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Letters

High prevalence of eosinophilic esophagitis and hypogammaglobulinemia in patients with Pitt-Hopkins syndrome

Pitt-Hopkins syndrome (PTHS) is a rare neurologic disorder associated with severe intellectual disability, developmental delay, and episodes of hyperventilation and apnea caused by mutations in the transcription factor 4 (*TCF4*) gene on chromosome 18q21.[1,2] Although previous studies have demonstrated a high prevalence of gastrointestinal symptoms in patients with PTHS, including constipation (80%), gastroesophageal reflux disease (37.6%), and excessive burping (28.7%),[3] an association with eosinophilic esophagitis (EoE) has not yet been described. Furthermore, although a recent case report described a patient with PTHS and common variable immunodeficiency,[4] the association between PTHS and recurrent infections remains poorly understood. The objective of this study was to assess the prevalence of gastrointestinal symptoms, EoE, and hypogammaglobulinemia among patients with PTHS.

We conducted a cross-sectional, digital survey of parents/guardians of individuals with PTHS between January and March 2024. The survey was created and disseminated in collaboration with the PTHS Research Foundation. Participants were asked questions about baseline demographics and coexisting immunodeficiency diagnoses. The presence of allergic conditions was assessed using questions derived from the 2021 National Health Interview Survey. The Pediatric Eosinophilic Esophagitis Symptom Score version 2.0[5] was used to assess the frequency and severity of gastrointestinal symptoms consistent with EoE. For the Pediatric Eosinophilic Esophagitis Symptom Score questions, responses of "sometimes," "often," and "almost always" were classified as positive. Variables were compared using Mann-Whitney *U* or Fisher exact tests, as appropriate, and analyses were completed in Stata. The study was approved by the University of Virginia Institutional Review Board for Health Sciences Research.

A total of 109 responses were reported at study closure. After excluding incomplete and duplicate responses, 76 unique responses were included. The baseline demographics of the respondents are described in Table 1 (median age 8.0 years, 50.7% male, 75.7% non-Hispanic White) and are similar to those previously reported in studies of PTHS.[3] A total of 17 participants (22.7%) reported a history of frequent infections. Furthermore, 8 participants (10.7%) reported a history of low IgG levels and 9 (56%) reported abnormal vaccine responses. One patient (1.3%) reported a diagnosis of common variable immunodeficiency.

In addition, 67.1% of the survey respondents reported a history of allergic conditions, including allergic rhinitis (40%), food allergy (26.7%), atopic dermatitis (31.1%), and asthma (13.7%). A confirmed diagnosis of EoE was reported in 6 respondents (8%). The most frequently reported gastrointestinal symptoms among those with EoE were as follows: stomach/belly aches, eating more slowly than others, heartburn, needing drinks to swallow food, and eating less than others. In respondents without a diagnosis of EoE, 10.3% to 56.7% reported symptoms consistent with this condition (Table 1). In particular, 9 (13.2%) non-EoE respondents reported that "food gets stuck." Only 24.6% of the respondents with gastrointestinal symptoms consistent with EoE reported having had an esophagogastroduodenoscopy (EGD), which is required to diagnose this condition. Of respondents who had an EGD, 24% reported taking a proton pump inhibitor and 53% reported eliminating some form of dairy or wheat from their diet.

In this study, we found that there was a high prevalence of hypogammaglobulinemia and gastrointestinal symptoms among patients with PTHS. In addition, a higher proportion of patients with PTHS reported other allergic conditions than is found in the general population—particularly food allergy and atopic dermatitis. Moreover, our finding that 8% of the PTHS population has a diagnosis of EoE is markedly higher than the estimate of 0.14% reported in the general population.[6] Among those without a diagnosis of EoE, many patients reported symptoms consistent with this condition, and most had never had an EGD. Because proton pump inhibitor use and diary/wheat avoidance are both treatments for EoE, it is possible that these interventions are controlling undiagnosed EoE, even among respondents who had had an EGD. These data suggest that EoE may be underdiagnosed in this population. Moving forward, both patients and providers should consider evaluating for these diagnoses in patients with PTHS presenting with allergic and gastrointestinal complaints.

PTHS can be caused by either a mutation in the *TCF4* gene or a deletion of this chromosome region (18q21). Interestingly, a cluster of genes encoding a family of protease inhibitors—SERPINs from clade B (SERPINB)—is located on chromosome 18q21.3. A recent genome-wide study identified this locus as conferring an increased risk for food allergy.[7] Moreover, these proteins are expressed in the esophageal epithelium, and their expression is down-regulated in patients with EoE compared with normal controls.[8] Mutations in *SERPINB3* have been identified in patients with EoE, and it is therefore thought that this family of proteins could potentially be involved in the pathogenesis of EoE. Although the exact function of this family of proteins is unclear, they appear to play a role in restoring the integrity of the esophageal epithelial barrier. It would be interesting in future studies to find whether patients with coexisting PTHS and EoE have differences in *SERPINB3* gene expression compared with those with PTHS alone.

TCF4, which is also known as immunoglobulin transcription factor 2, binds to the immunoglobulin enhancer region (E-box) and activates the transcription of immunoglobulin genes. In addition, previous murine models have revealed that *Tc4* is a critical regulator of B-cell and plasma cell development in the germinal centers.[9] It is,

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Table 1
Clinical Characteristics of the Population Stratified by EoE Status

Characteristic	EoE (n = 6)	Non-EoE (n = 71)	*P* value[b]
Age (y)[a]	5.5 (4-10)	8.0 (4-19)	.64
Male sex	3 (50.0)	36 (51.4)	.63
Race/Ethnicity			1.0
Non-Hispanic White	6 (100)	50 (74.6)	
Non-Hispanic Black	0 (0.0)	0 (0.0)	
Hispanic	0 (0.0)	5 (7.5)	
Asian	0 (0.0)	3 (4.5)	
Multiracial	0 (0.0)	6 (9.0)	
Other	0 (0.0)	3 (4.5)	
Atopic conditions			
Asthma	**3 (50.0)**	**7 (10.4)**	**.03**
Food allergy	**4 (66.7)**	**16 (23.2)**	**.04**
Allergic rhinitis	4 (66.7)	26 (37.7)	.21
Atopic dermatitis	**5 (83.3)**	**18 (26.5)**	**.009**
Any atopic condition	6 (100)	45 (59.2)	.17
Immunodeficiency			
Frequent infections	4 (66.7)	13 (18.8)	.02
Abnormal vaccine response	2 (33.3)	7 (10.3)	.15
Low IgG	2 (33.3)	6 (8.7)	.12
Any immunodeficiency	1 (16.7)	8 (11.6)	.54
Symptoms			
Stomach/belly aches	6 (100)	39 (56.7)	.08
Eat slower than others	5 (83.3)	34 (50.0)	.20
Heartburn	**4 (66.7)**	**21 (33.3)**	**.05**
Need drinks to swallow food	4 (66.7)	20 (30.3)	.09
Eat less than others	4 (66.7)	20 (29.8)	.08
Trouble swallowing	3 (50.0)	21 (30.8)	.38
Chest pain	2 (40.0)	12 (19.0)	.27
Nausea	2 (40.0)	12 (19.7)	.28
Food gets stuck	2 (33.3)	9 (13.2)	.16
Regurgitation	1 (20.0)	11 (16.2)	1.0
Vomit	1 (16.7)	7 (10.3)	.50

Abbreviation: EoE, eosinophilic esophagitis.
Significant values are denoted in bold.
NOTE. All values expressed as number (percentage), unless otherwise stated.
[a]Median (IQR).

therefore, possible that a variant in this gene could affect the humoral immune response.[4] Beyond the implications for patients with PTHS, understanding the impact of the *TCF4* gene on the pathogenesis of immune-mediated conditions may provide valuable insight into the development and propagation of immune responses in the general population.

Limitations of this study include the small number of patients and the sampling of subjects from an advocacy group, which may introduce volunteer bias. As a cross-sectional study, the results may also be influenced by unmeasured confounders. Finally, symptoms and their frequencies were provided by parental assessment, as patients with PTHS are often unable to verbally self-report symptoms. Therefore, these parental assessments may not be as accurate as self-reported symptoms.

Despite these limitations, this is the largest immunology study to date in a population of patients with PTHS, and our results demonstrate an increased prevalence of atopic conditions—including EoE—and immunodeficiency among patients with this disease. Providers should be aware of these associations when treating patients with PTHS and consider diagnostic testing for EoE and immunodeficiency when appropriate.

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References

1. Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, et al. Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). *Am J Hum Genet*. 2007;80(5):994–1001.
2. Amiel J, Rio M, de Pontual L, Redon R, Malan V, Boddaert N, et al. Mutations in TCF4, encoding a Class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. *Am J Hum Genet*. 2007;80(5):988–993.
3. de Winter CF, Baas M, Bijlsma EK, van Heukelingen J, Routledge S, Hennekam RCM. Phenotype and natural history in 101 individuals with Pitt-Hopkins syndrome through an internet questionnaire system. *Orphanet J Rare Dis*. 2016;11:37.
4. Malik S, Jeanpierre L, Cianferoni A, Ruffner M, Sullivan KE. A patient with Pitt—Hopkins syndrome with concomitant common variable immunodeficiency. *Am J Med Genet A*. 2024;194(4):e63490.
5. Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, et al. Pediatric Eosinophilic esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *J Allergy Clin Immunol*. 2015;135(6):1519–1528.e8.
6. Thel HL, Anderson C, Xue AZ, Jensen ET, Dellon ES. Prevalence and costs of eosinophilic esophagitis in the United States. *Clin Gastroenterol Hepatol*. 2025;23(2):272–280.e8.
7. Marenholz I, Grosche S, Kalb B, Ruschendorf F, Blumchen K, Schlags R, et al. Genome-wide association study identifies the SERPINB gene cluster as a susceptibility locus for food allergy. *Nat Commun*. 2017;8(1):1056.
8. Kottyan LC, Davis BP, Sherrill JD, Liu K, Rochman M, Kaufman K, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet*. 2014;46(8):895–900.
9. Wöhner M, Tagoh H, Bilic I, Jaritz M, Poliakova DK, Fischer M, et al. Molecular functions of the transcription factors E2A and E2-2 in controlling germinal center B cell and plasma cell development. *J Exp Med*. 2016;213(7):1201–1221.