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Prevalence of IgE mediated food allergy in children with inflammatory bowel disease Authors:

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To the Editor,

There has been a rapid increase in the number of children with both inflammatory bowel disease (IBD) and IgE mediated food allergy (FA) (1, 2). Similar factors have been implicated in their aetiology. Dysbiosis of the microbiome causes dysregulation of the immune system promoting the development of conditions such as IBD and FA (3). Abnormal intestinal barrier function is associated with both conditions (4, 5). The Th2 pathway is upregulated in both ulcerative colitis (UC) and FA with Th1 cytokines playing more of a central role in the pathogenesis of Crohn's disease (CD). In both IBD and FA, there are increased Th 17 cells and downregulation of Tregs (5). Very early onset IBD (< 2years) has been associated with dysfunctional interleukin 10 signalling (6). IL-10 is secreted by Treg cells which promote tolerance to food antigens (7). Despite the apparent overlapping pathogenesis and parallel increases in childhood prevalence of IBD and FA, data on coexisting prevalence is lacking. A weakness of existing studies is the dearth of supportive clinical evidence of FA to support serological findings of food sensitisation.

We hypothesise that the prevalence of IgE mediated FA in Irish children with IBD is greater than the prevalence of FA in the general population. In this study, we aim to report the prevalence of ever having a FA in children with IBD in Ireland and compare this to the published prevalence data of FA in Irish children.

Methods

The "Determinants and outcomes of children and adolescents with IBD" (DOCHAS) has established a prospective cohort of all Irish children (0-16 years) with newly diagnosed IBD in Children's Health Ireland at Crumlin (CHI), Ireland. Data on children diagnosed with IBD from December 2016 to August 2019 is presented here.

A diagnosis of IBD was made according to the revised Porto criteria, including the new diagnostic subtype of atypical ulcerative colitis (UC), which is clinically similar to typical UC (8) but unique to paediatric IBD.

Questionnaires were completed on behalf of all confirmed cases of IBD. The questions relating to FA were developed by a paediatric allergist and gastroenterologist to identify a current or previous history suggestive of IgE mediated food allergy (supplemental data. As the prevalence of FA changes with age, and the median age of diagnosis of IBD is much higher than that of FA, it was important to capture both a current and a previous history of FA.

In order for an adverse food reaction to be considered, it first had to be related to a common food allergen (peanut, treenut, milk, egg, fish, crustaceans, seeds, soya) or emerging regional allergens (tropical fruit, pine nut) The diagnosis was further strengthened as the history of reaction had to include symptoms suggestive of an IgE-mediated reaction (9, 10).

Results

1. Incidence of IBD in Ireland

In Ireland, 278 children, 16 years and under, were diagnosed with IBD over 33-months. This equates to an annual unadjusted incidence of 8.8 per 100,000 children per year.

2. Demographic and clinical characteristics of the children with IBD

Types of IBD were defined by the Porto criteria: Crohns Disease (CD) (N= 153,55%), UC (N=94, 34%), atypical UC (N= 18, 6%) and IBD-Undefined (N= 13, 5%). Median age at diagnosis was 12.8 years (0-4 years: N=3(1.4%), 5-9 years: N=43 (20.6%) and 10-17 years: N=163 (78%).

3. Prevalence of food allergy in children with IBD

Twenty-three (8.3%) reported ever having a FA. However, on review of the foods and symptoms of the reactions, 5 /23 cases were considered not to be true IgE mediated FA. Food implicated in these cases were berries, sweet potato, cinnamon and lactose; IgE mediated symptoms were not documented. Therefore, we report the overall prevalence of IgE mediated FA in this population as 6.5% (95% CI 4.1 to 10).

4. Clinical characteristics of children with IBD and FA.

Table 1 shows the characteristics of the 18 children with FA. The most common foods were peanuts (n=3) and egg (n=3). Four children had outgrown a FA (egg or milk) but all had remaining FA. The symptom profile of the allergic reactions for 4 of the cases were not documented. However, these cases involved egg, peanut, milk and nuts which are the most prevalent IgE mediated food allergens in Ireland (11). There was no statistically significant difference between the baseline characteristics of children with or without FA.

5. Food allergy in children with UC compared to CD.

There were similar proportions of children with UC (N=9) with FA compared to CD (N=8).

Proportionally, there was more FA in the children with UC (typical and atypical), 9/112 (8%, 95% CI: 3.7 to 14.7) compared to CD 9/153 (5.9%, 95% CI: 2.7 to 10.8). Of the 9 children with UC, 5 had atypical UC subtype. There was no statistically significant difference in the number of food allergy cases in UC compared to CD (Difference 2.1%, 95% CI: -4 to 8.3).

Discussion

There are very few studies looking at the coexistence of IBD and FA in childhood. Those that have been published report high prevalence of FA. However, these studies have small numbers of subjects. This study's main strength is that it represents an unselected national paediatric IBD cohort and thus includes all children diagnosed with IBD in the Republic of Ireland during the 33-month period of the study.

Published studies, to date, describe food sensitisation rates rather than clinical allergy. Feuille et al, in USA, report a high rate of FA (25%) among 89 paediatric IBD cases by self-reporting on questionnaires (12). In 28 Iranian children with IBD, FA as diagnosed by a positive skin prick test, was found in 17 (60.7%) (13). Diagnosis of IgE mediated food allergy should be based foremost on appropriate clinical history. In this study, the diagnosis of food allergy is determined on a

reported history of symptoms, highly suggestive of food allergy and of a reaction to recognised food allergens (10).

It is difficult to compare published studies due to differences in definitions of allergy, study populations and age groups, geographic variation and methodologies utilised . As such, prevalence rates of FA in healthy children vary across the world; 8% USA (3), 2-5.3% UK (14) and 3.8-11% Australia (1) .

This study reports an estimated FA prevalence of 6.5% (95% CI 4.1 to 10) in children with IBD in Ireland. This is considerably lower than previously published data in IBD as outlined above. These new figures are highly representative of the Irish paediatric IBD cohort.

The 6.5% FA prevalence rate in Irish children with IBD reported here is slightly higher than the 4.45% prevalence of FA reported by Kelleher et al in healthy Irish 2-year olds (11). Kelleher et al used both clinical history and oral food challenge (OFC) to define their cohort of allergic children. A limitation of this questionnaire study was that the DOCHAS project was not structured to facilitate OFCs.

In the absence of confirmatory testing, it is possible that there has been over reporting of FA. This could explain why the prevalence in the IBD cohort is slightly higher than the Irish population. Evidence of sensitisation in those with a history suggestive of FA would have strengthened the diagnosis in this study. In contrast, a weakness of most studies in this area, is the lack of supportive clinical evidence of food allergy to support the serological findings of sensitisation in children with IBD. It is important to highlight that evidence of sensitisation, in the absence of a clinical history can also overestimate prevalence as seen in the other studies described above.

Small sample size is a limitation of this study. In total only 18 cases of IgE mediated food allergy were identified in this cohort of IBD patients. This study is a good basis for future studies with larger cohorts to see if there is really any difference in prevalence with the general population As this study already includes the entire Irish cohort of children with IBD, future studies would need to include more populated nations or multinational studies in order to achieve a larger sample size. Despite their overlapping pathogenesis, this study did not show a significant increase in FA in children with IBD. Age may play an important role here. Median age of onset of FA occurs much earlier than IBD and therefore environmental factors (e.g. diet, microbiome, antibiotic use, vitamin D) may vary at different time points in a child's life. Overall, there were only 3 children with IBD

in the early onset (0-4 years) group, with 1 having FA. Genetic as well as epigenetic factors also have an important role in pathogenesis and most likely different in IBD and FA.

Although not reaching statistical significance, proportionally, more cases of FA were identified in those children with UC than in those with CD, with 27% of all FA children presenting with atypical UC. UC and CD have been shown to have differential cytokine profiles with UC associated with a TH2 cytokine environment. Atypical variants of UC have only been described since 2013 and present with macroscopic and microscopic features of UC that are found in paediatric but not adult patients (8). Larger studies will also be required to identify whether there is a real difference between the prevalence of FA in UC versus CD perhaps driven by an alternative cytokine milieu. The early onset IBD group will also be an interesting group to study in larger numbers. Other atopic conditions could also be studied.

To conclude, this study reports an estimated FA prevalence of 6.5% (95% CI 4.1 to 10) in children with IBD in Ireland. Unlike previous studies into FA prevalence in IBD, this is much closer in line with FA prevalence in general populations across the western world, albeit slightly higher than reported in the Irish birth cohort by Kelleher et al (11). However, longitudinal data in larger samples over a longer time period and in different populations alongside OFC to confirm FA diagnosis are necessary to further support these findings.

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Key Message:

Despite IBD and Food allergy having overlapping pathogenesis, there is a lack of data on their association in particular clinical evidence of food allergy rather than positive serology. We report the prevalence of IgE mediated food allergy in children with IBD as being 6.5% (95% CI 4.1 to 10) which is similar to the prevalence reported in children in general populations both in Ireland (4.5%) and worldwide.

Ethics approval:

This was received from the ethics committee at Children's Health Ireland at Crumlin.

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Table 1. Characteristics of 18 children with IBD and food allergy

Case	Gender	Age of diagnosis of IBD (Years)	Ethnicity	Type of IBD	FA outgrown	Current food allergy	Symptom profile of reaction
1	M	11	Celtic Caucasian	Atypical UC		Kiwi	Hives, swollen face
2	F	12	Celtic Caucasian	UC	CMP	Nuts	*
3	M	13	Celtic Caucasian	Atypical UC		CMP	Hives
4	M	12	Celtic Caucasian	CD	Egg	Cashew	Hives; swollen eyes; difficulty breathing
5	F	11	Celtic Caucasian	Atypical UC		CMP, egg	*
6	M	14	Celtic Caucasian	CD		Pine nuts	Swollen face, throat tightening
7	M	13	Celtic Caucasian	Atypical UC		Peanut, kiwi	*
8	M	10	Celtic Caucasian	Atypical UC	CMP	Nuts, egg	Hives; cough; difficulty breathing; swollen lip/eyes ; vomit
9	M	7	Celtic Caucasian	IBD-U		Peanut	*
10	M	15	Celtic Caucasian	CD		Peanut, egg	Difficulty breathing; swollen lip/eyes;
11	M	11	Celtic Caucasian	CD		Sesame, cashew	Hives; swollen face Difficulty breathing; cough; vomit;
12	F	16	Celtic Caucasian	CD		Pine nuts	Hives, swollen face
13	M	10.96	Celtic Caucasian	CD	CMP	Peanut	Hives, swollen face
14	F	3.43	Celtic Caucasian	CD		Pistachio, cashew, egg	Hives, swollen face, rhinitis; cough; itchy mouth, tight throat,
15	M	14.67	Celtic Caucasian	UC		Egg, peanut	Hives, facial swelling, breathing difficulty
16	F	4.87	Celtic Caucasian	CD		CMP, Peanut, hazelnut	Hives, swollen eyes, vomit, breathing difficulty
17	M	9.67	Celtic Caucasian	UC		Egg	Hives, swollen lips, vomit
18	M	11,46	Celtic Caucasian	UC		Banana, mango	Hives, swollen face

Table 2. Clinical features of children with IBD (N=278)	
Gender (N) %	
Male	185 (67)
Female	93 (33)
Median age at diagnosis (years) (lower quartile, upper quartile)	12.8 (12.4, 14.2)
0-4 years (N) %	3 (1)
5-9 years (N) %	55 (20)
10-17 years (N) %	220 (79)
Type of IBD (N) %	
Crohns disease	153 (55)
Ulcerative colitis	94 (33)
Atypical UC	18 (6)
IBD-U	13 (5)
Disease phenotype at diagnosis	
Crohns disease (Mod/ Severe: PCDAI >30)	57/153 (37)
Ulcerative Colitis (Severe: PUCAI 65-85)	29/94 (31)
Location of home (N) %	
Urban/town	182 (65)
Rural farm/isolated	96 (35)
Ethnicity (N) %	
Caucasian Celtic	250 (83)
Caucasian(non-Celtic)	17 (6)
Afro-Caribbean	1
Asian	2
Other	8 (4)
Breastfeeding (N) %	
Ever Breastfed	150 (54)

For 3 months or longer	72 (26)
LSCS (N) %	83 (29)
Personal hx of atopy (N) % (eczema, asthma, EOE)	75 (27)
Abbreviations: IBD: inflammatory bowel disease; IBD-U: inflammatory bowel disease undefined; UC: ulcerative colitis; LSCS: lower section caesarean section; PCDAI: paediatric Crohns disease activity index ; PUCAI: paediatric ulcerative colitis activity index: EOE: eosinophilic oesophagitis; Mod: moderate;	

1. Food allergy

Is the patient avoiding any food or foods because of an allergy test suggested that they were allergic to that food?

If the answer is yes please list the foods:

Has the patient ever had an immediate allergic reaction (within 2 hrs of eating) to a food?

Name the food or foods that caused the reaction. Food 1_____ Food 2_____ Food 3_____
Food 4_____

Have the patient ever been advised to carry an adrenaline pen?

Tick any of the following symptoms that the child experienced on ingestion of food:

	Food No 1	Food No 2	Food No 3	Food No 4
Name of food causing reaction				
Hives / sudden rash				
Sudden Itch				
Swollen /itchy Eyes				
Swollen lips				
Swollen face				
Sneezing/blocked nose				
Itchy tingling mouth				
Throat tightening				
Nausea/vomiting				
Difficulty breathing				
Cough				
Weakness/floppiness				
Collapse				
TREATMENT				
Went to GP				
Went to out of ours doc				
Went to Casualty				
Antihistamine by mouth				
Steroids (pink tablets) by mouth				
Adrenaline pen				
Injection in hospital				
Still avoiding the food Y/N				

