

REVIEW ARTICLE

Non-IgE-mediated gastrointestinal allergies—Do they have a place in a new model of the Allergic March

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Abstract

The rise in food allergy has been described as the “second wave” of the allergy epidemic, with some developed countries reporting a prevalence of 10% of challenge-proven food allergies. Recognition of the Allergic March has played a crucial role in identifying causality in allergic conditions, linking atopic dermatitis to food allergy and food allergy to other atopic disorders, thereby highlighting opportunities in prevention and the importance of early intervention. This publication will establish the value of weaving the less well-understood, non-IgE-mediated food allergy into the Allergic March and mapping its progression through childhood and its associated comorbidities. The proposed non-IgE-mediated Allergic March highlights the concomitant presentation of gastrointestinal symptoms and atopic dermatitis as early presenting symptoms in confirmed non-IgE-mediated allergies and the later development of atopic co-morbidities, including asthma and allergic rhinitis, similar to the IgE-mediated Allergic March. This publication highlights recent observations of a link between non-IgE-mediated food allergy in early childhood and functional gastrointestinal disorders in later life and also the reported occurrence of extra-intestinal manifestations at later ages. Although significant limitations exist in regard to the proposed evolution of the Allergic March model, the authors hope that this publication will influence the management of non-IgE-mediated gastrointestinal allergies and inform future research and interventions.

KEYWORDS

Allergic March, allergic rhinitis, asthma, atopic dermatitis, extra-intestinal manifestations, gastrointestinal tract, non-IgE mediated

1 | INTRODUCTION

The World Health Organization has suggested that allergy has reached epidemic proportions.¹ More than 50 years ago, an increase in asthma, allergic rhinitis and inhalant sensitization was recognized, and it is thought now that almost half of the population of Westernized countries suffer from one of the aforementioned allergic conditions.² More recently, the rise in food allergy has been described as the “second wave” of the allergy epidemic, with some developed countries reporting a prevalence of 10% of

challenge-proven food allergies in children.³ It has been well recognized that patients with one allergic manifestation are at significant risk of developing others and these often occur in a predictable temporal pattern. This association has been described as the Allergic March, most commonly observed in infants who have inherited an atopic tendency from one or both parents.⁴ Initial publications on the Allergic March suggested the onset of atopic dermatitis (AD) as first presenting symptom with immunoglobulin E (IgE) responses to food developing after this in early infancy, followed by asthma and allergic rhino-conjunctivitis with increased age.⁴⁻⁷ Although data in

support of the Allergic March are far from complete, a small number of longitudinal and cross-sectional studies have substantiated its validity.^{8,9} Recognition of the Allergic March has played a crucial role in understanding causality in allergic conditions, linking AD to food allergy and food allergy to other atopic disorders, highlighting opportunities in prevention and the importance of early intervention.¹⁰⁻¹² Although a publication by Bergman et al⁵ (1997) discussing the possible Allergic March from food allergy to the development of pollen allergy pointed towards data published in 1986 where the natural course of allergic manifestations begins with AD and food allergy-associated gastrointestinal disorders, the present Allergic March includes only IgE-mediated food allergies, whilst gastrointestinal manifestations of non-IgE-mediated allergies are currently not considered to be part of the progression of atopic disease. In the last decade, there has been an increase in research into the pathogenesis and prevalence of this delayed food allergy, which affects mainly the skin and the gastrointestinal tract.¹³ Although non-IgE-mediated allergies are not fully understood, recent publications have started to highlight their association with other atopic disorders and have begun to explore progression of this allergic disease.¹⁴ We therefore set out to map the progression of non-IgE-mediated allergies through childhood, its associated co-morbidities and link with IgE-mediated allergies.

2 | DEFINING NON-IGE-MEDIATED FOOD ALLERGIES

Non-IgE-mediated food allergy is an umbrella term for a group of immune-mediated allergic disorders with a delayed onset, where IgE has no, or limited involvement. Using the European Academy for Allergy and Clinical Immunology (EAACI) nomenclature, this allergic disorder encompasses different gastrointestinal allergies varying in presentation and includes food protein-induced allergic proctocolitis, food protein-induced enterocolitis syndrome (FPIES),

food protein-induced enteropathy, allergic dysmotility disorders [gastro-oesophageal reflux disorder (GORD) and constipation], eosinophilic gastrointestinal disorders (EGID), including eosinophilic oesophagitis (EoE) and non-IgE-mediated AD (Figure 1).¹⁵⁻¹⁸ According to the nomenclature of the National Institute for Allergy and Infectious Disease, EoE is classified as a mixed IgE and non-IgE-mediated allergy; however, this was published prior to the recent article by Simon et al,¹⁹ proposing EoE as a non-IgE-mediated allergic condition. For the purpose of this publication, EoE will be therefore discussed as a non-IgE-mediated condition, as per EAACI nomenclature. In addition, the authors defined a diagnosis of non-IgE-mediated allergies, as per current guidelines of elimination followed by re-introduction.²⁰ If this method was not used but the publication was applicable to the article, then it was highlighted in the text.

3 | THE NATURAL COURSE OF NON-IGE-MEDIATED GASTROINTESTINAL ALLERGIES AND THE ALLERGIC MARCH

The gastrointestinal presentations of non-IgE-mediated allergies are increasingly recognized, with the EuroPrevall study documenting challenge-proven prevalence of this cow's milk protein allergy (CMPA) between 0.13% and 0.72%.²¹ Although concerns related to that study have been highlighted in regard to the methodology which strongly favours IgE-mediated allergies, that study nevertheless highlights that many countries are recognizing delayed gastrointestinal symptoms as a prominent presentation of food allergy. The mean age of onset of symptoms of a cohort of children with various non-IgE-mediated gastrointestinal allergies, according to Meyer et al,¹⁴ was around 5 months of age; however, many children exhibited symptoms soon after birth. The latter study was performed in a tertiary centre, and data by Sladkevicius et al²² in a primary care setting in the United Kingdom (UK) found onset of gastrointestinal symptoms at a mean age of 3 months.

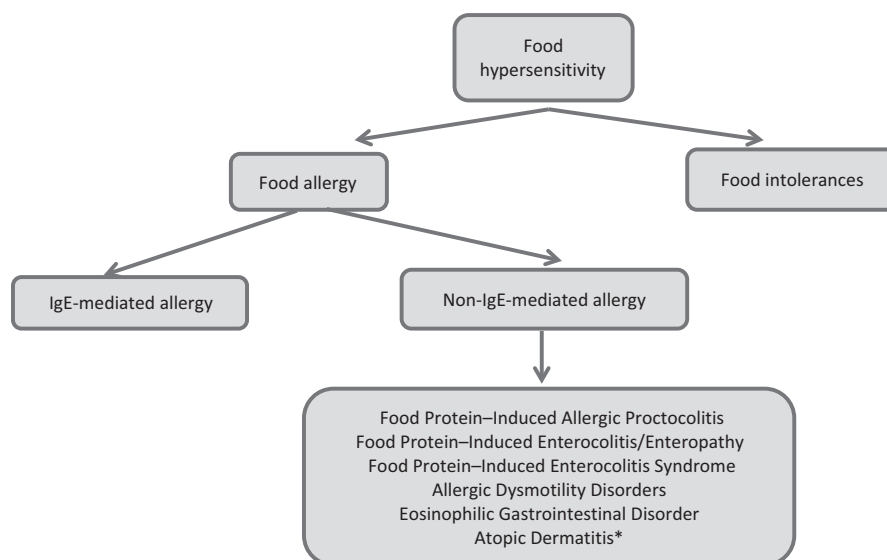


FIGURE 1 Food Hypersensitivity with subdivision of non-IgE-mediated allergic disorders adjusted from EAACI and NIAID Nomenclature (15).⁹⁹ *Atopic dermatitis can be IgE-mediated as well, but is often not associated with food allergy

Non-IgE-mediated gastrointestinal food allergic disorders are often classified into specific disorders, each having a different prevalence, mean age of presentation and natural history, and these all need to be considered, with specific relation to how they may fit into the non-IgE-mediated Allergic March. These are discussed individually below.

3.1 | Food protein-induced gastrointestinal dysmotility disorders

Allergic gastrointestinal motility disorders are common in infancy and early childhood, in particular food allergy-related GORD (not to be confused with common GOR) and constipation associated with allergic inflammation have been studied in the last decade.²³ Studies have found that around 23%-59% of children with GORD have a challenge-proven food allergy underlying their symptoms and this is reflected in the 2018 ESPGHAN/NASPGHAN Guidelines.²⁴⁻²⁷ Although questions remain in regard to the pathophysiology of food protein-induced GORD, Semniuk et al²⁸ found that children with CMPA-associated GORD (established through elimination diet) had significantly higher IL-4 and TNF- α , but manometry could not distinguish between food- and non-food-related GORD.²⁹ Data indicate that in the majority of children, symptoms of allergic GORD presented mainly within the first 6 months of life. However, there is great variation in documented onset of progression (4-102 months) but can present later depending on the recognition of symptoms and on the timing of introduction of cow's milk, which is the main offending allergen in food-associated GORD.^{25,30} The prognosis of food allergy-induced GORD is poorly described and difficult to establish; however, it is assumed that tolerance occurs at least within the age range (96% by age 4) previously described by Vanto et al for non-IgE-mediated allergies.³¹

Constipation can also occur as a result of non-IgE-mediated food allergies; 45% of children in a retrospective study on patients with confirmed non-IgE-mediated allergies (diagnosis based on elimination diet followed by reintroduction) by Meyer et al¹⁴ presented with this as one of their symptoms. However, studies investigating the association between food allergy and constipation are limited to 10 studies summarized in a systematic review.³² This systematic review only included studies that were randomized controlled, or having at least a control group, or having an oral food challenge after the improvement of symptoms following an elimination diet. From the two randomized controlled trials and case-control studies, the most common offending allergen reported is cow's milk, but response rate in studies range between 28% and 78% albeit in highly selected populations. As such, there remains disagreement as to its role in non-IgE-mediated food allergy; however, studies have found evidence of increased eosinophil and mast cell infiltration with rectal biopsy, which improves after an elimination diet of, in particular, cow's milk.^{33,34} The systematic review by Miceli-Sopo et al³² found that most children presented later, on average between 1 and 2 years of life, but 80% of patients achieved tolerance within 1 year after the diagnosis of food allergy-related constipation.

3.2 | Food protein-induced allergic proctocolitis

Food protein-induced allergic proctocolitis is a non-IgE-mediated condition that usually occurs within the first 3 months of life.^{14,35,36} It represents the benign end of the spectrum of non-IgE-mediated allergy, and in about 60% of cases, it occurs in breastfed babies whose mothers are ingesting cow's milk or soya protein.^{37,38} It has been suggested that both intestinal immaturity and marked eosinophilic infiltration, which may significantly alter tight junctions, may lead to increased intestinal permeability to food proteins in infants leading to proctocolitis. Eosinophils may be directly responsible for tissue injury in food protein-induced allergic proctocolitis because they can bind IgA, which are normally present in breastmilk, and undergo degranulation.³⁷ The majority of infants with food protein-induced allergic proctocolitis become tolerant to offending food allergens by around 14 months of age (± 11 months) according to several publications.^{36,39}

3.3 | Food protein-induced enteropathy

Although food protein-induced enteropathy, in particular related to cow's milk protein, has been described in the literature since the 1980 s,^{40,41} research into this allergic disorder has not evolved as much as other non-IgE-mediated conditions such as FPIES and EoE. This is most probably due to the observation that enteropathy does not occur exclusively related to food allergy. Nevertheless, from the published data, it is thought that children with food protein-induced enteropathy present with gastrointestinal symptoms in early infancy. Data on cow's milk- and soya-related enteropathy indicate presentation within the first 2 years of life, and although current data indicate that the majority outgrow this allergy by 24-36 months of age,^{13,16} a study from Kokkonen et al⁴² does indicate that this non-IgE-mediated allergy may persist into the early school years.

3.4 | Food protein-induced enterocolitis syndrome (FPIES)

A recent Australian population study found an incidence of FPIES to all foods in Australian infants (<24 months) of 15.4/100,000/year. More specifically, Katz et al⁴³ found the prevalence of milk FPIES at 0.34% of the paediatric population, similar to the retrospective survey from the United Kingdom that found a prevalence of 0.36%.⁴⁴ Cow's milk protein-induced FPIES typically occurs between 2 and 7 months of age^{45,46}; however, solid food FPIES (ie, rice, oat, fish) can occur much later as the introduction of complementary foods progresses after 6 months of age.⁴⁶⁻⁴⁸ Miceli et al⁴⁸ in the past had suggested that FPIES as a diagnosis should be considered until at least 2 years of age. However, it is already recognized in the International Consensus Guidelines of FPIES that this diagnosis can occur later in childhood and that egg, fish and shellfish FPIES has been described in a small adult case series.^{46,49,50} There are significant limitations in regard to the published data on age of onset in FPIES due to it

still being a poorly recognized disorder. Ludman et al⁴⁴ found that patients with FPIES in the United Kingdom had a mean symptom duration for 20.2 months, before a referral to a specialist allergy centre was made.

Assessments of the natural history of FPIES have yielded varying results: in three major studies, over 90% of the children with cow's milk-related FPIES, reactivity was lost by the age of 3 years and studies on solid FPIES have yielded similar results with only a small number of cases continuing to react beyond 5 years of age.⁵¹⁻⁵³ However, Caubet et al⁵⁴ found a later age of tolerance in their cohort from a tertiary referral centre: rice at a median age of 4.7 years, oat at 4 years, and soya at 6.7 years. Median age for milk tolerance in subjects with undetectable milk-specific IgE levels was 5.1 years (see below overlap with IgE-mediated allergies). In two recent studies on fish FPIES, tolerance was reported in 75% of children at around 5 years, and in the other, only 16% had achieved tolerance based on oral food challenge at 4.5 years, which may imply a longer time for tolerance acquisition for certain foods.^{50,55}

3.5 | Eosinophilic gastrointestinal disorders (EGID)

Of all of the allergic EGID, EoE is the most well-studied, and therefore, the pathophysiology is much better understood. A recent publication by Simon et al¹⁹ found that the mechanism by which eosinophilic inflammation appears is largely independent of IgE, but associations with IgE sensitization to food and environmental allergens (discussed further under section 4 and 5). Current diagnosis is based on the presence of 15 eosinophils per high-power field in the correct clinical context and exclusion of other causes of eosinophilia.^{19,56,57} Initially, this allergic disorder was described in older children; however, it is now well recognized that it can present in early infancy. Spergel et al⁵⁸ found that in their cohort of EoE children, the majority were diagnosed between 0 and 3 years; however, other studies have reported a higher number of diagnoses between the ages of 4 and 17 years.^{59,60} This phenomenon is most probably related to age of recognition of symptoms as well as access to early endoscopy. EoE has been described as a predominantly male disorder in both children and adults, being at least 3 times more prevalent in males than in females.⁶⁰ It is recognized that EoE is a chronic disease with little resolution of either symptoms or oesophageal eosinophilia without ongoing treatment well into adulthood.⁶⁰ DeBrosse et al⁶¹ found that at an average of 15 years after initial endoscopy in childhood, subjects with oesophageal eosinophilia (rather than confirmed EoE) had increased frequency of dysphagia and food impaction as young adults. However, there is one study highlighting a more positive outcome in a cohort of adults (18-28 years of age) with half of subjects reporting symptom resolution and 81% reporting overall improvement based on symptom improvement.⁶² Nevertheless, EoE is a condition that may continue in many children well into adulthood. This non-IgE-mediated allergic disorder is therefore distinctly different than other non-IgE-mediated conditions where data support outgrowing the allergy by early childhood.

4 | ASSOCIATION BETWEEN ATOPIC COMORBIDITIES AND NON-IGE-MEDIATED ALLERGIES

4.1 | Atopic dermatitis (AD)

Between 10% and 25% of children in developed countries present with AD within the first year of life. In two UK-based population study, one found that 11.2% of infants between 6 and 12 months had AD and in the other 24.4% of infants had AD by 3 months.^{4,63-66} In the traditional model of the Allergic March including IgE-mediated food allergy, AD is the first presenting atopic disease, which has been confirmed by several studies.⁶⁷ Tsakok et al⁶⁸ found that food sensitization was 6 times higher in the first 3 months of life in children with AD compared to controls. Several other studies focusing on specific allergens (ie, egg and peanut allergy) have found the same significant association between food allergy in early childhood and AD.⁶⁹

Data are pointing towards AD also being present early on in the non-IgE-mediated Allergic March.⁴ Sladkevikus et al²² found that 59% of children with both IgE- and non-IgE-mediated cow's milk protein allergy presented both with AD (diagnosed by general practitioner) and gastrointestinal symptoms, and these symptoms on average presented within the first 3 months of life. Caffarelli et al⁷⁰ noted this associated presentation already in a study in 1998, with 83% of children presenting with gastrointestinal symptoms, in particular diarrhoea, vomiting and regurgitation, also having AD. However, the latter study has not confirmed these gastrointestinal symptoms as non-IgE-mediated allergies. In recent years, with the growing recognition of non-IgE-mediated allergies several publications have found in children with various non-IgE-mediated allergic conditions (confirmed through elimination and reintroduction/challenge) coexisting AD. Both retrospective and prospective studies by the same research group on children with a variety of non-IgE-mediated gastrointestinal allergies found that 41.5% and 52% of children respectively had AD (diagnosed by paediatrician) when diagnosed with non-IgE-mediated gastrointestinal food allergies and the mean age of presentation was 5 months of age.^{14,71} This is similar to the data by Latcham et al who found that 44% of children non-IgE-mediated gastrointestinal allergies also had AD (diagnosed by paediatrician).⁷² Most recently, Hill et al⁷³ found that AD was independently and cumulatively associated with the later development of EoE. AD in cow's milk-related constipation seems less prominent, with Simeone et al⁷⁴ reporting 17% with concomitant AD (diagnosed by paediatrician), whereas in the cohort by Iacono et al⁷⁴ out of 65 children with cow's milk-induced constipation, only 3 had AD. However, AD is commonly documented as an allergic comorbidity in proctocolitis,⁷⁵ and in challenge-proven FPIES, Caubet et al⁵⁴ documented that 57% also had AD (diagnosed by allergists). Similarly, in over 50% of children from the EoE cohorts,^{58,76} there were other atopic co-morbidities present, including AD. Unlike the increasing evidence of association between IgE-mediated food allergy and AD, this is not yet fully understood for all non-IgE-mediated allergies although

data is emerging for EoE. However, studies by Majamaa et al^{77,78} have found that children with AD (paediatrician diagnosed and defined by Hanifin criteria) frequently have an atopic gastroenteropathy with minor morphological abnormality and increased permeability. It is thought that this association between the two atopic disorders may be related to enhanced eosinophil cationic protein and TNF- α .^{77,78} Although Bergman et al⁵ already in 1997 hinted towards both AD and gastrointestinal symptoms presenting early on in the Allergic March, and outside of EoE, it is unclear whether AD precedes gastrointestinal symptoms or vice versa. Caffarelli et al⁷⁰ therefore proposed that due to paucity of data, both occur together in early infancy. Causality can therefore not be attributed to either conditions in the non-IgE-mediated Allergic March, but certainly points towards associated atopic conditions.

4.2 | Asthma

Asthma also features in the IgE-mediated Allergic March; with Bergmann et al⁵ showing that there was a significant increase in asthma at 5 years of age with a history of AD within the first 3 months of life. More recently, the 5-year review of the atopic paediatric population cohort from Slovakia found that wheeze increased from 0.9% to 23.1% from infancy to toddlers. In that study, asthma was only diagnosed at 4 years, with a prevalence of 7.9%, of which 40% had infantile wheeze. Many children from that population cohort who developed wheeze/asthma also had AD in early infancy. Although population cohorts outside of EoE with non-IgE-mediated allergies do not yet exist, an association between asthma and gastrointestinal symptoms (not confirmed non-IgE-mediated allergy) has been found in children aged 4–8 years.⁷⁹ In the study by Caffarelli et al,⁷⁹ in particular abdominal pain, diarrhoea and vomiting were specifically reported in children with asthma. In the retrospective and prospective cohorts of children with confirmed non-IgE-mediated gastrointestinal food allergy, from Meyer et al¹⁴ and Lozinsky et al,⁷¹ 32% and 29% had asthma as a concomitant atopic co-morbidity, respectively. Also in EoE, a study on children between 7 and 18 years of age, it was found that 69.7% of subjects had either asthma (45.5%) or airway hyper-responsiveness.⁸⁰ The recent consensus guidelines on EoE by Lucendo et al⁵⁷ also agree that asthma (rhinitis and AD) is more common in EoE patients than in the general population. This has recently been confirmed through a primary care cohort, establishing the association between EoE and the Allergic March, that found that asthma was interdependently and cumulatively associated with EoE.⁷³ In allergic dysmotility disorders, evidence of an association was also found: a study on a small cohort of children, with an average age of 6 years, with cow's milk-induced constipation found that over 40% of children had a history of asthma and systematic review in 2010 has highlighted an association between GORD and asthma, with a weighted average prevalence of asthma in children with GORD of 22%.³² In the FPIES cohort from Caubet et al,⁵⁴ 25% had this as co-morbid disorder. The mean age of presentation from these studies varied between 3 and 10 years of age with the pathophysiological association between

the two disorders being poorly understood.⁷⁹ Studies have found duodenal histological changes and cytokine production of patients with asthma mimicking those observed in bronchial mucosa, and intestinal permeability to oral chromium (CrEDTA) CrEDTA also appears to be increased in asthma.^{81,82} Caffarelli et al⁷⁹ found in their study that many children with asthma experienced worsening of gastrointestinal symptoms with specific food ingestion and hypothesized that the association between gastrointestinal symptoms and asthma was most likely to be related to the children's atopic status rather than a metamorphosis of gastrointestinal disease into respiratory disease, asthma in this case. Thus, as with AD, causality cannot be inferred and progression and identifying risk factors for developing asthma later-on in non-IgE-mediated allergies cannot yet be established; however, it is clear from data that in some children with non-IgE-mediated gastrointestinal allergies, asthma is present.

4.3 | Allergic rhinitis

The increase in allergic rhinitis with the progression through the IgE-mediated Allergic March was already demonstrated by Bergmann et al⁵ who found sensitization to indoor (ie, cat, house-dust mite) and outdoor allergens (ie, grass and tree pollen) increase from 3% and 1.9% respectively at 1 year of age to 15% and 21.2% at 5 years of age. In a subsequent birth cohort study of Slovakian children aimed at establishing the dynamics of allergy development in the first 5 years of life, 1.3% of infants had rhinitis, which increased to 13.4% and 36.6% as toddlers and pre-school children.⁶⁷ Longitudinal studies do not yet exist on the progression of allergic rhinitis in non-IgE-mediated allergic patients, but many studies in non-IgE-mediated gastrointestinal allergies have also reported allergic rhinitis as an allergic co-morbidity. Meyer et al¹⁴ found that 45.1% of their retrospective cohort of children with proven non-IgE-mediated allergies had clinician-documented and paediatrician-diagnosed rhinitis, which is higher than the 38% noted in the retrospective analysis of the acute FPIES group.⁵⁴ Only one study could be found describing allergic rhinitis as atopic co-morbidity in cows' milk protein-associated constipation, an allergic dysmotility disorder.⁷⁴ In that study, children with AD and/or allergic rhinitis were grouped together and 53% had both or one of them.⁷⁴

The association between allergic rhinitis and non-IgE-mediated allergies is best demonstrated in EoE. The recent study by Hill et al⁷³ found that allergic rhinitis was associated with the subsequent diagnosis of EoE and vice versa. In addition, Moawad et al⁸³ showed a clear seasonal variation in EoE symptoms during pollen season in adults, and Miehlke et al⁸⁴ have found that in adults 68.8% also suffer from allergic rhinitis. This prevalence does not vary greatly from paediatric data, as Rezende al.⁸⁵ found that 74.2% had symptoms of allergic rhinitis. This association with EoE is closely linked to IgE sensitization, and from studies on children with EoE, they may present from 4 years of age also with allergic rhinitis. The later presentation of allergic rhinitis with other non-IgE-mediated allergies is poorly understood and causality cannot be inferred, but as with AD and asthma, it should be noted that children with non-IgE-mediated allergies in particular EoE may present later on with allergic rhinitis,

similarly to the traditional Allergic March, but further longitudinal studies are required to understand the progression through atopic co-morbidities better.

5 | OVERLAP BETWEEN NON-IGE-MEDIATED AND IGE-MEDIATED ALLERGIES IN THE ALLERGIC MARCH

There is clear overlap between IgE- and non-IgE-mediated allergic conditions, which needs to be taken into account in the progression of the proposed evolved model of the Allergic March. Concomitant IgE sensitization in all types of non-IgE-mediated gastrointestinal allergies in children has been described by Meyer et al¹⁴ where 29% of their cohort were shown to be sensitized to one or more food allergens; however, this was not confirmed with a food challenge. In children with FPIES, between 4% and 30% have been found to have positive IgE/skin prick test to one/more foods and this has been associated with prognosis; in particular, cow's milk FPIES has a worse prognosis if specific IgE was positive to the causative food.⁴⁶

In EoE, food and environmental allergen (in particular pollen) sensitization has been found in 75% and 79% of cases, respectively.^{19,86} Rezende et al⁸⁵ found that 71% of children were sensitized to either foods or environmental allergens, of which 68% were sensitive to at least one inhalant allergy and either house-dust mite or dog epithelia. The most common food allergens in EoE include milk, wheat, soya and egg, with 36% of children according to Erwin et al⁸⁷ having a positive specific IgE to milk ranging from 0.42 Ku/L to 12.5 KU/L. However, there is clear interplay between IgE-sensitization and EoE, with recent studies indicating immunotherapy for IgE-mediated allergy leading to the development of EoE in a small number of subjects and some symptoms improvement (not all) on elimination diets based on IgE testing. A recent retrospective review grouped patients into two groups, EoE with IgE-mediated food allergy (29%) and EoE without IgE-mediated food allergy (29%).⁸⁹ That study found that children with EoE and IgE-mediated food allergy presented were significantly younger (6.05 years vs 8.05 years) and early presentation was different in those with IgE-mediated allergy, who presented with urticaria alone (33%) or with a combination of urticaria and vomiting (33%), but systemic and respiratory responses were also seen in some patients. Furthermore, those with IgE-mediated food allergy had significantly more dysphagia, poor appetite, cough and gagging at presentation than children without IgE-mediated food allergy and heartburn was a much more common feature if IgE allergy was not present.⁸⁸ There is also emerging evidence that in a small cohort of children who have undergone oral immunotherapy (OIT) for IgE-mediated food allergies or grass pollen allergies, that they develop EGID as a side effect of the OIT.⁸⁹⁻⁹¹

Although EoE provides the best example of IgE sensitization also being present in non-IgE-mediated gastrointestinal allergies, it is known that IgE-mediated allergies may also occur in other

non-IgE-mediated conditions. It seems therefore prudent to also reflect this overlap in the updated Allergic March.

6 | FUNCTIONAL GASTROINTESTINAL DISORDER

The progression from onset of non-IgE-mediated food allergies and its association with gastrointestinal symptoms in later life have been highlighted by parents and observed by physicians for some time. Functional gastrointestinal disorders (FGID) are characterized by the presence of chronic or recurrent digestive symptoms without an underlying identifiable structural or biochemical abnormality.⁹² Bonilla & Saps reviewed the impact of early-life events and the development of FGID and found that early gastrointestinal inflammation, including acute bacterial gastroenteritis and CMPA, increased the risk of developing FGID.^{93,94} The suggestion that early-life CMPA increases the risk was based on 2 studies, one on children aged 10 years, with a history of CMPA diagnosed at less than 1 year of age. That study found that 45% of children (n = 56) had gastrointestinal symptoms when using milk and milk products freely.⁴² The authors of this study did acknowledge that the symptoms were mild and vague and labelled this as "residual intestinal disease." The second study, published by the same group found that 42% of children with a history of CMPA from less than 1 year of age had gastrointestinal symptoms at a mean age 8.1 years and 19.2% of this cohort had a confirmed diagnosis of FGID using the Rome III criteria. This was significantly higher than matched healthy controls without a food allergy history.⁹⁴ The association between non-IgE-mediated food allergies in early life and the later presentation of FGID is still poorly understood, but healthcare professionals need to be aware of a possible link, not only in the design of future longitudinal studies, but also to coordinate care for patients that may return in later childhood with different abdominal symptoms.

7 | EXTRA-INTESTINAL MANIFESTATIONS (EIM)

Although the gut-brain axis has been well described by many authors, the association between non-IgE-mediated gastrointestinal food allergies and extra-intestinal manifestations is relatively new.^{95,96} Dominguez-Ortega et al⁹⁷ described EIM in children with non-IgE-mediated food allergies and found them to be increased compared to a control group of IBD patients. In 84.4% of children with this food allergy, EIM were reported, including fatigue, mouth ulcers, joint pain/hypermobility (ie, Ehlers-Danlos syndrome), night sweat, poor sleep, headache and enuresis. The majority of children (231/53%) had 3 or more of these EIM, with symptoms presenting between 3 and 4 years of age according to current data. However, it may be that they do occur earlier, but current symptom recognition is dependent on children reporting them. Extra-intestinal manifestations have also been reported in EoE: Abonia et al⁹⁸ found an eightfold increased risk in having

connective tissue disorders (including joint hypermobility disorders like Ehlers-Danlos syndrome) related to oesophageal transcript profiling which identified a specific gene profile including COL8A2. Although connective tissue disorders have been linked to gastrointestinal symptoms in adults, there is to date no evidence of connective tissue disorders being a risk factor for EoE. Although EIMs seem more commonly reported in children with non-IgE-mediated allergies, there is insufficient evidence to suggest causality. However, this is an intriguing area that will require more exploration as part of the evolving non-IgE-mediated Allergic March.

8 | PROPOSED EVOLUTION OF THE ALLERGIC MARCH

From the aforementioned data, it is clear that non-IgE-mediated food allergies and atopic allergic disorders, including AD, asthma and allergic rhinitis, co-exist in children with non-IgE-mediated allergies. AD presents in early infancy, but this occurs at a similar time as the onset of non-IgE-mediated gastrointestinal food allergic symptoms, and therefore, causality either way cannot be inferred and either may be the first manifestation of the non-IgE-mediated Allergic March. The exception is EoE, as the recent study by Hill et

al⁷³ found the peak onset at 2.6 years of age, with AD and asthma starting earlier, thereby EoE being a late presentation of the Allergic March. Similarly, many children with non-IgE-mediated allergies also develop asthma and rhinitis, but with current data (outside of EoE), these have been documented only as concomitant atopic co-morbidities that occur from around 3 years of age and causality cannot be inferred. In EoE, rhinitis has been associated with IgE sensitization; however, similarly to other atopic co-morbidities in other non-IgE-mediated allergies, with current data a “march” from rhinitis to EoE cannot be assumed. (Figures 2 and 3).

In regard to progression of non-IgE-mediated gastrointestinal disorders, although the majority have their origin in early infancy, the prognosis varies, in particular as overlap between non-IgE-mediated conditions (ie, same patient having allergic dysmotility and food protein-induced allergic proctocolitis) has been documented.¹⁴ Although most of the other non-IgE-mediated food allergies are outgrown by school age, several studies hint towards a small subset of patients that continue beyond this age; in particular, this has been shown in FPIES. EoE is an exception in regard to prognosis, as it does not only present from early childhood, but continues beyond adolescence into adulthood. (Figure 2).

The reported presence of EIM in gastrointestinal allergy also needs to be considered in the progression of disease. New data

FIGURE 2 Proposed non-IgE-mediated Allergic March including all non-IgE-mediated allergic conditions, age of development and resolution, evolution of atopic co-morbidities and EIM

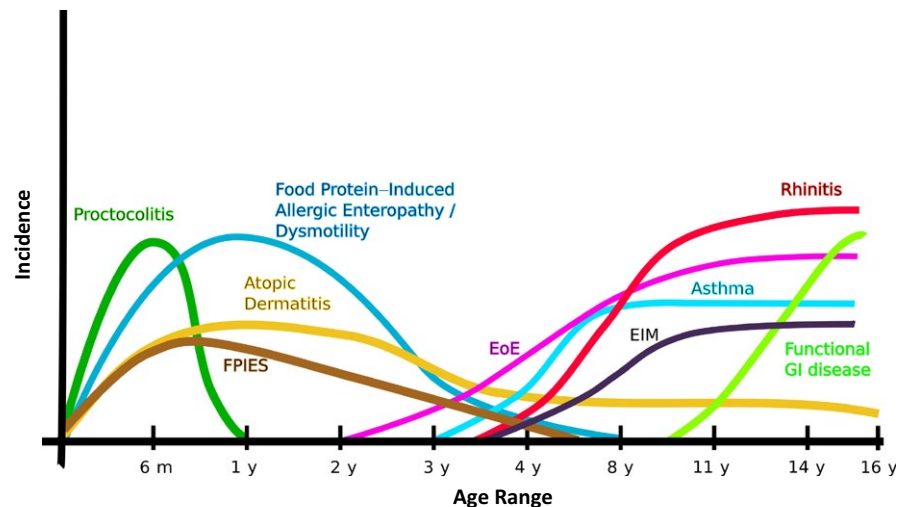
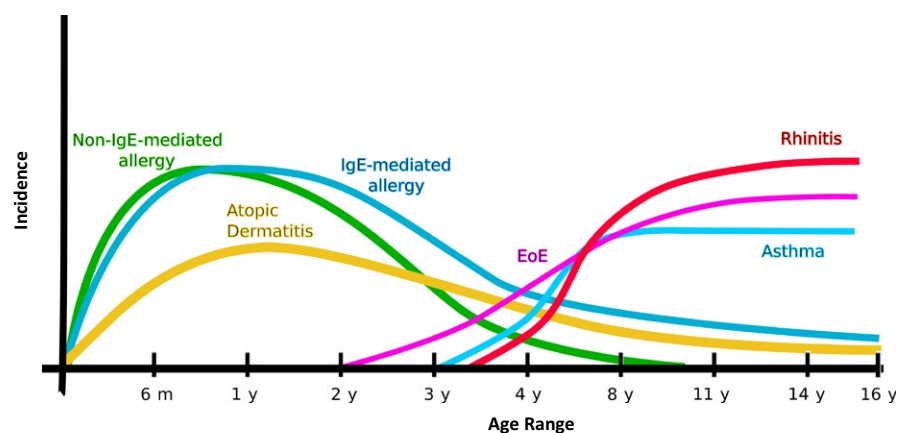


FIGURE 3 Proposed integrated IgE- and non-IgE-mediated Allergic March



also indicate a possible association between an early history of, in particular, cow's milk allergy and the development of FGID, that needs to be taken into account with future studies but should also be included in the clinical history taking of older children with FGID. (Figure 2).

Significant limitations to the proposed Allergic March exist as many included studies are retrospective, observational and there is a lack in longitudinal prospective and epidemiological data. In addition, due to the delayed nature of non-IgE-mediated allergies, diagnosis confirmation in older studies did not use the elimination and reintroduction technique and studies are often based on home reintroduction of foods with reported symptoms (outside of FPIES). This can lead to a real lack of precision in diagnosis and disease classification and may mean that other causes of the same symptoms cannot be ruled out. In addition, data on prognosis on many of the diagnoses are questionable.

Reported Atopic co-morbidities often were established through record review or the diagnosis relied on paediatrician opinion rather than a strict diagnostic criterion. The authors also acknowledge that significantly more data are required to elaborate on this new evolution of the newly proposed Allergic March model; however, similar to the original Allergic March, when published many years ago, the existing data points towards an association in atopic and non-atopic disorders that may guide the progression of research in non-IgE-mediated gastrointestinal allergies to enable better management strategies and co-operation between different medical specialities.

9 | CONCLUSION

This publication proposes for the first time a non-IgE-mediated Allergic March, indicating the age of presentation of various non-IgE-mediated gastrointestinal disorders, its association with AD, asthma and rhinitis. In addition to highlighting associations with atopic co-morbidities well-known to IgE-mediated allergies. The proposed non-IgE-mediated Allergic March also highlights the unique presentation of EIM and functional gastrointestinal disorders observed in later childhood. Although significant limitations are acknowledged by the authors to the current proposed non-IgE-mediated Allergic March, the hope is that having this better defined will inform future studies on prevention, intervention and changing the course of this allergic disease.

CONFLICT OF INTEREST

RM - academic lectures for Danone, Mead Johnson and Abbott, Research Funding Danone AF - academic lectures & consultancy for Danone, Mead Johnson and Abbott, Research Funding Danone. Director of KCL Allergy Academy, which receives funding from Danone, Mead Johnson & Abbott. ACL - no conflict of interest LM - academic lectures for Nutricia, Mead Johnson, ALK and Allergy Therapeutics, research funding Danone NS - academic lectures for Danone, Mead Johnson and Nestle

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