

Clinical Communications

High prevalence of developmental disorders in pediatric eosinophilic esophagitis (EoE): A single-center observational study

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Clinical Implications

- Children with eosinophilic esophagitis (EoE) have a high prevalence of Autism Spectrum Disorder and other developmental disorders, which is unique to EoE, suggesting that this may be due to shared immunologic pathways or overdiagnosis.

Eosinophilic esophagitis (EoE) is an emerging disease that appears to be increasing in prevalence, affecting approximately 1/1000 people in the United States.¹ It has recently been reported that individuals with EoE have an increased prevalence of autism spectrum disorder (ASD) and developmental delay.² ASD and other developmental disorders (DD) are common in children, affecting 0.5% to 3% and 17.8% of US children, respectively.³ Like EoE, these disorders are more common in males and are hypothesized to be related to immune system dysregulation.⁴ In this study, we sought to determine the prevalence of ASD and DD in our pediatric EoE population and examine whether children with comorbid ASD/DD have unique clinical characteristics compared with those with solely EoE.

A cross-sectional study of pediatric (≤ 18 years old) patients with EoE seen at the University of Virginia (UVA) from October 2015 to August 2019 was performed. Individuals with EoE were identified from the UVA Electronic Health Record (EPIC) using International Classification of Diseases, Tenth Revision (ICD-10) (K20.0) codes. A retrospective chart review was then performed to confirm the diagnosis of EoE according to consensus guidelines.⁵ The diagnoses of ASD and DD were defined per physician diagnosis, also using ICD-10 codes, as defined in this article's Online Repository at www.jaci-inpractice.org. Information on demographics, prematurity, presenting symptoms, comorbid atopic conditions (allergic rhinitis, asthma, eczema, self-reported food allergy, total IgE, allergic sensitization), and EoE measures (peak serum absolute eosinophil count, peak eosinophils/high-power field on biopsy, and peak EoE Endoscopic Reference Scores) was extracted from the medical record. As a standard definition does not yet exist for "disordered eating," this was defined as the presence of learned maladaptive behaviors, immature diet selection, or oral aversion. For comparison, the prevalence of ASD/DD among children with allergic rhinitis, asthma, atopic dermatitis, and type 1 diabetes was also assessed using ICD-10 codes. Differences in categorical variables were compared using χ^2 tests, and differences in means were compared using Mann Whitney *U* tests

(Stata 14.2, College Station, TX). Use of the data was approved by the UVA Institutional Review Board.

A total of 266 children with a diagnosis of EoE were identified, of whom 229 were confirmed to have EoE on chart review (median age at diagnosis, 6.5 years; interquartile range, 2–11 years). In the final study population, 29 children had a diagnosis of ASD (12.7%), and 70 children had a diagnosis of DD (30.6%), as shown in Table I. Children with ASD were more likely to be male (26 [90%] vs 139 [70%]; $P = .02$) and to present with disordered eating (13 [46%] vs 38 [19%]; $P = .001$) than those with EoE alone. Similarly, children with DD were more likely to be male (59 [84%] vs 106 [67%]; $P = .006$) and to present with disordered eating (25 [36%] vs 26 [16%]; $P = .001$) than those with EoE alone. Children with DD also presented with EoE earlier than those without DD (5.3 vs 7.5 years; $P = .001$). There was no difference in race, other presenting symptoms, allergic conditions, or EoE clinical characteristics between those with and without ASD/DD (Table II). The prevalence of ASD/DD in children with other IgE-mediated atopic disorders and in type 1 diabetes mellitus was lower than in children with EoE (Table I).

In this retrospective study of 229 children with EoE at an academic institution, we found that there was a high prevalence of both ASD and DD compared with the national prevalence (0.5%–3% and 17.8%).³ This was unique to EoE, as the prevalence of ASD/DD in children with other atopic disorders and type 1 diabetes mellitus was similar to national estimates. We further found that children with ASD/DD and EoE were more likely to be male, to present with EoE at an earlier age, and to endorse the symptoms of disordered eating. However, there was no difference in underlying allergic disease or clinical characteristics of EoE.

Our finding that children with EoE have a high prevalence of ASD/DD is consistent with data from other academic centers,² but to our knowledge, this is the first study to demonstrate that this is uniquely true with EoE, compared with other allergic and nonallergic disorders. Previous studies have similarly found that children with ASD/DD have a high prevalence of EoE⁶ and other self-reported allergic conditions.⁷ Although it is possible that this high prevalence of EoE is due to increased access to health care in medically complex children, it is also possible that there are shared immunologic pathways that promote the development of these conditions. Evidence for this hypothesis includes the observation that, compared with matched controls, unstimulated peripheral blood mononuclear cells from children with ASD produced higher levels of the Th2-associated cytokines IL-4, IL-5, and IL-13, which are known to be associated with EoE.⁸ Furthermore, a murine model of IL-4 deficiency demonstrated increased social interactions compared with wild-type mice, which suggests an interaction between social behavior and adaptive immunity.⁹ The shared role of type 2 allergic inflammation in the pathogenesis of both disorders supports the possibility of a link between them and warrants further study.

In this study, children with both ASD/DD and EoE were more likely to present with disordered eating than children without ASD/DD. Feeding disorders are common in children with ASD, affecting up to 75% of this population. It is thus possible that the

TABLE I. Prevalence of ASD and DD in children with EoE and other disorders

	Total	With ASD	With DD
EoE	229	29 (13)	70 (31)
Allergic rhinitis	15,772	549 (3)	2810 (18)
Asthma	13,829	450 (3)	2492 (18)
Atopic dermatitis	6,336	122 (2)	945 (15)
Type 1 diabetes	613	25 (4)	70 (11)

ASD, Autism spectrum disorder; DD, developmental disorder; EoE, eosinophilic esophagitis.
Values are depicted as n (%).

TABLE II. Differences in characteristics among children +ASD/DD and –ASD/DD and EoE

	ASD n = 29 (12.7)	No ASD n = 200 (87.3)	P value	DD n = 70 (30.6)	No DD n = 159 (69.4)	P value
Age at presentation (y)*	5 (3-8)	7 (2-11)	.28	4 (2-8)	8 (3-11)	.003
Male sex	26 (90)	139 (70)	.02	59 (84)	106 (67)	.006
Race/ethnicity			.85			.66
Non-Hispanic white	23 (79)	166 (83)		60 (86)	129 (81)	
Non-Hispanic black	3 (10)	15 (8)		5 (7)	13 (8)	
Other	3 (10)	19 (10)		5 (7)	17 (11)	
Atopic conditions						
Asthma	16 (55)	96 (48)	.47	33 (47)	79 (50)	.72
Allergic rhinitis	21 (72)	130 (65)	.43	49 (70)	102 (64)	.39
Eczema	10 (36)	89 (45)	.38	29 (42)	70 (44)	.78
Food allergy	7 (26)	58 (29)	.91	14 (21)	51 (32)	.10
Presenting symptoms						
Dysphagia	11 (39)	83 (42)	.82	23 (33)	71 (45)	.11
Food impaction	2 (7)	33 (17)	.20	7 (10)	28 (18)	.15
Abdominal pain	15 (54)	91 (46)	.42	27 (39)	79 (50)	.14
Vomiting	12 (43)	100 (50)	.48	36 (52)	76 (48)	.54
Poor weight gain/FTT	4 (14)	33 (17)	.77	13 (19)	24 (15)	.48
Disordered eating	13 (46)	38 (19)	.001	25 (36)	26 (16)	.001
EoE measurements						
ERFES score*	2.5 (2-3)	3 (2-3)	.73	3 (2-3)	3 (2-4)	.99
Eos/hpf*	40 (30-50)	37.5 (25-50)	.14	35 (25-45)	40 (25-50)	.37
Serum AEC*	325 (245-605)	505 (300-782)	.04	420 (270-690)	500 (300-780)	.17
Total IgE†	224 (132-379)	152 (113-204)	.43	122 (73-205)	177 (129-244)	.15

AEC, Absolute eosinophil count; ASD, autism spectrum disorder; CI, confidence interval; DD, developmental disorder; EoE, eosinophilic esophagitis; Eos/hpf, eosinophils/high-power field; ERFES, EoE Endoscopic Reference Score; FTT, failure to thrive; IQR, interquartile range.

Values are depicted as n (%) unless otherwise stated.

Bold values are statistically significant ($P < .05$).

*Median values (IQR).

†Geometric mean (95% CI).

increase we found in disordered eating is due to common behaviors in patients with ASD, such as food refusal and texture avoidance. It is also possible that the increase in disordered eating among the patients with DD is due to the fact that they were diagnosed with EoE at an earlier age than those without DD, when symptoms of feeding dysfunction predominate. However, our findings also support those of Heifert et al⁶ that providers should have an increased suspicion of EoE in children with ASD/DD who present with disordered eating. Identifying and treating an underlying medical disorder that could contribute to these symptoms could ultimately enhance the efforts to treat feeding disorders in children with these conditions.

This analysis is limited by the retrospective study design and reliance on provider documentation and ICD-10 codes. This was addressed by performing an in-depth chart review to confirm the

diagnoses of EoE and ASD/DD, but further misclassification could have occurred with other included variables. We were also unable to assess the prevalence of ASD/DD in other non-IgE-mediated gastrointestinal conditions due to limitations of using these ICD-10 codes and the small number of cases in our study population. As these conditions may be more appropriate comparison groups, it would be worthwhile to assess this in future, larger studies. This study is further limited by the potential for selection bias, as children with ASD/DD may have increased access to health care resources and endoscopic evaluation for EoE when presenting with disordered eating. This may have resulted in an overestimate of the prevalence of ASD and DD in this EoE population. We also acknowledge that this study was performed in a single, tertiary referral center and may not represent what is seen in community settings.

Despite these limitations, this is the first study to provide a comprehensive analysis of patients presenting with ASD/DD and EoE in the pediatric population. We found that the prevalence of ASD and DD in the pediatric EoE population is high, and whether this is due to shared immunologic and/or genetic pathways, or increased recognition of these disorders, is unknown and warrants further study.

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This work was funded by the National Institutes of Health through the following grants: K23AI123596 and R21AI151497.

Conflicts of interest: E. C. McGowan has received grants from the National Institutes of Health, the American Academy of Allergy, Asthma, and Immunology, and Food Allergy Research and Education; and consulting fees from Shire. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 23, 2020; revised September 14, 2020; accepted for publication September 16, 2020.

Available online ■ ■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2020.09.032>

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ONLINE REPOSITORY

Individuals with eosinophilic esophagitis were identified via the University of Virginia Electronic Health Record (EPIC) using the International Classification of Diseases, Tenth Revision (ICD-10) code (K20.0). The following ICD-10 codes were also

used: ASD (F84), developmental disorders of speech and language, scholastic skills, motor function, psychological development, and pervasive developmental disorders (F80, F81, F82, F88-89), allergic rhinitis (J30.1-2, J30.8-9), asthma (J45), atopic dermatitis (L20), and type 1 diabetes (E10).