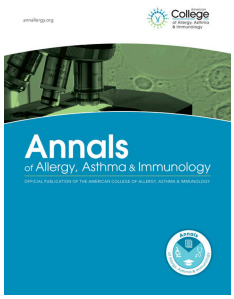
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Idiopathic Post-Prandial Diarrhea Responsive to Anti-histamines

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Chronic diarrhea affects 4-5% of adults [1]. Post-prandial diarrhea (PPD) represents a subset of these patients. Here, we present five cases of idiopathic PPD associated with concurrent dermatographia and chronic urticaria. The diarrhea occurred consistently and exclusively after meals, absent identifiable specific food allergens or food intolerances, and was mitigated by daily pre-treatment with H1 and H2 antagonists. We report herein the clinical presentations of these patients along with laboratory and other test results listed in Table 1.

A 29-year-old woman with chronic idiopathic urticaria presented with the chief complaint of 8-weeks of watery diarrhea beginning consistently 2-3 hours after meals, regardless of specific foods ingested. She reported past episodes of localized oral angioedema after ingestion of mango and tilapia, not associated with diarrhea. General physical examination was normal except for dermatographia. As shown in table 1, specific IgE to food allergens were negative and GI work up was normal. Diarrhea failed to improve with a lactose free diet and other elimination diets. Post-prandial diarrhea was entirely prevented by administration of cetirizine 10 mg q AM and famotidine 60 mg q AM.

A 26-year-old male reported a 13-year history of watery diarrhea after ingesting any meal or snack and experienced up to 10 PPD episodes/day. He also presented with concurrent untreated chronic idiopathic urticaria and pruritus. Physical exam was normal except for dermatographia. Serum specific IgE to suspected food allergens were negative and diarrhea persisted despite lactose elimination and avoidance of suspected foods. Serum tryptase and anti-tissue transglutaminase IgA (tTG IgA) were not elevated; 24-hour urinary prostaglandin F2α was normal (Table 1). Following initiation of cetirizine 10 mg BID, ranitidine 150 mg BID and doxepin 10mg at bedtime, the patient experienced 3-4 loose formed stools/day.

A 55-year-old female with chronic idiopathic angioedema presented with a main complaint of PPD unassociated with specific food triggers, that were accompanied by flushing and headaches in the past year. Physical exam revealed dermatographia. Serum tryptase and anti-tTG IgA as well as 24-hour urine n-methylhistamine and prostaglandin F2α were normal (Table 1). Gastroenterology work up was normal except for incidental finding of lymphocytic colitis on colon biopsy. Following treatment with levocetirizine

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10mg BID and ranitidine 150 mg BID, she experienced one daily well-formed stool in lieu of 2-3 post-prandial watery diarrhea events per day and without facial flushing.

A 43-year-old male with a history of chronic urticaria presented with one year of daily PPD, nasal congestion and facial flushing. He suspected this was associated with wheat ingestion, but diarrhea was not mitigated by wheat or lactose elimination diets. Physical exam was normal except for dermatographia. Serum specific IgE to food allergens, serum tryptase and anti tTG IgA were not elevated (Table 1). Following initiation of cetirizine 20 mg BID and ranitidine 150 mg BID, PPD decreased to 2-3 events per month.

A 63-year-old woman presented with 3-years of abdominal cramps and watery diarrhea occurring consistently 2 hours after eating, often associated with transient lip numbness, facial flushing and erythema of the chest. Unremitting post-prandial diarrhea resulted in a 20-lb. weight loss. The patient has a prior history of episodic facial and lip angioedema and a family history of hypothyroidism. No specific food triggers could be identified and the PPD did not respond to wheat or lactose free diets. She had a remote history of gastritis and gastric ulcer treated successfully 3 years earlier. Colonoscopy was normal. Physical examination revealed dermatographia. Serum tryptase, urinary mast cell mediators, food specific IgE and celiac serologic screening were normal (Table 1). Following initiation of fexofenadine 180 mg BID and ranitidine 150 mg BID, PPD and abdominal cramp events decreased to 3-4 meals per month from daily after each meal before treatment.

Patients were referred over a one-year period to a single allergy group practice. These cases characterize a previously undefined syndrome of: 1) idiopathic watery diarrhea occurring within 3 hours after eating, absent specific food allergies or intolerances; 2) current or remote chronic idiopathic urticaria/angioedema; 3) dermatographia; and 4) mitigation or prevention of PPD in response to daily treatment with H1 and H2 antihistamines. It is noteworthy that all these patients presented with PPD as their main complaint. Although all had dermatographia with active or prior history of chronic urticaria and/or angioedema, none had received daily H1 antihistamines or oral cromolyn. No triggering event

including viral illness was identified in any case. Although diarrhea has long been recognized as a GI manifestation of a variety of mast cell disorders [2], PPD occurring in patients with dermatographia and chronic urticaria that is not associated with specific food allergy or food intolerance has not been described in the medical literature. Prick skin testing to food allergens was not possible in these cases due to dermatographia. Specific food allergy or intolerances to wheat and lactose, however, were excluded by non-elevated serum specific IgE for multiple foods and lack of benefit from elimination diets. Underlying GI disorders including inflammatory bowel disease (IBD) were excluded by grossly normal colonoscopies. Celiac disease was excluded based on serologic testing.

In patients presenting with PPD, one must consider in the differential diagnosis: maldigestion due to bile acid malabsorption; celiac disease; IBD; irritable bowel syndrome with diarrhea (IBS-D); systemic mastocytosis (SM); and mastocytic enterocolitis. Bile acid malabsorption was excluded based on the absence of obstructive jaundice and IBD was excluded by colonoscopy. Celiac disease were excluded by negative tissue transglutimase IgA (see Table 1), while patients were ingesting gluten. IBS-D does not usually present with diarrhea exclusively after eating and affected patients do not consistently respond to anti-histamines [3-5]. These patients cannot be classified as having mast cell activation syndrome (MCAS)[2] or SM using accepted criteria because none exhibited elevated tryptase or urinary biomarkers during their symptomatic periods prior to initiation of treatment. Furthermore, although GI symptoms in MCAS may include diarrhea or abdominal pain, these often occur spontaneously in MCAS and not exclusively after eating as observed in our patients. It is noteworthy that these patients exhibited mild cutaneous symptoms (urticaria, flushing) and not anaphylactic manifestations characteristic of MCAS. Our patients cannot be classified as "mastocytic enterocolitis", a pathological finding described by Jakate et al in patients presenting with chronic diarrhea, in whom diarrhea was not characterized as being post-prandial nor responsive to antihistamines [6].

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 postprandial diarrhea. Histamine has known

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effects on bowel motility and all four histamine receptors have been detected in gastrointestinal tissues [7,8]. In human studies, H1, H2 and H4 receptor stimulation was demonstrated to increase GI motility [9,10] The physiologic role of mast cells in the GI 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 H1R and H2R stimulation by histamine mediates PPD. It is unknown if other mast cell mediators or H4 receptors also mediate elicitation of PPD in patients with this syndrome.

This series of cases describes a previously unrecognized clinical entity of idiopathic postprandial diarrhea responsive to antihistamines. Antihistamine responsive PPD is seen in patients with chronic idiopathic urticaria and/or dermatographia and can be distinguished from MCAS. Thus, all patients with chronic urticaria or angioedema should be queried about GI symptoms. This syndrome should also be considered in the differential diagnosis of patients presenting with food intolerance after excluding food allergy and other GI disorders. Future studies are necessary to identify the prevalence and natural history of this syndrome and to evaluate optimal treatment regimens.

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Table 1: Clinical characteristics of patients with chronic histaminergic diarrhea.

Patient	**1**	**2**	**3**	**4**	**5**
Age	29	26	55	43	63
Sex	F	M	F	M	F
Serum Specific IgE	Normal Egg white, Mango, Milk, Tomato, Shrimp, Soybean, Peanut, Wheat and Codfish.	Normal Egg white, Milk, Tomato, Shrimp, Soybean, Peanut, Wheat and Codfish.	Not done	Normal Egg white, Milk, Tomato, Shrimp, Soybean, Peanut, Wheat and Fish.	Normal Egg white, Milk, Peanut, Wheat, tree nut, Strawberry, Banana
GI work up	Normal upper endoscopy & colonoscopy	Normal upper endoscopy & colonoscopy	Normal upper endoscopy & colonoscopy Colonic biopsy - lymphocytic colitis	Not done	Upper endoscopy showed gastritis and ulcers; Normal colonoscopy; normal colon & small bowel biopsies
Random serum tryptase	Not Done	4.6 mcg/L	5.6 mcg/L	3.5 mcg/L	2.8 mcg/L
Urinary prostaglandin F2α levels	Not Done	1467 pg/mg Cr (Normal: <5205)	<948 pg/mg Cr (Normal: <5205)	Not done	1485pg/mg Cr (Normal: <5205)
Urinary n-methylhistamine	Not Done	Not Done	141 mcg/g (Normal: 30-200)	Not done	142mcg/g (Normal: 30-200)

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Anti-tissue transglutaminase IgA	Not done	Normal	Normal	Normal	Normal

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