

Review

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Non-IgE mediated food allergies in breastfed children: A clinical challenge

Rosan Meyer^{1,2,3} and Imke Reese⁴

¹Department Medicine, Imperial College London, London, ²Department Nutrition and Dietetics, Winchester University, Winchester, Great Britain, ³Faculty of Medicine, KU Leuven, Belgium, ⁴Nutrition therapy, Munich, Germany

Key words

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Abstract. The prevalence of non-immunoglobulin E (IgE) mediated food allergy is poorly established outside of cow's milk allergy, with a challenge-proven adjusted incidence ranging between 0.13 and 0.72%. The presence and presentation of non-IgE mediated allergy in exclusively breastfed infants is highly debated. The dilemma this poses for healthcare professionals and parents, is on the one hand the unwarranted elimination and therefore health risk to the breastfeeding mother and on the other hand under-recognition of a food allergen being a culprit in the non-IgE mediated symptoms of breastfed infants. Current international guidelines recommend exclusive breastfeeding ideally until ~ 6 months of age and the German guidelines 4 – 6 months. It is also acknowledged that breastfeeding should be promoted also within the population of food-allergic infants. This review paper aims to assess non-IgE mediated food allergies in breastfed infants using an evidence-based approach and provides clinicians working with these patients with practical guidance.

infants from different European countries, found a challenge-proven adjusted incidence ranging between 0.13 and 0.72% [1]. In the United Kingdom, non-IgE mediated CMA was more prevalent than IgE mediated CMA, conversely, no non-IgE mediated CMA was reported in Iceland, Spain, Germany, Greece, and Lithuania [1]. The latter highlights an important problem with the current prevalence data on non-IgE mediated allergy, in that it is difficult to diagnose and often poorly recognized [2].

There is limited data of non-IgE mediated allergy involving other common allergens in children (i.e., soya, wheat, egg). Although this is reported in observational studies and healthcare professionals working in food allergy also have made this observation, the elimination of these food allergens is often based on experience rather than clinical research [3].

The presence of food allergy in exclusively breastfed infants remains a highly debated topic. The most commonly quoted study in breastfed infants is on CMA by Høst et al. [4] from 1988. This study found that 0.5% of the 2.2% children diagnosed with a challenge-proven IgE mediated CMA presented whilst being exclusively breastfed [4]. However, this is data on IgE mediated allergy and not non-IgE mediated allergy, but

Introduction

The prevalence of non-immunoglobulin E (IgE) mediated food allergy is poorly established outside of cow's milk allergy (CMA). The EuroPrevall Study, based on over 12,000

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Correspondence to: Rosan Meyer, RD, MSc Nutrition, PhD, Department Medicine, Imperial College London, Lpndon, GB, r.meyer@imperial.ac.uk

does imply plausibility of reactions occurring in breastfed infants. Current guidelines [5, 6, 7] recommend exclusive breastfeeding ideally until ~ 6 months of age [8], with German guidelines suggesting 4 – 6 months, and acknowledge that breastfeeding should be promoted also within the population of food-allergic infants. This paper aims to provide an evidence-based overview of the diagnosis and management of non-IgE mediated food allergy in breastfed infants.

Can food allergens through breastmilk lead to symptoms?

At the heart of the debate of non-IgE mediated allergy in breastfed infants, is the question to whether maternally consumed food allergens can lead to symptoms. A recent scoping review found 27 studies assessing bovine milk protein in breastmilk that included data on the type of sampling method, the sampling time, the lactation stage, maternal allergy status, and, most importantly, the impact on the infant [9]. This publication found the presence of β -lactoglobulin, a bovine milk protein, in human breastmilk at similar levels previously published by Høst and Halcken (range 0.9 – 150 $\mu\text{g/L}$) [9, 10]. Interestingly, they found that in some breastmilk samples, β -lactoglobulin was detected up to 7 – 10 days after stopping the consumption of cow's milk [9]. This review found a significant correlation between high levels of β -lactoglobulin in breast milk to clinical manifestations such as diarrhea, vomiting, colic, or eczema, which are all typical non-IgE mediated symptoms [11, 12]. Additionally, one study found that most of the infants with CMA reacted to cow's milk challenge through human milk with the appearance of eczema in addition to, in some patients, diarrhea, abdominal pain, and regurgitation, at β -lactoglobulin level concentrations between 0.01 and 11.54 ng/mL [13].

The correlation of clinical manifestations and β -lactoglobulin does however not prove causality. This was argued by Munblit et al. [14] in 2020, who, based on a theoretical calculation, suggested that only 1 in 600 breastmilk samples, would contain sufficient β -lactoglobulin to elicit a reaction in 1% of the most sensitive patients with CMA. Indeed, in the publication by Franco et al. [9]

this point was also considered with only a few samples from three studies reaching a level of β -lactoglobulin $\geq$ eliciting dose for 1% (ED01) of allergic individuals, and in no case did the samples contain beta-lactoglobulin in concentrations $\geq$ ED05 [12, 15, 16]. The probability therefore, according to this publication, of having enough β -lactoglobulin in breastmilk to trigger an allergic reaction has been estimated at 1 : 2,893 [9].

There are several problems with the aforementioned theoretical calculations. The first and most obvious is that the ED01 and ED05 have been based on IgE mediated allergy. Additionally, the testing method, maternal atopy, and the pathophysiology of non-IgE mediated allergy has not been considered in calculating potential reactions of cow's milk protein through breastmilk. Studies have shown marked difference in human breastmilk between allergic versus non-allergic mothers, including the levels of short-chain fatty acids [17], which impact the gut microbiota of the infant. Additionally, protease inhibitors and apolipoproteins were present in much higher concentrations in breastmilk of allergic versus non-allergic mothers. These proteins have been suggested to be linked to both allergy and asthma [18]. Levels of β -lactoglobulin have also been found to be higher in the breastmilk of allergic mothers [19]. It has been hypothesized that maternal allergy status may impact on the digestion and absorption through a gut that may have increased permeability and therefore explain the higher level of β -lactoglobulin [9]. Differences in the composition of breastmilk in atopic versus non-atopic mothers have also been documented, which may also impact on how infants respond [12, 16, 20]. Finally, the authors of the recent scoping review have suggested that the quantitative evaluation of bovine β -lactoglobulin in human milk by ELISA could give rise to misleading interpretations. The inconsistency of the results obtained with immunochemical methods has been demonstrated in studies when samples previously positive for ELISA were not confirmed by high performance liquid chromatography and tandem mass spectrometry (HPLC-MS) [21]. Franco et al. [9] therefore suggest that a new analytical perspective for the detection of food allergens in human milk from intact proteins to digested peptide fragments is considered.

Table 1. Non-IgE mediated allergic disorders, symptoms, and differential diagnoses (taken from the European Academy for Allergy and Clinical Immunology position paper on the management of non-IgE mediated allergies in breastfed infants) [27].

Non-IgE mediated food allergy	Cardinal symptom	Additional symptoms	Differential diagnoses
Food protein-induced enterocolitis syndrome (FPIES) [28]	Acute FPIES: Vomiting 1 – 4 hours after ingestion Chronic FPIES: intermittent but progressive vomiting and diarrhea	Acute FPIES: pallor, lethargy, hypovolemia, hypotension, diarrhea Chronic FPIES: faltering growth	Gastro-esophageal reflux disease, sepsis, inborn errors of metabolism, pyloric stenosis, malrotation, intussusception, gastroenteritis with vomiting
Food protein-induced allergic proctocolitis (FPIAP)	Blood in stool	Occasional loose stools, mucous in the stools, painful flatus, anal excoriation	Gastrointestinal infections, fissures Infantile polyp, necrotizing enterocolitis, Meckel's diverticulum, intussusception, infantile inflammatory bowel disease (rare)
Eosinophilic esophagitis (EoE)	Intermittent vomiting, abdominal discomfort, feeding difficulties	Faltering growth	Gastro-esophageal reflux of infancy, infantile inflammatory bowel disease
Food protein-induced constipation	Straining with soft stools	Fecal impaction, bloating, abdominal pain	Normal straining associated with infancy, idiopathic constipation, Hirschsprung's disease
Food protein-induced gastro-esophageal reflux disease	Intermittent painful vomiting/regurgitation	Faltering growth, feeding difficulties, back-arching with pain	Gastro-esophageal reflux of infancy, acute gastroenteritis, food poisoning
Food protein-induced enteropathy (FPE)	Failure to thrive, diarrhea	Mucus and, bloating, abdominal pain, faltering growth, hypoalbuminemia	Sepsis, congenital disaccharide malabsorption, metabolic disorders, chronic kidney disease, neglect, secondary lactose intolerance, chronic FPIES, autoimmune enteropathies, epithelial dysplasia syndromes, cystic fibrosis, immunodeficiencies and/or chronic infection, coeliac disease

All of the aforementioned studies discuss the presence of bovine β -lactoglobulin in breastmilk and the potential to cause non-IgE mediated CMA, but other allergens such as soya, wheat, and egg have been detected in breastmilk and therefore also have the potential to elicit non-IgE mediated food-allergic reactions, but data to substantiate this is sparse and primarily based on clinical experience [22, 23].

Diagnosis

The diagnosis of non-IgE mediated allergy in breastfed infants is further complicated, because many of the symptoms (i.e., diarrhea, constipation, regurgitation, colic-type pain) overlap with pediatric functional gastrointestinal disorders (FGID) and other commonly occurring childhood diseases. Vandenplas et al. [24] performed a worldwide assessment of FGID and found that 29% of infants suffered from regurgitation and 18% and 9% from constipation or diarrhea, respectively. The risk of overdiagnosis of non-IgE mediated CMA based on frequently used guidelines, which include these com-

mon symptoms, has been documented, with two recent publications [14, 25]. Neither of these publications however have acknowledged the fact that none of the guidelines suggest the application of symptoms without an allergy-focused history that includes a feeding history (including an assessment of the maternal diet) and considering this in context of the presenting symptoms, growth assessment of the infant, consideration of other diagnosis, and allergy testing (where appropriate). Whilst overdiagnosis is a risk, one also needs to acknowledge that underdiagnosis and delay in diagnosis still occurs as well [1, 26]. It is therefore critical, that the diagnostic process for a non-IgE mediated allergy starts with an allergy-focused history and eliminating differential diagnoses (Table 1).

There are currently no recommended biomarkers for the diagnosis across the spectrum of non-IgE mediated allergies, which includes the breastfeeding infant presenting with these delayed symptoms. Some studies have proposed atopy patch testing to determine “delayed sensitisation” [29], however, this test has yielded conflicting results [30, 31, 32]. Additionally, inconsis-

tencies with patch test procedure and solution use was highlighted by Gonzalez et al. [33] in a study in 2018 on non-IgE mediated CMA. As a result of the poor reproducibility of patch testing, international guidelines do not recommend patch testing as a routine test for the diagnosis of non-IgE mediated allergies [5, 34].

IgG and IgG4 testing have also been suggested to support a diagnosis of non-IgE mediated allergy, but these tests have little established clinical validity and their use is also not recommended in routine clinical practice [35], alongside tests of gastrointestinal permeability and mucosal inflammatory markers [36, 37]. In breastfed infants with FPIAP, fecal blood is a cardinal symptom; however, testing for fecal occult blood has also been shown to be non-specific and unreliable in both the diagnosis and resolution of symptoms in non-IgE mediated allergies [38].

Whilst the absence of specific IgE is an expected characteristic of non-IgE mediated food allergies, some children may present with overlapping disease and allergic comorbidities associated with IgE sensitization (i.e., atopic dermatitis) [39, 40]. This has been reported in FPIES, eosinophilic esophagitis (EoE), and other recognized non-IgE mediated conditions where symptoms of atopic dermatitis, co-existing IgE mediated allergy and IgE mediated environmental allergies have been reported [40, 41]. An allergy-focused history should therefore guide the decision to perform targeted IgE/SPT [39, 40], but the interpretation of results requires careful consideration and may require oral food challenges (OFCs).

Finally, endoscopy is commonly reported in research related to the diagnoses of various non-IgE mediated allergic conditions, including EoE, where this is an essential diagnostic tool. As this procedure can be technically difficult in young infants and requires full anesthesia, the EAACI position paper suggests that endoscopy only be performed when there is a strong suspicion of an alternative diagnosis or unremitting symptoms [27].

Dietary management

The maternal dietary elimination of offending allergens remains the mainstay for

dietary management of non-IgE mediated allergies in breastfed infants. The most commonly reported allergen is cow's milk, but a non-IgE mediated allergy in breastfed infants to soya, egg, and wheat has also been described [42, 43]. All of these allergens contribute significantly to the maternal diet and have the potential to negatively impact on the nutritional status of the breastfeeding mother [44] as well as the micronutrient content of breastmilk [45, 46]. It is therefore important to avoid unnecessary elimination diets and support the mother and child with nutrient optimization and targeted micronutrient supplements (i.e., vitamin D) where necessary.

The length of a diagnostic elimination diet in non-IgE mediated food allergies varies according to guidelines but is usually between 2 and 4 weeks. Clinicians need to also take into account that circulating β -lactoglobulin can be detected up to 7–10 days after the elimination [9]. Lozinsky et al. [41] found that the majority of children with non-IgE mediated allergy had improvement of symptoms within 4 weeks; however, data were mainly based on non-breastfed children. All guidelines recommend the reintroduction or challenge for the confirmation and also assessment of tolerance [5, 34]. Outside of FPIES (where guidelines for challenges have been published) [47], almost no data exist on the reintroduction/challenge for confirmation of non-IgE mediated allergies. In the breastfed infant with non-IgE mediated allergies, an additional question is raised to whether reintroduction should occur through the mother's diet or as a complementary food in the infant's diet. There is no data to guide the decision for clinicians, and therefore the EAACI guidelines suggest that this decision should primarily be driven whether the child is still exclusively breastfed or whether complementary food/formula feed has been introduced [27]. In infants that have complementary foods/or some hypoallergenic formula as part of their diet, a direct reintroduction (through standard infant formula or foods) is likely to yield a less ambiguous result and lead to the faster expansion of tolerated foods, whereas the introduction through the maternal diet may take longer to provide an answer and only confirms a tolerance to low levels of β -lactoglobulin, but not cow's milk and its derivatives in normally consumed amounts.

Table 2. Clinical practice points on the diagnosis and management of non-IgE mediated allergy in breastfed infants.

An allergy-focused history is the cornerstone of the diagnosis of a non-IgE mediated allergy in breastfed infants.
Most research has been published on cow's milk as common culprit food, but egg, soya, and wheat may also need to be considered.
Current guidelines suggest a trial of 2 – 4 weeks of maternal elimination diet (with symptom improvement) followed by the reintroduction of the offending allergen (with symptom deterioration) to confirm a diagnosis.
No biomarkers are recommended for non-IgE mediated allergies, unless there are symptoms of an IgE mediated allergy.
Unwarranted dietary elimination should be avoided, as this increases the nutritional risk for the mother and infant.
Targeted micronutrient supplementation should occur following a dietetic assessment.
There are no clear guidelines on how to re-introduce food allergens in breastfed infants, outside of data on the milk ladder and challenge guidelines for FPIES.

The updated iMAP guidelines on non-IgE mediated allergies, recommend in exclusively breastfed children that cow's milk products should be reintroduced in the mother's diet in previously consumed amounts over a 1-week period [48]. The latter recommendation was made based on data from Järvinen et al. [13] in a challenge-proven non-IgE mediated cow's milk-allergic breastfed cohort. In this cohort, 16/17 infants reacted within a mean time of 21 hours (2 – 80 hours) after the reintroduction of cow's milk in the lactating mother's diet. Although it is well known that other allergens (i.e., egg, soya, wheat) do transfer through breast milk [22, 49], there are no studies on the reintroduction to confirm food allergies for these foods in breastfed infants, and therefore the protocol is heavily influenced by local practice.

For breastfed infants with non-IgE mediated allergies who are already on solids, there is also very limited data. The iMAP guidelines provide a consensus-based milk ladder, which has been constructed on the existing data that heating and fermentation reduces the allergenicity of cow's milk [50, 51, 52]. This step-wise reintroduction approach has gained popularity and, from what is known, is safe [53], but there is to date no data on efficacy and there is a need for standardization [54]. For other allergens (i.e., egg, soya, wheat) there is only one study by Meyer et al. [55] describing the re-introduction using a ladder approach. Whilst this study provides some guidance, it is heavily influenced by local practice.

Conclusion

Non-IgE mediated allergies in breastfed infants remains a complex diagnosis that needs careful clinical consideration. There is the concern of both over- and underdiagnosis and most importantly the nutritional risk for the mother when unwarranted elimination diets are used.

Table 2 summarizes the clinical practice points from this publication for clinicians working in this field for their day-to-day practice.

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