patch test results, and the absence of known risk alleles supported the decision to proceed with graded reintroduction.

A protocol for slow graded reintroduction of oxcarbazepine was developed after review of available literature.^{1,9} The protocol began with an in-clinic graded challenge of 0.06 mg of oxcarbazepine (1/10,000th the final daily dose) followed by 30 minutes of observation then 0.6 mg (1/1,000th the final daily dose) followed by 60 minutes of observation. She tolerated both challenge doses and was discharged home asymptomatic with instructions for slow graded reintroduction. The daily dose was doubled every 48 hours. She successfully reached the maintenance dose without adverse events through a 27-day slow graded reintroduction of oxcarbazepine

Disclosures: Authors have nothing to disclose.

Funding Sources: Dr Phillips is supported by grants P50 GM115305, P30 AI110527, R34 AI136815, and R21 AI139021 from the National Institutes of Health and the National Health and Medical Research Council of Australia.