CME

Extraintestinal Manifestations in Children With Gastrointestinal Food Allergy

G. Domínguez-Ortega, O. Borrelli, R. Meyer, R. Dziubak, C. De Koker, H. Godwin, C. Fleming, N. Thapar, M. Elawad, F. Kiparissi, A.T. Fox, and N. Shah

ABSTRACT

Objectives: The presence of extraintestinal manifestations (EIM) in children with gastrointestinal (GI) food allergy (GIFA) is greatly debated. In the present study we assessed the prevalence of EIM in children with GIFA and investigated whether their presence is helpful in the allergy-focused history-taking process.

Methods: The medical records of all children with a proven diagnosis of GIFA were reviewed along with those of children diagnosed as having inflammatory bowel disease (IBD) as controls. Data regarding age at onset, age at diagnosis, atopic family history, atopic comorbidities, GI symptoms, and EIM were recorded.

Results: Data from 436 children with GIFA and 74 children with IBD were included in the analysis. EIM were documented in 368 children with GIFA, including fatigue (53.0%), allergic shiners (49.1%), mouth ulcers (39.0%), joint pain/hypermobility (35.8%), poor sleep (34.4%), night sweats (34.4%), headache (22.7%), and bed-wetting (17.7%). The proportion of patients with EIM was higher in the GIFA group compared with that in the IBD group (368/436 [84.4%] vs 40/74 [54.1%]; $P < 0.001$). Segregating the GIFA group into children with and without atopic comorbidities, both atopic (276/30; 89.9%) and nonatopic (93/130; 71.5%) children showed higher proportion of EIM than children with IBD ([40/74; 54.1%], $P < 0.01$ and <0.05, respectively).

Conclusions: GIFA are commonly associated with a wide range of EIM, which appear to represent important and specific clinical features of this group of conditions. Their recognition in taking an allergy-focused history may play an important role for both diagnosis and management.

Key Words: allergy history, atopy, extraintestinal manifestations, gastrointestinal food allergy

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Food allergy (FA) is defined as an adverse immune response occurring reproducibly on exposure to a given food (1). Gastrointestinal (GI) food allergies (GIFA) may cause a variety of clinical manifestations, and depending on the underlying mechanism they are classified as immunoglobulin E (IgE)–mediated, non-IgE–mediated, and mixed immune reactions (2,3). It is believed that in the United Kingdom between 2.2% and 5.5% of infants in the first year of life experience FA, affecting the skin, respiratory, and/or GI tract (4). Commonly reported GI symptoms of GIFA include vomiting, diarrhoea, constipation, bloating, and abdominal pain (1,5). The suspicion of non-IgE–mediated GIFA is mostly reliant on clinical history, physical examination, and elimination diet with subsequent food challenge; given screening tests, such as skin prick tests, specific IgE (sIgE) tests, and atopy patch tests, have been shown to lack specificity and sensitivity (2,6). Although the double-blind placebo-controlled food challenge is considered the criterion standard for diagnosis of GIFA, it is difficult to perform because symptoms are typically delayed, either requiring long in-patient admissions or relying on parental symptom reporting at home. Moreover, there is a paucity of standardised protocols for challenging delayed type of GIFA. Despite these difficulties in identifying the patients with GIFA, an accurate diagnosis is essential because the cornerstone of management is avoidance of offending food antigens. Such an exclusion diet in early childhood not only is nutritionally challenging (7) but also has a significant impact on the quality of life of children and their families, and significant morbidity and financial and emotional cost (8,9).

Although the presence of extraintestinal manifestation (EIM) as signs and symptoms outside the common clinical picture of other atopic conditions has been reported in the literature for decades, to the best of our knowledge it has not been specifically documented in children with GIFA. Theoretically, patients with GIFA could have a genetic predisposition to experience atopy, even if they have not manifested any other atopic condition yet, which could appear later in life. Therefore, we hypothesised that children with GIFA had EIM irrespective of their previously defined atopy history. We chose inflammatory bowel disease (IBD) as a control group because EIM are well documented and recognised by clinicians in this condition with a prevalence of 21% to 40% (10–12). The presence of these EIM (eg, mouth ulcers) raises awareness in the clinicians that IBD may be present in that patient. From our own clinical observations we were struck by just how common extraintestinal symptoms were in the GIFA group and wanted to highlight how common these were when compared with an IBD group and could raise clinical awareness that FA was present in this group of patients especially because this is a condition suspected purely on clinical grounds. We therefore aimed to assess the prevalence and characteristics of EIM in children with GIFA seen in our clinical setting and compare these with children with IBD.

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From the Department of Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust Institute of Child Health, London, UK.

Address correspondence and reprint requests to Neil Shah, MD, MRCP, Division of Mucosal Immunology, Department of Paediatric Gastroenterology, Great Ormond Street Hospital for Sick Children, Great Ormond Street, WC1N 3HZ London, UK (e-mail: neil.shah@gosh.nhs.uk).

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METHODS

Subjects

All patients' records in the gastroenterology database from 2002 to 2009 were analysed in the present retrospective observational study. Patients who had a diagnosis of FA were reviewed individually and only included in the study if the documented medical diagnosis had been confirmed by a successful elimination diet followed by reintroduction of the food with reappearance of symptoms (2). Exclusion criteria included incorrect contact details, refusal to partake in the study, or ambiguity regarding the diagnostic process. As a control group, children with a definitive diagnosis of IBD were randomly selected from the department database. The present study was performed in accordance with the Declaration of Helsinki, and was approved by the ethics committees of our institution.

Data Collection

All case notes were reviewed by 1 researcher using a standard data collection sheet to avoid bias. In the study group, age of onset, age at diagnosis, symptoms, comorbid atopic disease, family history of atopy, dietary management, and medication (data not shown in the present article) were recorded from the medical notes. The atopy diagnosis was based on the clinical history. If a patient had a history of asthma, allergic rhinitis, atopic dermatitis, or IgE-mediated food reaction, this was considered atopic. Information on blood tests, including total IgE, sIgE, and total IgA, was also documented if available. The study group was divided into 2 subgroups: GIFA with atopy and GIFA without atopy. In addition, a standard data sheet collected on all our GI-allergic patients was cross-checked with the notes and a telephone discussion was then performed with parents to confirm all of the clinical features documented in the medical notes, including EIM (Table 1). The latter was also used over the telephone or in a face-to-face interview with parents to assess the EIM in the patients with IBD. We also asked them about the additional clinical problems of pyoderma gangrenosum and erythema nodosum that are well recognised EIM in IBD.

Statistics

The χ^2 test was used to assess differences in prevalence of atopic comorbidities, EIM, and GI symptoms between groups. The Mann-Whitney U test was used to analyse differences in age (at time of appointment, of onset of symptoms, and age at diagnosis). The Spearman rank correlation coefficient was performed to measure the association between age and number of EIM. Significance was set at $P = 0.05$. Measures of central tendency are presented as medians. The data were analysed using SPSS version 20 (IBM SPSS Statistics, Armonk, NY).

RESULTS

A total of 615 patient records were identified as diagnosed as having GIFA. Data from 436 children (median age 124.5 months [9–307], 202 girls and 234 boys) with GIFA were included in the analysis, whereas 179 patients were excluded. The study population included in the analysis was divided into 2 subgroups: GIFA with atopy (306, 70.2%) and GIFA without atopy (130, 29.8%). A total of 74 children (36 girls) with IBD were included as control group: 39 (52.7%) with Crohn disease (median age 163 months, range 47–203), 24 (32.4%) with ulcerative colitis (median age 155.5 months, range 59–214), and 11 (14.9%) with unclassified IBD (median age 156 months; range 85–195).

Atopy

In the GIFA group, 306 (70.2%) had at least 1 atopic condition: 231 (53%) atopic dermatitis, 189 (43.3%) allergic rhinitis, and 137 (31.4%) asthma. Conversely, 130 (29.8%) patients with GIFA had no known atopic condition. A majority (295/436 [67.7%]) of children had an atopic family history: in 19.7% both parents had atopic disease (including eczema, asthma, hay fever, or FA); 26.4% and 16.3% of children had an atopic family history of mothers and fathers, respectively, and 5.3% had an atopic history of siblings. Children with a family history of atopy experienced more frequently a known atopic comorbidity than children without it (230/295 [78.0%] vs 76/141 [53.9%], $P < 0.001$). There were 65 of 141 (46.1%) children without a family history of atopy and no known atopic comorbidities. A total of 50% of the nonatopic patients (65/130) did have a family history of atopy.

Sex and Age

Both GIFA and IBD groups were homogeneous in sex (53.7% vs 51.4% of boys, respectively, NS). There was no significant difference in age (months) between the GIFA subgroups (atopic 126.5 [9–307] vs nonatopic 116.5 [18–265], NS). The median age of the patients with IBD was significantly higher

TABLE 1. Template of questions used to establish extraintestinal manifestations

Headaches
Chronic headaches that are reported by child to parent and require medication or affect daily activities and/or periods of feeling/looking faint

Fatigue/lethargy
Obvious lack of energy in child compared with other children their age—unable to complete sports or full days of school or other noted activities

Poor (interrupted) sleep
Frequently waking up at night with obvious discomfort and difficult to console

Night sweats
Chronic sweats in the night that drench the child's sheet, pillow, and pyjamas and they wake up with a hot body temperature and wet hair

Dark rings under eyes (''atopic shiners''/Dennie-Morgan folds)
Noticeable dark rings under eyes that are not seen in other children their age and must be for extended periods of time

Joint pain/hypermobility
Chronic and debilitating pain in joints and causing mobility issues

Nocturnal enuresis (bed-wetting)
Continual bed-wetter for an abnormally high age

Mouth ulcers
Recurrence of mouth ulcers

compared with that of the allergic group (162 months [47–214] vs 124.5 months [9–307], $P = 0.001$); however, there was no correlation between age and number of EIM in the IBD group ($r = -0.041$, $P = 0.727$) or in the GIFA group ($r = 0.041$, $P = 0.394$).

The median age at onset of GI allergy symptoms in the GIFA group was 5 months (1–56), and the subgroup analysis revealed that in those children with atopy the median age was 6 months (range 1–156) and in those without comorbidities it was 4 months (range 1–86) (NS). Because our hospital is a tertiary referral centre, patients with GIFA were diagnosed later than could be expected in primary or secondary care. On average, patients with GIFA were first seen at median age 63 months (range 1–260), those with atopy at 54.5 months (range 1–217), and those without atopy at 68 months (range 2–260) (NS).

Gastrointestinal Symptoms

The most commonly documented GI symptoms in the allergic group were abdominal pain (392, 89.9%), diarrhoea (353, 81.0%), abdominal distension/bloating (322, 73.9%), vomiting (253, 58%), constipation (203, 46.6%), and rectal bleeding (156, 35.8%). Comparing the patients with GIFA with atopy with those without, there was a significant difference in the prevalence of both diarrhoea (256 [83.7%] vs 97 [74.6%], $P < 0.05$) and abdominal distension (242 [79.1%] vs 80 [61.5%], $P < 0.001$). Conversely, we did not find any significant difference among abdominal pain (279 [91.2%] vs 113 [86.9%], NS), constipation (150 [49%] vs 53 [40.8%], NS), vomiting (185 [60.5%] vs 68 [52.3%], NS), and rectal bleeding (109 [35.6%] vs 47 [36.2%], NS).

Extraintestinal Manifestations

The proportion of patients with EIM was higher in the GIFA group than in the IBD group (368/436 [84.4%] vs 40/74 [54.1%], $P < 0.001$). Segregating the GIFA group into children with and without atopic comorbidities, this proportion was also higher in both atopic (276/306, 89.9%) and nonatopic (93/130, 71.5%) children compared with children with IBD (54.1%, $P < 0.001$ and <0.05, respectively). The majority of children with GIFA (231/53%) had ≥ 3 of these EIM (atopic group 180 [58.8%], nonatopic group 51 [39.2%]) versus the IBD group: 7 (9.5%), $P < 0.001$. The prevalence of each EIM in both patients with GIFA and patients with IBD is shown in Table 2.

All EIM, except headache, were significantly more common in the GIFA group than in the IBD group. Although most of the EIM were significantly more frequent in the atopic versus nonatopic patients with GIFA, night sweats, poor sleep, and bed-wetting were not. Interestingly, all EIM, including headache, were significantly more common in the atopic group than in the IBD group. In the nonatopic group, fatigue, poor sleep, night sweats, and allergic shiners were significantly more frequent than in the IBD group (Table 3). None of our patients with IBD presented or had presented any EIM in the skin, for example, erythema nodosum or pyoderma gangrenosum.

Immunoglobulin Blood Tests

Total IgE was measured in 330 patients of the GIFA group (236 were atopic; 94 were nonatopic). The available blood results indicated a median total IgE within normal limits for all allergic groups: GIFA group, 29.5 (0–11,456) kU/L; atopic GIFA, 35.90 (0–11,456) kU/L; and nonatopic GIFA, 23.55 (2–4233) kU/L (NS). The median IgA level for the GIFA group was 0.66 g/L (normal range 0.4–2.0 g/L). sIgE results to food protein were available in 295 (67.5%) children, which included milk, egg, soy, and wheat. From these patients, only 88 (29.9%) had ≥ 1 sIgE that was positive (>0.35 kU/L). No children in the present analysis had atopy patch testing to foods performed.

DISCUSSION

In the present study we have described EIM in children with GIFA and found them to be increased compared with a control group of patients with IBD. Atopic conditions have been described in the literature to be associated with each of the EIM reported in the present study: fatigue (13), allergic shiners (14,15), mouth ulcers (16), joint pain/hypermobility (17), night sweats (18), poor sleep (19,20), headache (21,22), and enuresis (23), although the mechanisms are not fully understood. We have described the presence of all of them in a large cohort of children with GIFA. The majority of them (70.2%) were classified as atopic because they had a known diagnosis of asthma, eczema, or allergic rhinitis. Those who were classified as nonatopic GIFA also presented an increased number of EIM compared with the IBD group; therefore, in the absence of a positive atopic history, these EIM could by themselves lead the clinician in the suspicion of GIFA.

The first report of EIM in atopy related to allergic shiners and was published in 1966 (14). Since then, allergic shiners have been

TABLE 2. Comparison of extraintestinal manifestation prevalence between gastrointestinal food-allergic patients and patients with IBD and within allergy subgroups

	GIFA versus IBD, %		Atopic GIFA versus nonatopic GIFA, %	
EIM	IBD group, n = 74	GIFA group, n = 436	GIFA atopic, n = 306	GIFA nonatopic, n = 130
Allergic shiners	13.5	49.1***	53.9	37.7**
Fatigue	20.3	53***	57.2	43.1**
Night sweats	4.1	34.6***	37.6	27.7
Poor sleep	6.8	34.4***	37.3	27.7
Mouth ulcers	14.9	39***	43.8	27.7*
Joint pain/hypermobility	18.9	35.8**	39.5	26.9*
Bed-wetting	5.4	17.7*	19.3	13.8
Headache	12.2	22.7	26.8	13.1**

EIM = extraintestinal manifestation; GIFA = gastrointestinal food allergy; IBD = inflammatory bowel disease.
*** $P < 0.001$.
** $P < 0.01$.
* $P < 0.05$.

TABLE 3. Comparison of extraintestinal manifestation prevalence between patients with IBD and gastrointestinal food-allergic patients with and without atopy

	IBD versus atopic GIFA, %		IBD versus nonatopic GIFA, %	
EIM	IBD group, n = 74	GIFA atopic, n = 306	IBD group, n = 74	GIFA nonatopic, n = 130
Allergic shiners	13.50	53.90***	13.50	37.70***
Fatigue	20.30	57.20***	20.30	43.10**
Night sweats	4.10	37.60***	4.10	27.70***
Poor sleep	6.80	37.30***	6.80	27.70***
Mouth ulcers	14.90	43.80***	14.90	27.70
Joint pain/hypermobility	18.90	39.50***	18.90	26.90
Bed-wetting	5.40	19.30**	5.40	13.80
Headache	12.20	26.80*	12.20	13.10

EIM = extraintestinal manifestation; GIFA = gastrointestinal food allergy; IBD = inflammatory bowel disease.
*** $P < 0.001$.
** $P < 0.01$.
* $P < 0.05$.

typically attributed to atopy, especially to allergic rhinitis. We have found allergic shiners to be more frequently reported in both GIFA groups, atopic and nonatopic, than in the IBD group, and, even more remarkably, no significant difference was found between atopic and nonatopic GIFA allergic shiners. Atopy coexists with the chronic fatigue syndrome in >50% of adult patients (13), in whom possible cellular immune mechanisms have been implicated, although, again, it has not been described in the paediatric age group. We have shown that fatigue is the most frequent EIM in patients with GIFA and that its presentation is significantly higher irrespective of being atopic or nonatopic compared with the IBD group. A recent study on a large cohort of Chinese schoolchildren has shown that night sweats are associated with the presence, among others, of atopic diseases (eczema and allergic rhinitis) (18). In our study, night sweats were significantly more frequent in our atopic and nonatopic children with GIFA compared with the IBD group, and no significant difference was found between the former subgroups. Sleep disorders have also been described in atopic conditions, especially in those children with eczema (24,25). Asthma has also been related to sleeping disturbances (19,20). It has been reported that there is an increased risk of nonatopic asthma in children following frequent nocturnal awakening during the first 3 years of life. Nonatopic asthma developed later in life than the preexisting sleep disturbance. We report an increased frequency of poor sleep in our cohort of patients with GIFA irrespective of their atopic known background. Poor sleep is an EIM usually presented in these patients early on in life. These findings strongly support that EIM can aid the diagnoses of GIFA, even sooner than any other atopic condition is manifested.

Taking into account the symptom profile, it is also tempting to consider whether the EIM are reflective of a broader autonomic dysfunction. It has been previously described that in patients with both allergic rhinitis and atopic dermatitis, autonomic dysfunction reflecting abnormalities in sympathetic and parasympathetic balance and function was manifested as alterations, among others, of heart rate variability and/or transepidermal water loss (26,27). It is therefore feasible that autonomic dysfunction may in part explain symptoms of night sweats, nocturia, disrupted sleep, and dizziness experienced by these children.

A significant number of children in our study also reported headaches. The difference between both groups is the only one in our study that is not significantly higher in the GIFA group, although it is significant in the atopic subgroup compared with the IBD group. Headache has been associated with FA (21,28), atopy (21), and IBD (29) previously, which could explain the lack of statistically significant difference between the GIFA group and IBD group.

Several studies have described joint hypermobility in adult patients with GI symptoms and other nonspecific complaints including autonomic dysfunction symptoms (migraine, allergy, rash, nocturia, dysuria, flushing, night sweats, fever, lymph gland pain, and poor sleep) (30,31). The joint–gut axis has previously been described in children (32). The children with GIFA having EIM in our study shared many of the symptoms described in these studies. In line with these reports, another study (17) has shown that adult patients with food-related GI symptoms were found to have a high incidence of arthralgia and/or joint swelling. We have found a significant increment in the prevalence of arthralgia and joint hypermobility in our patients with GIFA compared with the IBD group.

Many of these EIM, in present practice, would be dismissed as insignificant/nonexistent or as behavioural manifestation, and probably not related to the GI symptoms. We believe, and have demonstrated, that they are important and should be included as part of the GIFA-focused history in the context of a disease that lacks specific and validated diagnostic tests.

The present study has limitations, including individual physician variation, that may have influenced our results, and despite extensive attempts to exclude ambiguity including telephone review with 1 researcher and all parents on the present study it would be difficult to eliminate this totally. The present study was also performed in a tertiary GI specialist centre that could be receiving the most severe cases with GIFA and may not reflect the GIFA seen in primary or secondary care, and this needs to be taken into account when interpreting the data.

Because the present study was retrospective, we were able to document only the presence and absence of single/groups of EIM during the course of care at our hospital. We found this to be a limitation of the present study because linking this to a specific age would be greatly biased by either the lack of or poor documentation by the clinicians.

In conclusion, the present large retrospective study on children with GIFA compared with those with IBD highlights that EIM are significantly more frequent in the former group. We have also shown that these EIM are important clinical features both in patients with GIFA with known atopic comorbidities (atopic dermatitis, allergic rhinitis, asthma) and in those without them, supporting the hypothesis that GIFA is part of the atopic predisposition. The

number of EIM presented in a given patient is increased in the GIFA group compared with that in the IBD one. EIM should therefore become an important part of a good allergy-focused history taking by the clinicians involved in the care of these patients because they can lead them in the suspicion of GIFA.

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