Non-Immunoglobulin-E mediated gastrointestinal food allergy in children: diagnosis, management and clinical impact

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PhD 2019

Non-Immunoglobulin-E mediated gastrointestinal food allergy in children: diagnosis, management and clinical impact

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Thesis submitted in partial fulfilment of the requirements of the Manchester Metropolitan University for the degree of Doctor of Philosophy

Faculty of Health, Psychology and Social Care

Manchester Metropolitan University

2019

ABSTRACT

Background: Despite all research published in the last decades, the prevalence of food allergy in the paediatric population has continued to increase and is nowadays recognized as a significant public health problem. In the United Kingdom, studies have found that between 2.2% and 5.5% of the infants in the first year of life present with proven food allergies, with the prevalence of cow's milk protein allergy, the most common form of non-IgE food allergies, ranging between 1.9% and 4.9%. The diagnosis of non-IgE mediated food allergy is a real challenge due to its delayed onset, with symptoms occurring hours to days after ingestion of the culprit and mainly affecting the gastrointestinal tract. Allergy tests have shown limited use in these patients, and the diagnosis relies heavily on the recognition of symptoms and an allergy-focused history. The treatment is based on diet elimination, which can lead to the development of nutritional disorders and negative impact on the child's quality of life.

Objectives: The aims of the publications included in this thesis are, first, to prospectively investigate the required length of elimination diet to achieve symptom improvement during the diagnostic process; second, to evaluate the knowledge of primary health care professionals about diagnosis and management of cow's milk protein allergy, to compare with parents views and opinions, and to better understand diagnosis tools, treatment and tolerance in infants diagnosed with non-IgE food allergies; third, to evaluate possible impacts of the elimination diet on growth and nutrients deficiencies; and fourth, to analyse the potential impact of non-IgE mediated gastrointestinal allergies on the quality of life of the affected children and their families.

Methods: Children with suspected non-IgE mediated gastrointestinal food allergies were recruited and followed prospectively at a large tertiary gastroenterology department in the United Kingdom (UK) from December 2011 to November 2013. This study was designed to investigate the impact of non-IgE mediated food allergies on quality of life, as well as to establish symptoms, children's growth and the characteristics and impact of dietary elimination. The knowledge and journey of diagnosis of cow's milk protein allergy among general practitioners were studied via surveys. Eosinophilic colitis in infants was studied through a systematic review.

Results: In non-IgE mediated gastrointestinal food allergies the required time to achieve symptom improvement following the initiation of the elimination diet was four weeks in 98% of our patients. All symptoms individually and collectively have statistically improved after commencing the elimination diet ($p <0.001$). Regarding cow's milk protein allergy, parents and general practitioners have very different perceptions about the course of the disease and the families' journeys. An extensive review of the literature found that eosinophilic colitis occurred more frequently in male infants, younger than six months old. Half were exclusively breastfed at the time of the diagnosis. Patients on a diagnostic four-week elimination diet showed an improvement in the weight-for-age and weight-for-height. It was also noted that 60% of the cohort had low vitamin D intake and a higher number of patients had a low intake of copper, zinc, and selenium. Non-IgE mediated food allergies have a negative impact on the quality of life of the affected children and their families.

Conclusions: The "Discovering the effect of non-IgE mediated allergies on children and their families" is a landmark study in the paediatric food allergy field. This well-designed study investigated and elucidated some important characteristics and clinical features of this group of patients. Its impact is reflected in the number of publications derived from the results of this cohort, a large number of citations and the impact in clinical practice worldwide as much more is now known about this condition. Studies investigating preventative measures for the development of food allergies in childhood are also essential in the future.

ACKNOWLEDGEMENTS

I am grateful to my supervisors, Professor Caroline Haigh and Dr Gayatri Nambiar-Greenwood, for their guidance and support during the writing of this thesis.

I would like to thank Professor Rosan Meyer, for her guidance over the last five years. Without her support, guidance, patience and teaching this project would not have been possible.

I would like to thank Dr Neil Shah. I will be forever grateful to him for giving me the opportunity to work at the most renowned Children's Hospitals in the World under his inspirational approach to training Paediatric Gastroenterology.

I would like also to acknowledge the Gastroenterology Research team, Georgina Wallis, Heather Godwin, Kate Reeve, Ru-Xin M Foong and Robert Dziubak, for working with me in the "Discovering the effect of non-IgE mediated allergies on children and their families" study. I have learnt a lot from you all.

I would like to thank my colleagues and supervisors from Brazil and Australia. They are part of my past and future history and had valuable contribution to my carrier as a doctor.

Thank you to my parents, Sergio and Sonia and to my brother Fernando for all the support, guidance, patience and love, for incentive during my PhD year, but also for all my choices during my life so far.

This thesis is dedicated to my husband Daniel L. Rolnik and my son, André. Thank you for all support, patience and love, without you both this project would never been possible.

And my final thanks go to all the families and children who took part in the studies.

ABBREVIATIONS

BCE: Before Current Era

BMI: Body Mass Index

CMPA: Cow’s milk protein allergy

FPIAP: Food protein-induced allergic proctocolitis

FPIES: food protein induced enterocolitis syndrome

GPs: General Practitioners

IgE: Immunoglobulin E

HRQoL: health-related quality of life

NHS: National Health System

NIAD: The National Institute of Allergy and Infectious Diseases

NICE: The National Institute for Clinical Excellence

PedQL$^{\text{TM}}$: Pediatric Quality of Life Inventory

PedQL FIM$^{\text{TM}}$: Family Impact Module of the Pediatric Quality of Life

SD: Standard deviation

UK: United Kingdom

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1. INTRODUCTION

1.1 Overview

The understanding that food could cause adverse reactions in some individuals comes from Before the Current Era (BCE). Among the earliest documents is the Shi Jin-Jing (“Interdictions concerning food”) by the Chinese emperors Shen Nong (~2735 BCE) and Huang Di (2698-2598 BCE) in which they advised individuals with skin lesions (probably atopic dermatitis and urticaria) to avoid certain foods (Cohen, 2008). Hippocrates (460-377 BCE), in Ancient Greece, elevated the knowledge about food allergy as he recognised that food could cause adverse reactions and even death in some individuals (Cohen, 2008; Wuthrich, 2014). In his theory, the presence of “hostile humours” in some persons made them “suffer badly” after food ingestion. Nowadays, “hostile humours” are recognised as Immunoglobulin E (IgE) antibodies (Cohen, 2008; Sampson, 2016). Case reports of food hypersensitivity became more frequent in medical literature in the 17th century. In 1906, the term allergy was coined, introducing a new era of better understanding the function of the immune system (Igea, 2013).

The prevalence of food allergy in the paediatric population has increased in the last three decades, reaching epidemic numbers (Platts-Mills, 2015). The main food allergens in childhood are cow’s milk, hen’s egg, soy, wheat, fish and shellfish, peanut and tree nuts (Meyer, 2008).

Food allergy is currently recognised as a significant public health problem in western countries (Boyce et al., 2010; Burks et al., 2012) affecting 4-8% of all children (Gupta et al., 2011) and up to 10% of infants (Osborne et al., 2011). In the United Kingdom (UK), between 2.2% and 5.5% of the infants in the first year of life are diagnosed with proven food allergies (Venter et al., 2006), with the prevalence of cow’s milk protein allergy (CMPA) ranging between 1.9% and 4.9% (Fiocchi et al., 2010) and for hen’s egg and soy 2% and 1.9%, respectively (Clark et al., 2010; Katz et al., 2014).

The diagnosis and management of food allergy in infants and children pose a substantial economic burden and resource implications to national health systems worldwide. For the UK’s National Health System (NHS), the total cost of managing

CMPA in the first 12 months following the first consultation with the general practitioner (GP), has been estimated at £1,381 per patient and £25.6 million for an annual cohort of 18,350 infants. The main cost drivers are multiple GP visits (44%), clinical nutrition preparations (38%) outpatient visits (9%) and hospital admissions (6%)(Sladkevicius et al., 2010).

Despite all the research in the last decades and the increasing number of children with this disease, there remain many unanswered questions related to the pathophysiology, management, and prevention, which require further research.

1.2 Food allergy epidemic

The prevalence of food allergies has been rising in the last few decades, reaching epidemic proportions (Pawankar et al., 2008). The “first wave” of the allergy epidemic was described more than 50 years ago with the increase in the prevalence of asthma and allergic rhinitis (Prescott et al., 2013). The rise in food allergy is now described as the “second wave” of the allergy epidemic.

Although there is a lack of high-quality articles in the literature, multiple population-based cohort studies using other markers for the diagnosis of food allergy, such as hospital admission rates for food anaphylaxis, have provided consistent evidence that this increase in prevalence is real (Tang and Mullins, 2017).

It is uncertain if the increase in the prevalence of food allergy is due to a rise in the incidence (increase in the number of new cases) or to changes in the nature of the disease (persistence of food allergy throughout adolescence and adulthood). Probably both play a role in the rising incidence of the disease.

There is robust evidence that the prevalence of food allergy is increasing in western countries. Data from national databases have shown that hospital admission due to anaphylaxis has increased in the last ten to twenty years in the UK and United States of America (Turner et al., 2015; Rudders et al., 2014). In the UK, hospital admission for food anaphylaxis doubled from 1.2 to 2.4/10,000 between 1998 and 2012 (Turner et al., 2015). Although there are only a few published studies on the subject, it is possible to hypothesise that Africa and Asia may also have an increase in food allergy prevalence in the coming years with the economic growth and the adoption of a more westernized lifestyle. A study in China evaluated children aged 0-24 months and showed an increase in food allergy from 3.5% to 7.7% between 1999 and 2009 (Hu et al., 2010). Moreover, studies reported that children of East Asian and African ethnic origin who are raised in the western environment have an increased risk of food allergy when compared with western Caucasian children (Keet et al., 2014; Koplin et al., 2014).

1.2.1 Leading hypothesis for the rise of food allergies

The reasons why food allergy is on the rise are unclear. Multiple theories have been generated, but at present, there is insufficient evidence, with the majority based on epidemiological and ecological studies. Berni Canani et al. (2019) suggested that the epidemiology of food allergy is possibly influenced by epigenome-genome-environment interactions leading to gut microbiota alterations (dysbiosis) and consequent alterations on the immune system function (Figure 1) (Berni Canani et al., 2019). Postnatal factors, which are common and modifiable, are probably linked to the rise of food allergies (Allen and Koplin, 2016). Randomized controlled trials are required to evaluate the hypothesis and to generate more robust evidence.

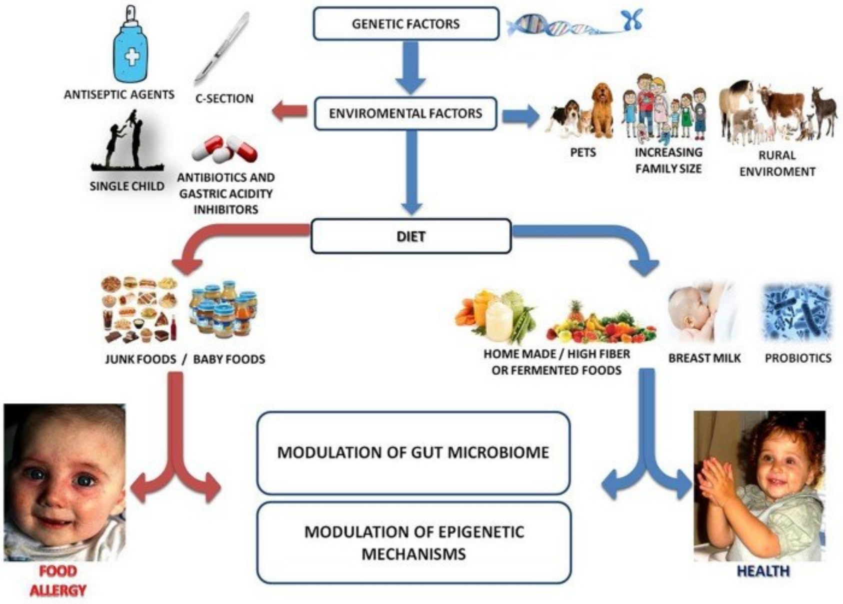

Figure 1.1- Scheme proposed by Berni Canani et al. (2019) about how genetic, environmental and dietary factors could influence the gut microbiome and consequently contribute to the occurrence and rise of food allergy during childhood – Taken from Berni Canani et al. (2019)

Nowadays, the five leading hypotheses for the increasing prevalence of food allergies are known as the “5Ds”: dry skin, diet, dogs, dribbles and vitamin D (Allen and Koplin, 2016).

1.2.1.1 Dry Skin

Many studies have shown a strong association between eczema (also known as atopic dermatitis) and both IgE mediated and non-IgE mediated food allergies. Martin et al. (2015) demonstrated that infants diagnosed with eczema are five times more likely to develop IgE mediated food allergies by one year of age (Martin et al., 2015). Another study analysed infants with eczema and controls in the first three months of life and showed that the food sensitisation rate was six times higher in the eczema group (Tsakok et al., 2016). Latcham et al. (2003) studied children with non-IgE mediated gastrointestinal food allergies and found that 44% of them have also been diagnosed with eczema by a paediatrician (Latcham et al., 2003). The mechanism underlying the association between food allergies and eczema is not well understood yet. The “dual allergen hypothesis” (Lack, 2012) proposes that children may become allergic to food through a damaged and inflamed skin (eczema), with food particles penetrating through a disrupted skin barrier and setting up an abnormal immune response, leading to allergic sensitisation.

In contrast, it is proposed that early oral exposure (consumption) to food proteins stimulates the immune system towards a tolerant response, preventing the development of food allergy (Lack, 2012) (Figure 2). The Learning Early About Peanut study is the first randomized trial that evaluated the “dual allergen hypothesis.” Du Toit et al. (2015) showed that early introduction of peanuts in the diet of infants diagnosed with severe eczema reduced the development of peanut allergy by 86% when compared to those who excluded peanut from their diets (Du Toit et al., 2015). Further research is required for a better understanding of the association between eczema and food allergies.

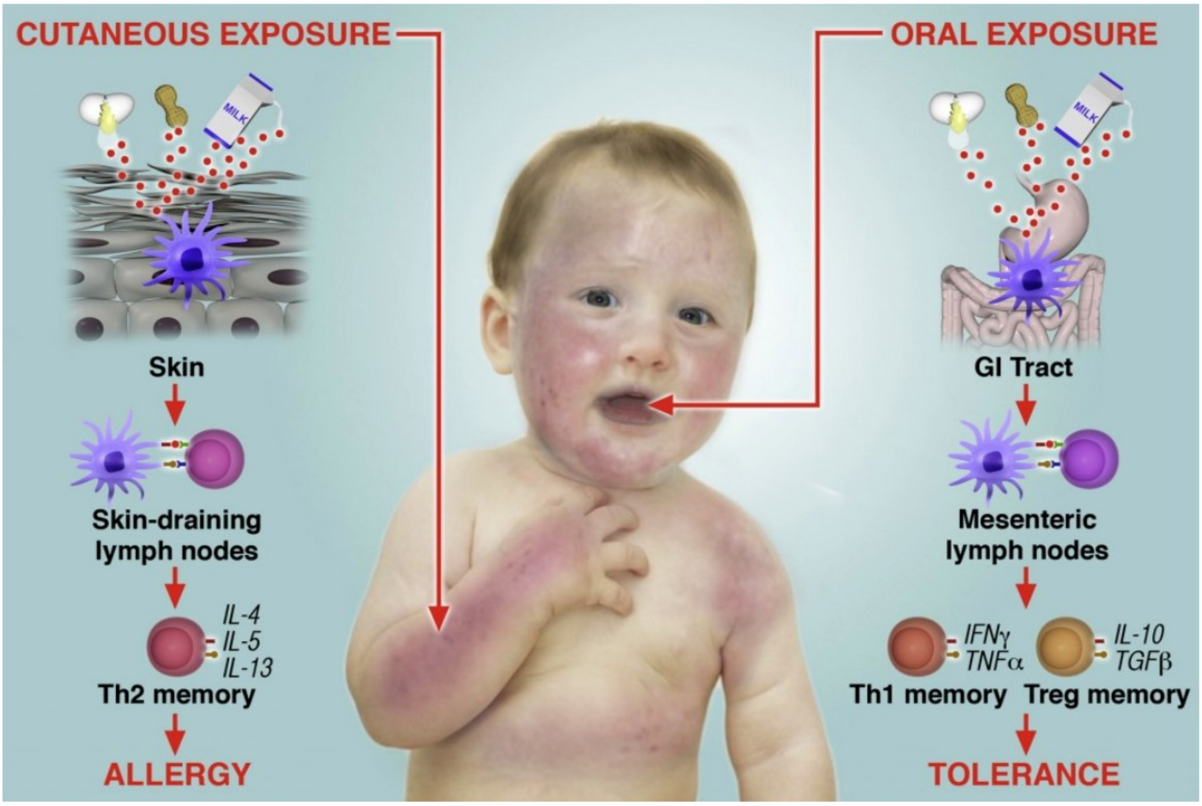

Figure 1.2 – The "dual allergen hypothesis" proposes different immune responses depending on the via of exposure (cutaneous or oral) to food allergens during infancy – taken from Lack G (2012).

1.2.1.2 Diet

Possibly, time of exposure to allergens and quality and variety of the diet are essential topics to be investigated and discussed when evaluating the association between diet and the development of food allergy. As discussed above, the Learning Early About Peanut study showed that early introduction of peanut in the diet (between 4 and 11 months of age) drastically reduced the development of peanut allergy when compared to avoidance in children with severe eczema (Du Toit et al., 2015). Although the Learning Early About Peanut study is the only randomized trial that evaluated food allergy outcomes related to the early introduction of food, other observational studies also demonstrated that a delay in the introduction of egg, cow's milk and wheat in children's diet might be associated with an increased risk of those food allergies (Katz et al., 2010; Koplin et al., 2010; Poole et al., 2006). Nowadays, guidelines from allergy experts' bodies suggest the introduction of solids including allergenic foods (cow's milk, egg, wheat, peanut, nuts, fish and sesame) between four and six months of age, while the World Health Organization still recommends the introduction of solids after six months of age (Koplin and Allen, 2013). The ideal age for food introduction during infancy is still debatable, and further knowledge and research are required.

Studies have also shown the importance of exposing infants to a high-quality and varied diet. Roduit et al. (2014) evaluated a cohort of 856 children from birth to six years of age. They found that increased diversity of complementary foods introduced in the first year of life was associated with a reduced risk of food allergy or food sensitization (Roduit et al., 2014). Furthermore, a case-control study found that an infant diet that includes high levels of fruit, vegetables, and home-prepared meals is associated with less food allergy by two years of age (Grimshaw et al., 2014).

1.2.1.3 Dribble and Dogs (microbial exposure)

In the last 50 years, the populations of industrialised countries have been through significant changes in lifestyle, including sanitation and family size (reduced number of children). During this period, there was a decline in infections and an increase in allergies and autoimmune diseases; however, the underlying mechanism for this change is not yet understood.

Strachan described that an increased number of siblings in a household was protective against the risk of developing allergic rhinitis (Strachan, 1989). The protective mechanism is possibly related to a shared microbiota, which potentially contributes to microbiota diversity, and shared exposure to common childhood infections between siblings. Studies have shown that the protective effect of the increased number of siblings can also be extended to food sensitisation and allergy (Marrs et al., 2013). The hypothesis that microbiota diversity is protective against the development of allergies is known as the “hygiene hypothesis.”

The Healthnuts group, from Australia, has also demonstrated that dog ownership has a protective effect on food allergy risk (Koplin et al., 2012). This finding contributes to the idea that sharing microbes and parasites (with siblings or domestic animals) can reduce the risk of developing a food allergy.

Following the idea of the “hygiene hypothesis”, researchers investigated the potential protective role of probiotics in allergy prevention. However, a systematic review concluded that there is still not enough evidence (Koplin et al., 2012) to support this intervention.

1.2.1.4 Vitamin D

It is well recognised that the prevalence of food allergy has increased and the levels of vitamin D in the population have decreased in the last few decades. Studies have estimated that up to 50% of the population in Western countries are vitamin D insufficient and up to 10% are vitamin D deficient (Ginde et al., 2009; Mansbach et al., 2009).

Interestingly, hospital visits (emergency department) for food allergy, prescription of adrenaline for anaphylaxis treatment and hypoallergenic formulas are more common in regions further from the equator (Mullins et al., 2009; Mullins et al., 2010; Rudders et al., 2010). These findings appear to be independent of longitude, physician density, and socioeconomic status, potentially reflecting lower vitamin D exposure. More studies are required for a better understanding and evaluation of the association between food allergy and low levels of vitamin D.

1.3 Classification of food allergy

The National Institute of Allergy and Infectious Diseases (NIAID) published in 2010 a guideline to assist health care professionals in making appropriate decisions when evaluating patients that had adverse reactions to food. Firstly, they classified adverse food reactions into two large groups: Immune mediated and non-immune mediated (Figure 3) (Boyce et al., 2010). The formerly included food allergies and coeliac disease and the latter included food intolerances primarily (for example lactose intolerance).

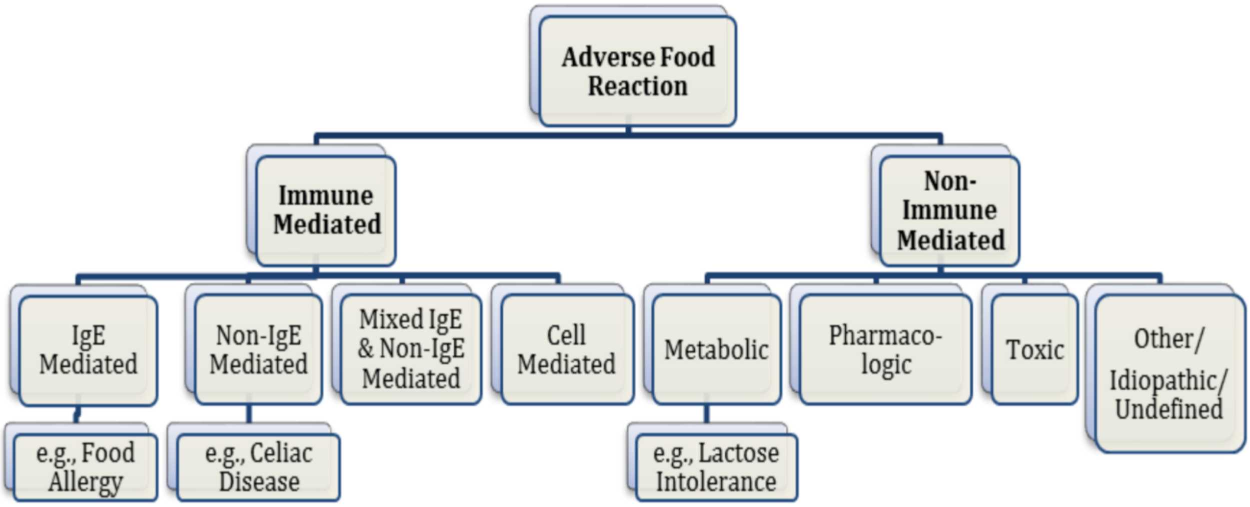

Figure 1.3 – Classification of adverse reactions to food. Figure based on the Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report (Boyce et al., 2010).

Subsequently, food allergies have been further classified into three categories: Immunoglobulin E (IgE) mediated, Non-IgE mediated and mixed IgE and non-IgE mediated (Figure 4) (Boyce et al., 2010).

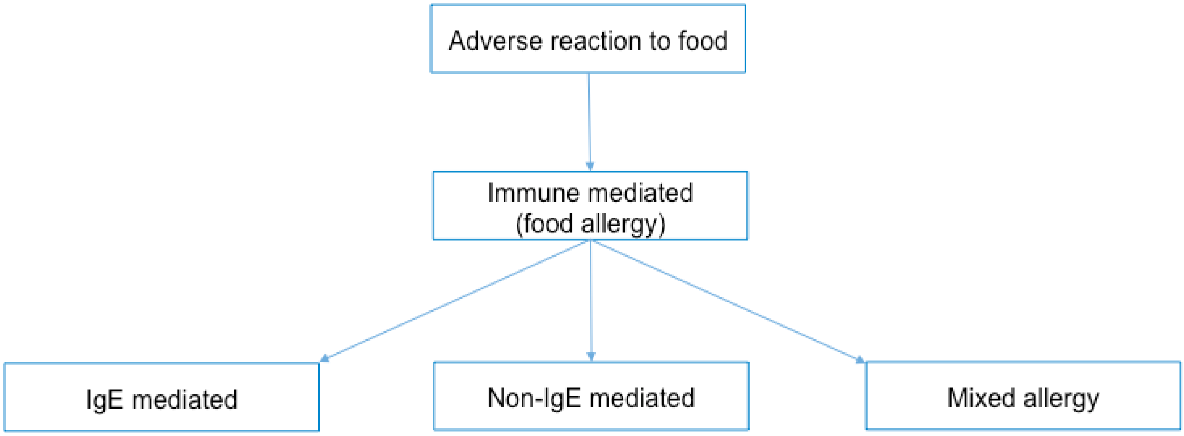

Figure 1.4 – Classification of food allergies – adapted from the guideline of NIAID (Boyce et al., 2010).

The pathophysiology of IgE mediated food allergy is well studied and understood. The literature on this subject is plentiful, and many guidelines have been published. The allergic symptoms can occur immediately and up to two hours after the ingestion of the food allergen. The symptoms are objective and include lips swelling (cutaneous angioedema), rash, urticaria, itching, sneezing, wheezing and in the severest form, systemic reaction leading to anaphylaxis (Muraro et al., 2014b). Allergy tests for this immediate type of reaction are well established and include skin prick test and specific IgE blood tests (to specific allergens and their components) (Berin, 2015; Boyce et al., 2010; Walsh and O'Flynn, 2011).

Conversely, the pathophysiology of non-IgE mediated food allergy is not entirely understood, and the diagnosis can be challenging due to the delay of symptoms onset that can occur up to 72 hours after the consumption of the food allergen. The National Institute for Clinical Excellence (NICE) guidelines (Walsh and O'Flynn, 2011) highlight that non-IgE mediated symptoms generally affect both the gastrointestinal tract and skin and the most common symptoms include abdominal or colicky pain, vomiting, diarrhoea or constipation, blood and/or mucus in the stools, food aversion and eczema. Complicating the diagnosis is the fact that the aforementioned symptoms also occur in other gastrointestinal disorders, like infantile colic and lactose intolerance, and are not specific to food allergy (Walsh and O'Flynn, 2011). Allergy tests have limited value in this group (Boyce et al., 2010; Mowszet et al., 2014). Therefore the diagnosis is based on the oral food challenge test in which there is a symptom improvement during the elimination diet followed by reappearance of the symptoms during the food challenge (Heine, 2015).

1.3.1 Definition and Classification of Non-IgE mediated allergies

Non-IgE mediated food allergies correspond to a group of immune mediated allergic diseases with a delayed onset, where IgE has no or limited involvement. Non-IgE mediated food allergies is an umbrella term that includes different gastrointestinal allergic disorders and non-IgE mediated atopic dermatitis.

The non-IgE mediated gastrointestinal food allergy encompasses food protein-induced allergic proctocolitis (also known as eosinophilic colitis) food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy, and eosinophilic gastrointestinal disorders (Caubet et al., 2017).

1.3.1.1 Food protein-induced allergic proctocolitis (eosinophilic colitis)

Food protein-induced allergic proctocolitis (FPIAP) is the infantile form of eosinophilic colitis. This disorder typically presents in the first three months of life, and its primary clinical manifestation is the presence of blood in the stools (haematochezia), which may be visible blood in the stools or microscopic (Meyer et al., 2013; Nowak-Wegrzyn et al., 2015). FPIAP is a common and frequent form of non-IgE mediated food allergies, and it is estimated that it accounts for up to 60% of the cases of haematochezia in healthy infants (Atanaskovic-Markovic, 2014; Nowak-Wegrzyn et al., 2015). Affected infants typically appear well and thriving; however, other symptoms such as mucous in the stools, gas, colic-like symptoms, and increased frequency of bowel movements can also be present. The commonest causative food is cow's milk, although soy, egg and wheat may also play a role (Meyer et al., 2013). FPIAP is a cell-mediated inflammation of the distal sigmoid colon and rectum characterized by oedema and erosions of the mucosa; histological examination shows eosinophilic infiltration of the epithelium and *lamina propria* (Figure 5) (Odze et al., 1993). It is believed 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 (Tsabouri et al., 2017). According to several publications, the majority of infants with FPIAP will become tolerant to the offending foods by around 14 months of age (± 11 months) (Erdem et al., 2017; Lake, 2000).

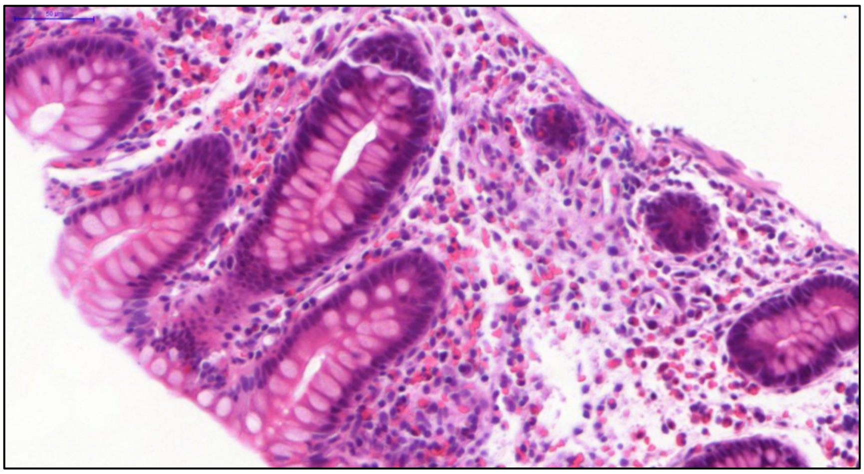

Figure 1.5 – Optical microscopic photography of the colonic mucosa demonstrating numerous eosinophils infiltrating the *lamina propria*.

1.3.1.2 Food protein-induced enterocolitis syndrome (FPIES)

FPIES can be classified as acute or chronic. The acute form of this disorder is characterized by profuse vomiting, frequent accompanied by pallor and/or lethargy one to four hours after the ingestion of the food culprit, with hypotension occurring in 15% of the cases. Diarrhoea may also be present (Burks et al., 2011; Nowak-Wegrzyn et al., 2015). Conversely, the chronic form of FPIES is characterised by malabsorption syndrome, with the main symptoms being failure to thrive, anaemia, diarrhoea and intermittent emesis (Caubet et al., 2017). The most common food allergens are cow's milk, soy and cereals (rice and oats). FPIES to cow's milk and soy usually begins in the first three to six months of life, and FPIES to solid foods usually starts at six to seven months of life, during the complimentary food introduction process (Caubet et al., 2017; Nowak-Wegrzyn et al., 2015). A retrospective survey estimated the prevalence of cow's milk FPIES in the UK as 0.36% of the paediatric population (Ludman et al., 2014). The pathophysiology of this disorder is poorly understood. There is a lack of studies in the literature, but as a non-IgE mediated allergy FPIES is considered a T-cell mediated disease. More studies are required for a better understanding of the natural history of the disease. However, present data suggest that in 85% of the children with cow's milk-induced FPIES the condition will have spontaneously resolved by five years of age (Ruffner et al., 2013) and 50% of the children with rice or oats-induced FPIES will have the symptoms resolved by four to five years of age (Caubet et al., 2014; Ruffner et al., 2013).

1.3.1.3 Food protein-induced enteropathy

Food protein enteropathy is the non-IgE gastrointestinal mediated allergy that affects the small intestine. It shares clinical features with chronic FPIES, characterized by failure to thrive, abdominal distension and diarrhoea. Although food protein enteropathy has been described in the literature since the 1980s (Walker-Smith, 1992; Walker-Smith et al., 1989), there is still a large gap of knowledge about this disorder, which is probably related to the fact that enteropathy does not occur exclusively associated with food allergy. Food protein enteropathy usually starts between two and nine months of age, with the majority outgrowing this allergy by 24 to 36 months of age (Bierme et al., 2017; Nowak-Wegrzyn et al., 2015).

1.3.1.4 Eosinophilic gastrointestinal disorders

Eosinophilic gastrointestinal diseases are a group of chronic diseases characterised by a range of symptoms caused by eosinophilic inflammation and infiltration of various segments of the gastrointestinal tract (Aceves et al., 2012). It can be classified according to the site of the infiltration: eosinophilic oesophagitis, eosinophilic gastroenteritis and eosinophilic colitis (Aceves et al., 2012). Little is known about the pathophysiology, pathogenesis, epidemiology, clinical manifestations, treatment and prognosis of eosinophilic gastrointestinal diseases.

1.4 Pathogenesis of non-IgE mediated gastrointestinal food allergy – mechanism of the disease

The pathogenesis of the non-IgE mediated gastrointestinal food allergies is poorly understood, and the precise underlying mechanism is almost unknown (Caubet et al., 2017; Nowak-Wegrzyn et al., 2015). Probably, the lack of understanding is related to the fact that endoscopies and biopsies are not routinely performed in children, and also to the fact that this group of diseases is poorly recognised and studied in clinical practice.

It is known that these disorders have eosinophilic dominated inflammation. Eosinophilic infiltration may significantly alter tight junctions, which may lead to increased intestinal permeability to food proteins and continuity of the inflammatory process (Tsabouri et al., 2017). It is also believed that the mechanism is mediated by cellular immunity with T-cells having a pivotal role.

Among the non-IgE mediated gastrointestinal food allergies, FPIES has been the most investigated. Nevertheless, the pathophysiological mechanism remains unknown. Studies have suggested that the T-cells, with the secretion of pro-inflammatory cytokines, may influence the intestinal permeability (Benlounes et al., 1999; Shek et al., 2005). Conversely, others have been questioning the role of T-cells in this disorder, suggesting that T-cells could be linked to achieving tolerance acquisition to food allergens (Karlsson et al., 2004). FPIAP (eosinophilic colitis) is in the benign end of the non-IgE mediated gastrointestinal food allergies spectrum, with the majority of infants not being exposed to an invasive investigation (endoscopy and biopsy), which is probably one of the main reasons contributing to the lack of understanding of its pathogenesis.

More research is warranted for better clarification and understanding the pathogenesis of non-IgE mediated gastrointestinal food allergies.

1.5 Diagnosis and Treatment

1.5.1 Diagnosis

The diagnosis of non-IgE gastrointestinal food allergies relies on a detailed history, physical examination, and improvement of symptoms during the trial of elimination diets and reappearance of symptoms during oral food challenges (Caubet et al., 2017; Nowak-Wegrzyn et al., 2015).

Published guidelines by the European Academy for Allergy and Clinical Immunology (EAACI) have outlined components of an allergy-focused history in children with food allergies, which include atopic family history, growth assessment and linking symptoms to possible trigger foods before embarking on an elimination diet (Skypala et al., 2015).

The most common gastrointestinal symptoms are vomiting, abdominal discomfort/pain, irritability (also described as screaming/back arching), diarrhoea or constipation (with excessive straining and soft stools), food aversion or refusal and blood and/or mucous in the stools (Venter et al., 2017).

Allergy testing has limited use in non-IgE mediated gastrointestinal food allergies. Skin prick test and serum specific IgE are negative in the majority of the patients (Nowak-Wegrzyn et al., 2015). The atopy patch test is not recommended due to low sensitivity and conflicting reports on its diagnostic accuracy (Mowszet et al., 2014). Invasive tests, such as endoscopy and biopsy, are usually not indicated.

The diagnosis of non-IgE mediated gastrointestinal food allergies is based on clinical improvement, following an elimination diet and the reappearance of the symptoms during the food challenge (Koletzko et al., 2012). The required length for the diagnostic elimination diet varies significantly among guidelines, with the majority of them ranging from four to eight weeks (Fiocchi et al., 2010; Koletzko et al., 2012).

The oral food challenge remains the gold standard after the resolution of the symptoms under an elimination diet. In cases of FPIAP and food protein-induced enteropathy, the oral food challenge can be performed at home and documented with a food diary, due to the delayed onset of symptoms. For FPIES, due to the risk of profuse vomiting and hypotension, the oral food challenge should be supervised by a doctor in an appropriate monitored setting (Caubet et al., 2017; Nowak-Wegrzyn et al., 2015).

1.5.2 Treatment

The mainstay of management of non-IgE mediated food allergy is the total elimination of the food allergen(s) and its derivatives (Caubet et al., 2017; Koletzko et al., 2012; Nowak-Wegrzyn et al., 2015; Venter et al., 2017). The most common foods eliminated are cow’s milk, egg, soy and wheat, and in a significant proportion of patients multiple foods elimination are required for symptom improvement (Meyer et al., 2013). Follow-up with a multidisciplinary team, with a focus on dietary and nutritional support, is indicated for this group of patients.

In breastfed children, a maternal elimination diet of the offending food(s) is recommended. However, if breast milk is not available a suitable hypoallergenic formula (extensively hydrolysed or amino acid formula) is required (Fiocchi et al., 2010; Koletzko et al., 2012).

Current guidelines for CMPA, including ESPGHAN, BSACI and Milk Allergy in Primary Care (MAP/iMAP), suggest that extensively hydrolysed formula should be used as the first option for treatment in infants when the prescription of a hypoallergenic formula is necessary. Exceptions are for infants with severe reactions, faltering growth, non-resolving severe atopic dermatitis or enteropathy where an amino acid formula is the indicated choice (Figure 6) (Luyt et al., 2014; Venter et al., 2017; Venter et al., 2013).

Most of the patients with non-IgE mediated food allergies will develop tolerance to the allergenic foods during childhood. The time for achieving tolerance varies and, in a few cases, the condition can be persistent through adolescence and adulthood. The majority of patients with FPIAP and food-protein induced enteropathy resolve in early childhood. For patients with the diagnosis of FPIES, it is recommended to perform oral food challenges every 12-18 months to assess tolerance acquisition (Caubet et al., 2017; Nowak-Wegrzyn et al., 2015).

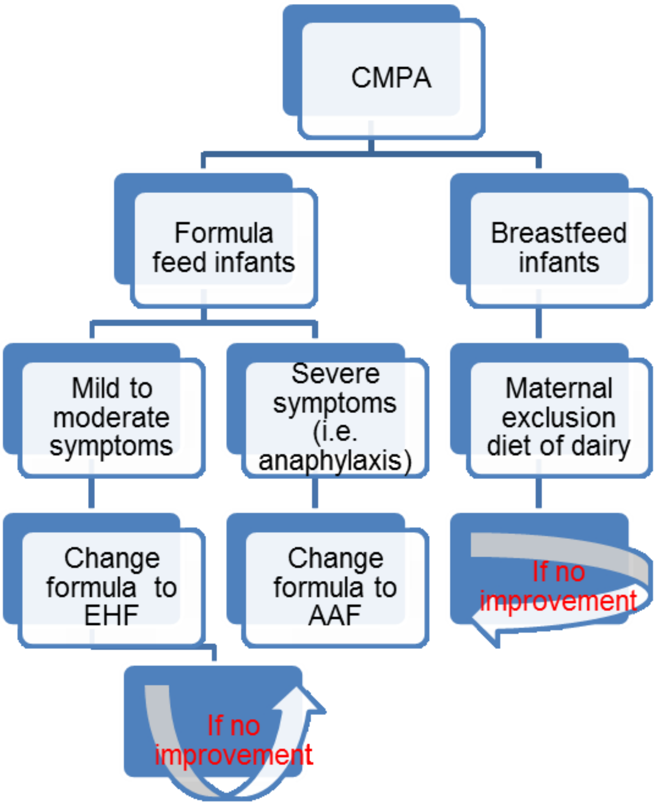

Figure 1.6 - Adapted algorithm CMPA treatment (Koletzko et al., 2012; Venter et al., 2017).

1.6 Dietary impact

As mentioned previously, the treatment of non-IgE mediated food allergies relies on the avoidance of the offending allergens from the diet. The eight most common foods eliminated (cow's milk, hen's egg, soy, wheat, peanut, tree nuts, fish and shellfish) during the treatment have an important contribution to children's diet, as they have indispensable macro and micronutrients.

Advances in the management of food allergies, including individualised dietary evaluation and advice, supporting of breastfeeding and assisting in the choice of hypoallergenic formula (when breastfeeding is not possible) may minimize the risk of developing nutritional disorders. However, as nutritional management can be challenging in this group of patients, reports of growth deficiency, micronutrients deficiency (vitamins and minerals) and feeding difficulties are still frequent.

1.7.1 Growth Disorders

Several studies analysed the impact of food allergies on children's growth. The majority of these studies reported that children with food allergies have lower growth parameters when compared with non-allergic children.

The most affected parameters are weight-for-height (wasting) and height-for-age (stunting), in keeping with chronic malnutrition. Growth parameters also seem to be negatively correlated with the increasing number of foods eliminated from the diet, in particular, if three or more foods are eliminated, and cow's milk is avoided.

Nonetheless, nearly all studies evaluated children with IgE-mediated food allergies. Few studies analysed the impact of non-IgE mediated gastrointestinal food allergies on growth parameters. Vieira et al*.* (2010) studied children with non-IgE mediated CMPA through a large observational cross-sectional study. The authors found a very high proportion of wasting and stunting among allergic children (15.1% and 23.9% respectively) (Vieira et al., 2010).

Therefore, children diagnosed with food allergies require particular attention for growth disorders and ideally should be treated by a multidisciplinary team. It is essential to measure weight and height in every clinical appointment and to plot the measurements on appropriate growth charts. A referral to a dietician is recommended if any concerns regarding growth are raised.

1.7.2 Micronutrients deficiency

Studies investigating children with food allergies through food diaries and food questionnaires have reported low micronutrient intakes as a result of the elimination diet. The low consumption by its own is already a risk factor for vitamin and mineral deficiencies (Christie et al., 2002; Noimark and Cox, 2008). Moreover, in this group of patients, medication (for example corticosteroids) and inflammation can also affect these micronutrients.

Vitamin D and calcium are the most known and described deficiencies in food allergic patients. However, deficiencies of iron, folic acid, B vitamins and omega-3 fatty acids were also reported in this group of patients (Christie et al., 2002). Recently, concerns about trace elements, such as zinc and magnesium, have also been raised in allergic children (Ojuawo et al., 1996; Toyran et al., 2012).

Cow's milk allergy is frequent, and its elimination from the diet has an impact on calcium intake and vitamin D. Low vitamin D and calcium intake have been frequently reported in cow's milk allergic patients, including severe cases resulting in nutritional rickets (Meyer, 2018). Quantifying calcium in the diet is not difficult, and can be done through food diaries; however, it is challenging to quantify vitamin D intake, since sunlight exposure is the primary source of this vitamin (Meyer, 2018).

Recently, bone mineral density has been the focus of studies in children with CMPA. Milk and dairy products contribute to 45-49% of the daily intake of calcium in children aged two to 18 years old (Auestad et al., 2015). For this reason, children with CMPA eliminating cow's milk from their diet are at risk of low calcium intake. Low calcium intake is associated with decreased bone formation and reduced bone remodelling (Dupont et al., 2018). Studies comparing patients with CMPA and healthy controls have investigated calcium intake and bone mineral density. Mailhot et al. (2016) found that 61% of children with CMPA had calcium intake below the American Recommended Daily Allowance compared to 26% of healthy controls

(Mailhot et al., 2016). The authors also showed that lumbar spine bone mineral density z-scores were significantly lower in children with CMPA (Mailhot et al., 2016). Jensen et al. (2004) compared CMPA children that were avoiding cow's milk for at least four years and healthy controls, showing that the allergic group had reduced bone mineralisation and the bone age was delayed by a mean of 1.4 years (Jensen et al., 2004). Children on an elimination diet can also have low intake and deficiency of proteins, zinc and potassium, that also impact on bone health (Dupont et al., 2018).

To reduce the impact of the elimination diet in children with food allergies, a dietary assessment should be part of the clinical management, and when required supplementation with vitamin and minerals should be prescribed.

1.7.3 Feeding difficulties

Many children with food allergies will eventually develop feeding difficulties, particularly in cases of non-IgE mediated gastrointestinal food allergies (Meyer, 2018). Meyer et al. (2014b) found in a retrospective study of children with non-IgE mediated gastrointestinal food allergies that 40.2% of the parents reported feeding difficulties (Meyer et al., 2014b). This symptom is highly associated with vomiting and poor growth (Meyer, 2018), and likely occur because children who feel unwell after eating are more likely to avoid ingesting food to prevent recurrence of the symptoms.

1.8 Quality of life

Food allergies can have a significant impact on the quality of life of the affected children and their families. Many aspects, such as diagnosis process, elimination diet, combination and severity of symptoms play a role in this process. Studies have documented that food allergies can cause a considerable psychological and emotional impact on children and their families when compared to children without food allergies (Morou et al., 2014).

Parents, in particular mothers, commonly report feelings of anxiety and fear, (King et al., 2009; Roy and Roberts, 2011), with the delayed diagnosis being the starting point. It is constant the worry of inadvertent exposure to food allergens leading to allergy reactions that can result in anaphylaxis in children with IgE mediated allergies or in worsening of the symptoms for days or weeks in children with non-IgE mediated allergies.

The treatment of food allergy consists of eliminating from the child's diet the food allergen(s) causing the allergic reactions. The anxiety and the fear of accidental exposure are present daily. Diet elimination has a significant impact on social activities for both the child and his/her family and to their emotional well-being (Franciosi et al., 2012). The burden of planning meals, sourcing allergen-free foods, avoiding cross-contamination and trusting others to keep the elimination diet is enormous (Rouf et al., 2012).

The number of foods eliminated from the diet also has a negative association with quality of life. Studies have shown increased levels of anxiety in children who were required to eliminate two or more foods from their diets (Venter et al., 2015). Moreover, Cummings et al. (2010) found a negative correlation between eliminating multiple foods and health-related quality of life (Cummings et al., 2010). These findings are probably related to children and families experiencing restrictions with food, including difficulties with school lunches and shopping (Valentine and Knibb, 2011).

The impact on the quality of life of children diagnosed with IgE-mediated food allergies families is well studied and documented. Specific quality of life questionnaires have been developed and validated for this group of patients and their families, and the European Academy of Allergy and Clinical Immunology published a position article guiding the clinicians in how to use these questionnaires (Muraro et al., 2014a). Conversely, there is a paucity of data in the literature assessing the impact of non-IgE mediated gastrointestinal food allergies on the quality of life of the sufferers and their families. Although the European Academy of Allergy and Clinical Immunology has acknowledged the need for validated tools for this group of patients (Muraro et al., 2014a), until this moment, no health-related quality of life questionnaire has been developed and validated.

To date, the only publication evaluating health-related quality of life in non-IgE mediated gastrointestinal food allergies is from Greenhawt et al. (2016) The authors studied FPIES, and showed a significant impact on daily function of families in various domains of health-related quality of life (Greenhawt et al., 2016).

The diagnosis and treatment of food allergies pose a burden not only to children and their families but also to national health systems worldwide. Sladkevicious et al. (2010) estimated the total cost of managing CMPA in the UK in the first 12 months following the first consultation with the GP, at £1,381 per patient and £25.6 million for an annual cohort of 18,350 infants. Non-IgE gastrointestinal CMPA accounted for 59% of their cohort (Sladkevicius et al., 2010)

Although the published literature evaluating the burden of non-IgE mediated gastrointestinal food allergies is scarce, it is possible to hypothesize that the parental and patient frustration, anxiety and impact in the quality of life lie in the delays in diagnosis, lack of effective treatments and lack of validated diagnostic tests.

Non-IgE mediated gastrointestinal food allergy is an important entity in paediatrics. It has a complex diagnosis, management and adds a significant burden into patients and families' quality of life. Given the knowledge gap about this condition in the literature, the aims of the publications included in this thesis are, first, to prospectively investigate the required length of elimination diet to achieve symptom improvement during the diagnostic process; second, to evaluate the knowledge of primary health care professionals about diagnosis and management of cow's milk protein allergy (the most common form of non-IgE food allergies) and to compare with parents views and opinions; and to better understand diagnosis tools, treatment and tolerance in infants diagnosed with eosinophilic colitis; third, to evaluate possible impacts of the elimination diet on growth and nutrients deficiencies; and fourth, to analyse the potential implications of non-IgE mediated gastrointestinal allergies on the quality of life of the affected children and their families. My contribution for each one of the studies included in this thesis is summarised in the Appendix.

2. ELIMINATION DIET AND THE DIAGNOSIS OF NON-IGE MEDIATED GASTROINTESTINAL FOOD ALLERGIES

The second chapter of this thesis is based on the publication of the time to symptom improvement using elimination diets in non-IgE mediated gastrointestinal food allergies published in the Pediatric Allergy & Immunology journal (Lozinsky et al., 2015b). This is the main article derived from the data of the “Discovering the effect of non-IgE mediated allergies on children and their families” study. (Lozinsky et al., 2015b)

This project was designed to investigate, as a primary outcome, the impact on the quality of life and also establish, symptoms, growth and dietary elimination in non-IgE mediated gastrointestinal food allergies in childhood as little is known about this condition. Children with suspected non-IgE mediated gastrointestinal food allergies were recruited and followed prospectively at a large tertiary gastroenterology department in the UK from December 2011 to November 2013.

When designed, one of the main objectives of this project was to address the controversy of the required length of the elimination diet to achieve symptom improvement. The definitive diagnosis of the non-IgE mediated gastrointestinal food allergy is based on clinical improvement following an elimination diet and the reappearance of the symptoms during oral food challenge (Boyce et al., 2010; Walsh and O'Flynn, 2011), since allergy tests have minimal value for this condition (Meyer et al., 2013). However, the recommended length of the diet varies widely between different guidelines, from two to 12 weeks (Koletzko et al., 2012). Moreover, there is a paucity of data in this regard, with the knowledge being based on experts’ opinions and in studies of children with cow’s milk protein allergy (single food allergy).

Although the elimination diet is a fundamental tool for the diagnosis of non-IgE-mediated gastrointestinal food allergy, it is of equal importance to determine the period to be followed during the diagnosis process, avoiding it to be too short or too long. The first can lead to a false-negative result and the latter to an increased risk of nutritional deficiencies (Meyer et al., 2014a).

Families of children aged four weeks to 16 years old without non-allergic comorbidities with suspected non-IgE mediated gastrointestinal food allergies, who were required to initiate an elimination diet as part of their diagnosis investigation, were invited to take part in this study.

The Likert Scale of Gastrointestinal Food Allergy Symptom Questionnaire (GIFASQ) was used in this study. This tool was previously developed based on symptoms of 437 children with proven gastrointestinal food allergy. The GIFASQ was then validated in a prospective observational study where data of 77 participants were analysed (Dominguez-Ortega et al., 2013).

The GIFASQ was administered prior to starting the elimination diet and again four weeks after it. If the child has not improved after four weeks in the diet, the family was advised to continue it for another four weeks, and a questionnaire was administered again when eight weeks of elimination diet were reached. The Likert scale questionnaire measured the severity of the nine most common symptoms of non-IgE mediated gastrointestinal food allergies (diarrhoea, constipation, vomiting, rectal bleeding, abdominal pain, flatus, bloating, screaming/back arching/irritability, food aversion) individually (0 to 5) and collectively (0-45). Children were only enrolled in the study if there was an improvement in their symptom score after the elimination diet when compared to their baseline score.

During recruitment, 252 children with suspected non-IgE mediated gastrointestinal food allergies were identified. From those, 91 were excluded because they did not want to take part in the study, were not reachable or had other comorbidities. Therefore 161 participants were initially enrolled in the study, of which 30 participants did not improve on the elimination diet. These participants were excluded and subsequently diagnosed with functional gastrointestinal diseases (22 participants) or other gastrointestinal disorders, like inflammatory bowel disease (8 participants). Therefore, data from 131 children were analysed.

All patients participating in this study attended a clinical research visit where anthropometric measurements, skin prick test and collection of demographic data were performed. In this same visit, participants received individualised dietetic advice to help the families with the elimination diet process.

In this study, I found that the time to symptom improvement following the initiation of the elimination diet was four weeks in 98% of our patients. All symptoms individually and collectively have statistically improved after commencing the elimination diet ($p < 0.001$). The median score dropped from 19/45 (IQR: 14 to 24) to

7/45 (IQR: 4 to 12) after the elimination diet (p <0.001). Despite the improvement in symptoms, the majority of the participants had only partially improved.

No statistical difference was found in the percentage of symptom improvement and the number of foods eliminated or the type of food excluded (soy, milk, egg or wheat).

The results of this study confirmed for the first time in literature that an elimination diet for four weeks should be sufficient for the diagnosis of non-IgE mediated gastrointestinal food allergies in the majority of children, establishing a standardised duration for the elimination diet in the clinical diagnostic work out of non-IgE food allergies. This study has been awarded the Editor's choice of Paediatric Allergy and Immunology issued in August 2015, was cited various times and were discussed in the European Academy of Allergy and Clinical Immunology Conference, in June 2015, as one of the highlight articles of the year studying Non-IgE mediated gastrointestinal food allergies.

Strengths and limitations

The "Discovering the effect of non-IgE mediated allergies on children and their families" study was designed to be a prospectively follow up study of a large cohort of children with non-IgE mediated gastrointestinal food allergies to gain more in-depth knowledge about this condition. It was the first study to confirm the required length of the elimination diet in the diagnostic process of this disease. The main limitation of this study was the absence of a food challenge after 4-8 weeks elimination diet to conclude the diagnostic gold standard of this condition. Another limitation is that this is a parental report questionnaire-based study and, hence, the study may be biased, as it is known that non-IgE mediated gastrointestinal food allergies can impact on the quality of life of families, leading to over-reporting of symptoms by parents.

Publication

1. https://www.ncbi.nlm.nih.gov/pubmed/25963794

Lozinsky, A. C., Meyer, R., De Koker, C., Dziubak, R., Godwin, H., et al. (2015b). ‘Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies’. *Pediatric Allergy and Immunology,* 26(5) pp. 403-408.

Pediatric Allergy and Immunology

ORIGINAL ARTICLE **Food allergy**

Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies

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To cite this article: Lozinsky AC, Meyer R, De Koker C, Dziubak R, Godwin H, Reeve K, Dominguez Ortega G, Shah N. Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies. *Pediatr Allergy Immunol* 2015: **26**: 403–408.

Keywords
elimination diet; non-IgE-mediated allergy; time to improvement

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Accepted for publication 7 May 2015

DOI:10.1111/pai.12404

Abstract

Background: The prevalence of food allergy has increased in recent decades, and there is paucity of data on time to symptom improvement using elimination diets in non-Immunoglobulin E (IgE)-mediated food allergies. We therefore aimed to assess the time required to improvement of symptoms using a symptom questionnaire for children with non-IgE-mediated food allergies on an elimination diet.
Methods: A prospective observational study was performed on patients with non-IgE-mediated gastrointestinal food allergies on an elimination diet, who completed a questionnaire that includes nine evidence-based food allergic symptoms before and after the exclusion diet. The questionnaire measured symptoms individually from 0 (no symptom) to 5 (most severe) and collectively from 0 to 45. Children were only enrolled in the study if collectively symptoms improved with the dietary elimination within 4 or 8 weeks.
Results: Data from 131 patients were analysed including 90 boys with a median age of 21 months [IQR: 7 to 66]. Based on the symptom questionnaire, 129 patients (98.4%) improved after 4-week elimination diet and only two patients improved after 8 weeks. A statistically significant difference before and after commencing the elimination diet was seen in all nine recorded symptoms (all $p < 0.001$), and in the median of overall score ($p < 0.001$).
Conclusion: This is the first study attempting to establish time to improve after commencing the diet elimination. Almost all children in this study improved within 4 weeks of following the elimination diet, under dietary supervision.

The prevalence of food allergy in the paediatric population has increased in recent decades and is recognized as a significant public health problem (1, 2). The major causative food antigens in children are cow's milk, hen's egg, soya, wheat, peanuts, tree nuts and fish/seafood. In the United Kingdom (UK), studies have found that between 2.2 and 5.5% of the infants in the first year of life present with proven food allergies (3), with the prevalence of cow's milk protein allergy (CMPA) ranging between 1.9 and 4.9% (4) and for egg and soya 2% (5) and 1.9%, respectively (6).

According to the recent guideline from the National Institute of Allergy and Infectious Disease (NIAID), food allergy can be classified into three groups: IgE-mediated, non-IgE-mediated and mixed IgE and non-IgE-mediated (2). The pathogenesis of IgE-mediated food allergy is well characterized, with symptoms occurring immediately and up to 2 h after ingestion. The allergy-focused history, in addition to either skin

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Abbreviations
NIAID, National Institute of Allergy and Infectious Disease; IgE, Immunoglobulin E; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; WAO, World allergy organization; DRACMA, Diagnosis and rationale for action against cow's milk allergy; EAACI, European Academy of Allergy and Clinical Immunology; ACG, American College of Gastroenterology; CMPA, Cow's milk protein allergy; MAP, Milk allergy in primary care; HAF, Hypoallergenic formula; SPT, skin prick test; UK, United Kingdom.

prick test or specific IgE testing, has been shown to be useful tools to aid diagnosis for IgE-mediated allergy (2, 7). On the other hand, the pathophysiology of non-IgE-mediated food allergies is not well understood and reactions are typically delayed, manifesting up to 72 h following ingestion (2, 7). Allergy testing, skin prick test, specific IgE or patch testing are of limited diagnostic value in this group (8). The diagnosis therefore is based on clinical improvement, following an elimination diet and the reappearance of the symptoms during food challenges (2, 7–9).

The recommended length of the diagnostic elimination diet varies greatly in published guidelines, with data mainly based on CMPA. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (10), the European Academy of Allergy and Clinical Immunology (EAACI) (11), the Milk Allergy in Primary Care (MAP) Guidelines (12), the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines (4) and Vandenplas et al. (13) suggest an elimination diet for at least 2 weeks and up to 4 weeks in cases of gastrointestinal manifestations to judge the response. However, both the American College of Gastroenterology (ACG) (14) and the ESPGHAN guideline (15) on eosinophilic esophagitis suggest a longer period to evaluate the response to exclusion diet, ranging from 4 to 8 and to 12 weeks. There is paucity of data on time required for an elimination diet to be performed for the improvement in symptoms on non-IgE-mediated food allergies that affect the gastrointestinal tract. The decision on the length of an elimination diet is therefore based on consensus expert opinion and recommendations range from 2 to 12 weeks (10).

The importance of the length of elimination diet is two-fold; if an elimination diet is discontinued prematurely, this would lead to false-negative results as it was too short a time to diagnose a non-IgE-mediated food allergy; conversely, unnecessarily prolonged elimination diets may increase the risk of nutritional deficiencies (16, 17). It is consequently vital to ensure that the period of elimination is neither too short nor too long. We therefore aimed to assess the time required to improvement of symptoms using a symptom questionnaire for children with non-IgE-mediated gastrointestinal food allergies on an elimination diet.

Methods

A prospective, observational study was performed at a large tertiary gastroenterology department, in the UK. Ethical approval was obtained for this study. Parents of children aged 4 weeks–16 years without non-allergic comorbidities (i.e. cerebral palsy, cardiac disorders), who were required to follow an elimination diet for the diagnosis of suspected food protein-induced gastrointestinal allergies, were approached to take part in the study. A Likert Scale Questionnaire (Table 1), that has previously been developed (18), was administered prior to starting the elimination diet and again at 4 weeks after starting the food elimination. If the child did not improve

Table 1 Previously published Likert scale symptom questionnaire (18)

Symptoms: please indicate which symptoms your child experiences?

	Please indicate the severity of the symptoms						What **age** did it start:	Score at follow-up
	None	Mild		Moderate		Severe		
Diarrhoea: (loose, watery, frequent stools)	0	1	2	3	4	5		
Constipation: (excessive straining, low frequency, hard stools)	0	1	2	3	4	5		
Vomiting: (unexplained vomiting, often associated with abdominal pain)	0	1	2	3	4	5		
Rectal bleeding: (bleeding from the bottom when passing a stool, fresh blood)	0	1	2	3	4	5		
Abdominal pain: (affects daily functioning such as school and sleep)	0	1	2	3	4	5		
Wind/flatus: (excessive burping and painful wind)	0	1	2	3	4	5		
Bloating: (bloated/extended stomach that is hard when pressed)	0	1	2	3	4	5		
Screaming/back arching: (screaming associated with back arching and kicking legs out straight)	0	1	2	3	4	5		
Food aversion: (pushes away food, gags, holds food in mouth, spits/throws food, cries during meals)	0	1	2	3	4	5		

after 4 weeks, they continued on the elimination diet and the questionnaire was administered again after 8 weeks. The questionnaire measured severity of nine symptoms (diarrhoea, constipation, vomiting, rectal bleeding, abdominal pain, flatus, bloating, screaming/back arching/irritability, food aversion) individually from 0 (no symptom) to 5 (most severe) and collectively from 0 to 45. The research team administered the questionnaire to all patients. Children were only enrolled in the study if symptom scores improved with the dietary elimination within 4 or 8 weeks.

We assessed change of individual symptom scores before and after the elimination diet and grouped the patients into three categories: total improvement when the score reduced to zero, no improvement when the score was same at the beginning and at the end of the study, and partial improvement when severity score dropped, but symptoms were still present.

Patients attended a research clinic appointment following enrolment, where the research dietitian and nurse recorded demographic data, anthropometrics and a skin prick test was performed. In addition to the above, all children had individualized dietetic advice including standard diet sheets outlining the labelling law, how to avoid hidden sources and suitable nutritious alternatives. Skin prick test was performed where medically possible in children to establish IgE sensitization to milk, egg, soya, wheat, peanut, tree nuts and fish. A positive control with histamine and a negative control with saline were performed in all the tests. The test was performed using a standardized method (19) with fresh semi skimmed milk and Stallergenes allergen solutions (France). Wheal sizes > 3 mm were considered positive.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21 (Armonk, NY). Continuous variables are presented as medians with interquartile ranges, and categorical variables are presented as frequencies. To compare differences between symptom scores before and after food intervention, we used Wilcoxon signed rank test. To ascertain the differences in percentage symptom improvement between number of foods excluded (one, two, three and four-or-more foods) and between exclusion of a particular food (milk, egg, wheat, soya), we used Kruskal–Wallis test and Mann–Whitney U–tests, respectively. All tests were two-sided, and p-value was set to 0.05.

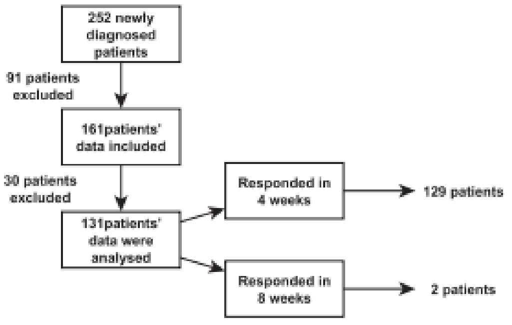

Figure 1 Patient's inclusion and time to improve with diet elimination.

Table 2 Number of symptoms

Number of symptoms	n	%
One	1	0.8
Two	5	3.8
Three	9	6.9
Four	24	18.3
Five	31	23.7
Six	33	25.2
Seven	14	10.7
Eight	11	8.4
Nine	3	2.3

Table 3 Combinations of food exclusion

Combination	Frequency	%
Hypoallergenic formula only	14	10.7
Single food	20	15.3
Cow's milk and soya	30	22.9
Cow's milk, soya and other†	3	2.3
Cow's milk, soya and egg	8	6.1
Cow's milk, soya, egg and other†	5	3.8
Cow's milk, soya, egg and wheat	18	13.7
Cow's milk, soya, egg, wheat and other†	18	13.7
Other combinations	15	11.5

†Other – i.e. gluten, potato, rice, fruits and vegetables.

Results

We identified 252 outpatients with suspected non-IgE-mediated gastrointestinal food allergies between December 2011 and November 2013 that were eligible for inclusion in the study. Ninety-one patients were excluded because they did not want to partake in the study, were unable to attend/not reachable or had non-atopic comorbidities. Therefore, 161 children were enrolled in the study, of which 30 patients did not improve on the elimination diet. These were excluded and subsequently diagnosed with functional gastrointestinal diseases (22 patients) or others gastrointestinal disorders (8 patients) (Fig. 1). Data for 131 patients were analysed, including 90 (68.7%) boys, and the median age of the cohort was 21 months [IQR: 7 to 66]. Based on the symptom questionnaire, 129 patients (98.4%) improved after a 4 week elimination diet and the remaining two patients improved after 8 weeks.

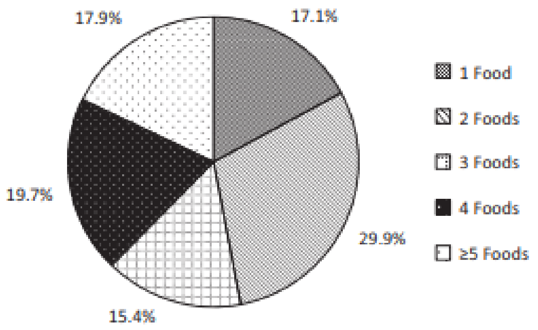

Figure 2 Number of foods eliminated in children enrolled in this study.

Before commencing the elimination diet 11.5% of patients in our cohort presented with one to three symptoms, 67.2% had four to six symptoms and 21.4% had seven to nine symptoms (Table 2).

The patients were managed with different exclusion diets. The most common food eliminated was cow's milk protein, which 94.9% of children avoided (Table 3) and the majority of the children avoided at least two foods for symptom improvement (Fig. 2).

In our cohort, we had 14 patients who were exclusively on a hypoallergenic formula (HAF), 43 on HAF and foods and 49 patients were on alternative over-the-counter milk, for example almond milk and rice milk, and food. Amino acid formula was prescribed in 54 patients, whilst extensively hydrolysed formula was used in three patients.

A statistically significant difference before and after commencing the elimination diet was seen in all nine recorded symptoms ($p < 0.001$). Overall, the median score dropped from 19/45 [IQR: 14 to 24] to 7/45 [IQR: 4 to 12] after the elimination diet ($p < 0.001$) (Fig. 3). In terms of symptoms improvement, bloating/abdominal distension, diarrhoea and constipation were the symptoms that improved the least following the elimination diet, whereas vomiting and rectal bleeding improved notably more (Fig. 4). Taking the total score into account, overall 85.5% had partial improvement, 10.7% had a recovery of 90% or more and 3.80% had no overall recovery. The latter group, although not improved in total score, had improvement in some of the individual symptoms; hence, they were included.

We did not find any statistical significance in percentage symptom improvement between one, two, three and four-or-more foods excluded: 61.5%, 52.7%, 60% and 51%, respectively, $p = 0.736$. Similarly, we did not find differences in percentage symptom improvement between patients who had soya exclusion: 53.4% vs. those who did not have soya excluded 55.9%, $p = 0.657$; those who excluded egg 51.1% vs 56.5%, $p = 0.201$; those who excluded wheat: 48.3% vs 60%, $p = 0.130$; and those who excluded milk: 54.6% vs. 30.8%, $p = 0.289$.

IgE sensitization to food allergens was tested in 99/131 (75.5%) patients. Of this cohort, SPT > 3 mm was only found in 10 children (10.1%) to various food allergens: 2 to fresh milk, 3 to egg, 1 egg and milk, 1 to hazelnut, 1 to hazelnut and walnut and 2 to peanut.

Discussion

This study sets out to investigate the time required for symptom improvement in children with suspected non-IgE-mediated food protein-induced gastrointestinal food allergies. The clinical presentation of this non-IgE-mediated food allergy is characterized by heterogeneous gastrointestinal symptom manifestations and lack of conclusive tests, with the final diagnosis mainly based on the improvement of symptoms with the exclusion diet (2, 7). In this study, we found that 98% of our patients had symptom improvement by 4 weeks after the initiation on an elimination diet, whilst two patients required a further 4 weeks for symptom improvement to set in. Although a range of between 2 and 12 weeks for the elimination diet have been recommended by current guidelines, the majority, including ESPGHAN (10), EAACI (11), the MAP (12), DRACMA (4) and Vandenplas et al. guidelines (13) suggest around 4 weeks of exclusion diet to judge the response and improvement. The

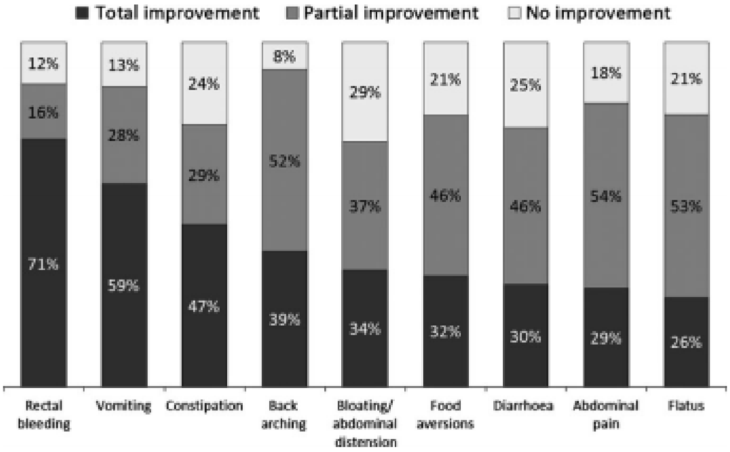

Figure 3 Analyses of symptoms improvement after introduction of exclusion diet.

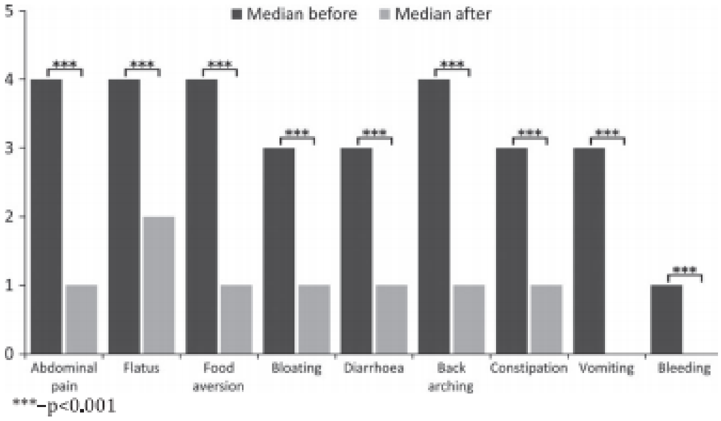

Figure 4 The median symptom score before and after the elimination diet with associated statistical significance.

exception in recommended length of time for dietary elimination to obtain symptom improvement seems to be for patients with eosinophilic esophagitis who may require up to 12 weeks for symptom improvement. Guidelines for length of elimination in the latter diagnostic cohort are largely based on histological improvement. It may therefore be that symptom improvement is also seen earlier, as experienced in our study, but that histological remission may only occur at a later stage (15).

To the best knowledge of the authors, this study confirms for the first time, that an elimination period of 4 weeks should be sufficient for the majority of children with this type of allergy. It is important though to note that all children in this study did receive appropriate dietetic advice at the beginning of the elimination diet. This would have enabled parents to totally remove the allergen and may have impacted on the recovery time. Several studies have been published highlighting the positive impact of giving appropriate dietary advice to families of children with food allergy, and we hypothesize that this most probably has also made an impact on recovery time. (20, 21).

Although patients in our cohort presented with significant symptom improvements following the elimination diet, it was clear that some symptoms only partially responded and some did not improve at all. We found that 70% of children improved with rectal bleeding; however, only around 30% of children totally improved if they had diarrhoea, pain and food aversions. For feeding difficulties, partial responses are understandable as entrenched food refusal behaviours are common and would not resolve within 4 weeks, but for others such as diarrhoea, our data would suggest other mechanisms are at play. Inflammation of intestinal tract may not involve just an inflammatory response but also an enteric nerve activation, which may explain the partial response to dietary elimination in some and the need in a small number for longer elimination diets. In non-IgE-mediated allergies, it has been demonstrated that atopic food-responsive patients on histological examination have a higher number of mast cells and eosinophils and there is a complex interaction between these cells and activation of the enteric nerves (22–26). Borrelli et al. (27) evaluated 18 children with allergy-related constipation and 15 with non-allergy-related constipation, demonstrating that in the study group, there was an increased density of mast cells in rectal mucosa with close proximity to the submucosal rectal nerves compared with the control group. After 6–8 weeks on oligoantigenic diets, the food allergy group showed a significant decrease in the mast cells numbers and the proximity of those with the nerve fibres. Schäppi et al. (28) reported similar findings when studying gastric biopsies of 10 atopic and 6 non-atopic children suffering from dyspepsia. Therefore, it is plausible that the recovery of the gut depends not only on the grade of inflammation but also on the presence and stabilization of mast cells mediator release and the neuro-immune interactions. Until the pathophysiology of food protein-induced gastrointestinal allergy is known, one can only hypothesize on why there is a difference in response to dietary elimination. The use of mast cell stabilizers, antihistamines and steroids has been used in children where symptom improvement has only been partial (29); however, the evidence for these medications is limited.

This study has some limitations, including that it is a questionnaire based study, so the information about symptoms and the improvement are based on parental report, which may be biased, as this condition is known to affect the quality of life of families (30). However, we only had two researchers assessing symptom improvement, and wherever possible, the same researcher performed the before and after assessment. Another limitation of the study is the fact that children did not have a food challenge at 4 or 8 weeks after the confirmation of the improvement of symptoms. The main reason for this was that, for those where symptom improvement was only partial, further medical management was required. In addition to this, for many parents, this was the first time in a long period that their child was better and they were not keen to challenge, as it had taken months for symptom improvement to occur.

Conclusion

This is the first study attempting to establish time to improve after commencing a dietary elimination. The majority of patients showed improvement after 4 weeks of starting the elimination diet, in line with current guidelines. From this study, we can therefore recommend that following individualized elimination advice from a dietitian, an elimination diets should be followed for at least 4 weeks to lead to symptom improvement in children with non-IgE-mediated food protein-induced gastrointestinal allergies. However, it is important to note that it is common for some of the symptoms to not fully improve. Further larger studies that are adequately powered to allow age stratification analysis and further research are required on both the pathophysiology and the role of medications in this cohort.

Acknowledgments

This study was funded by the Great Ormond Street Children Hospital Charity. We would also like to acknowledge all parents and children that participated in this study.

Competing interests

Funding for this study was obtained through Great Ormond Street Charitable Fund. None of the authors have any competing interests related to this publication.

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3. THE JOURNEY OF CHILDREN WITH NON-IGE MEDIATED COW'S MILK PROTEIN ALLERGY AND A SYSTEMATIC REVIEW OF EOSINOPHILIC COLITIS

The third chapter of this thesis focuses on two publications. The first one reports the medical and parent journey of cow's milk protein allergy (CMPA) (Lozinsky et al., 2015a), the most common allergen in non-IgE mediated gastrointestinal food allergies. This publication documents the knowledge of General Practitioners (GPs) in the UK regarding the diagnostic criteria and the management of this allergy and the opinion and the views of affected families during the diagnostic process. The second publication reports the results of an extensive systematic review of the literature regarding characteristics, symptoms, treatment, and outcomes of infants with eosinophilic colitis, which is the most typical presentation of non-IgE mediated gastrointestinal food allergies in childhood (Lozinsky and Morais, 2014).

CMPA affects 1.9-4.9% of infants (Fiocchi et al., 2010). In the majority of the cases, the symptoms tend to develop in the first few months of life, and the diagnosis pathway can be challenging for parents and GPs with delays in the diagnosis and suboptimal treatment (Sladkevicius et al., 2010).

The first publication is a survey-based study and was distributed to all areas in the UK. Two separate surveys were developed (one for GPs and one for parents) using qualitative and quantitative research methods and were distributed online via large websites (Doctors.net.uk for GPs and OpinionHealth for families). GPs who had seen at least one case of a child with CMPA in the past year and parents of an infant diagnosed with CMPA in the past year were eligible to take part in the survey. In this publication (Lozinsky et al., 2015a), the team and I evaluate the GPs' self-reported knowledge on CMPA diagnosis, management, and educational needs. We also report the experiences of parents of infants with CMPA about the same topics.

In total, 403 GPs and 300 parents completed the survey. It was clear from the results that parents and GPs have different perceptions about the journey of the disease. GPs acknowledge that, ideally, the diagnosis of CMPA should take four weeks based on recent guidelines; however, it took them a median of 8 weeks to diagnose the cases they were faced with. Parents reported that took, on average, ten weeks and four visits to health care professionals before a diagnosis has been reached. Both GPs and parents felt the burden of the disease, with the majority of the GPs stating that they are working in an over-stretch situation regarding time and budget. Parents reported an impact on their family's quality of life mainly related to time to reach the diagnosis and their child's symptoms. The vast majority of GPs acknowledged more training and support is required to improve the diagnosis and treatment of CMPA in the primary care setting in the UK.

One of the most frequent presentations of non-IgE mediated gastrointestinal food allergy in infants and children is eosinophilic colitis, which is characterized by the presence of blood in the stools and is frequently caused by CMPA. In the second publication of this chapter (Lozinsky and Morais, 2014), I report the combination of all cases of infants with eosinophilic colitis found in the literature (English, Portuguese and Spanish) from 1966 to 2013 intending to broaden the knowledge of this frequent manifestation of non-IgE mediated gastrointestinal food allergy.

Thirty-two articles were included, evaluating a total of 314 infants, with the majority of them being male and younger than six months old. Half of the infants were exclusively breastfed at the time of the diagnosis. Allergic tests were negative in the majority of infants. Rectal biopsies were performed in 84% of infants with eosinophilic infiltration being the central finding. In most cases, the treatment was the removal of cow's milk from the mother and/or child's diet with the disappearance of the bleeding. Seventy-eight percent of patients that were submitted to an oral provocation test by 12 months of age showed tolerance to cow's milk protein.

Both studies have a significant clinical impact. The first one highlighted the importance of creating meaningful and continuing education programmes for GPs, as they are usually the first port of call for parents with children exhibiting symptoms of non-IgE mediated food allergies. Developing tools and aids through guidelines can also help and shorten the time to diagnosis. Public health programmes and educational tools for parents are also essential to increase the awareness of CMPA and reduce the burden on families and health care professionals. The second study filled a knowledge gap regarding what was known about eosinophilic colitis in infants and was cited several times in the literature. Before this study, the information was diluted in case reports and small studies.

Strengths and limitations

Both studies have limitations. The main limitation of the first publication is that it is a survey-based study distributed online, with self-rated questions so that bias may exist, whether from parents who had a bad experience during their children's diagnosis or from GPs that have faced difficult and challenging cases of infants with CMPA. Nevertheless, the study has had a high rate of response from all areas of the UK, which can minimize the subjectivity of the results and is likely to be representative from different resource settings in the country. The main limitation of the second publication is that this study is a compilation of cases based on a literature review, not being able to account for the heterogeneity of studies that may have applied different methodologies. However, it represents and summarises the knowledge of this disease from accumulated data in the last 54 years.

Publications

1. https://www.ncbi.nlm.nih.gov/pubmed/27417366

Lozinsky, A.C., Meyer, R., Anagnostou, K., Dziubak, R., Reeve, K., et al. (2015a) 'Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents'. *Children*, 2(3) pp. 317-329.

2. https://www.ncbi.nlm.nih.gov/pubmed/24131740

Lozinsky, A. C. & Morais, M. B. (2014). 'Eosinophilic colitis in infants'. *Jornal de Pediatría,* 90(1) pp. 16-21.

Children **2015**, *2*, 317-329; doi:10.3390/children2030317

OPEN ACCESS

children

ISSN 2227-9067

www.mdpi.com/journal/children/

Article

Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents

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Academic Editor: Jonathan M. Spergel

Received: 30 May 2015/ Accepted: 13 July 2015 / Published: 21 July 2015

Abstract: Cow's milk protein allergy (CMPA) is the most common food allergy in infants and can affect a family's quality of life. The purpose of this paper is to evaluate the knowledge and experience of general practitioners (GPs) in terms of CMPA diagnosis and management and to explore the views of parents on the current diagnostic process. Two surveys were conducted in June 2014, which collected data from GPs and parents of infants diagnosed with CMPA in the United Kingdom. The questionnaires included quantitative and qualitative questions, which measured self-reported knowledge, management and perceived treatment progression, and the educational needs of GPs. We also explored parents' experiences of local healthcare support in relation to CMPA. A total of 403 GPs and 300 parents completed the surveys. The main symptoms of CMPA and diagnosis period differed between GPs and parents. Other key points include different perceptions on symptom presentation and improvement, lack of awareness from GPs about current guidelines, and the significant burden on both families and GPs. This is the first study attempting to establish GP and parental experience in diagnosing CMPA. It is notable that the difference can be improved through training, appropriate diagnostic tools and improved communication between physicians and parents.

Keywords: cow's milk protein allergy; knowledge; quality of life

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1. Introduction

Cow's milk protein allergy (CMPA) is the most common food allergy in children, affecting between 1.9%–4.9% of infants [1]. Symptoms tend to develop in the first few months of life and the resolution rates vary according to the type of allergy. Patients with non-immunoglobulin E (IgE)-mediated allergies tend to have outgrown this by 2 years of age [2], while children with IgE-mediated allergies do so at about 3 years old [3].

The guideline from the National Institute of Allergy and Infectious Disease (NIAID) classifies food allergies into three categories: IgE-mediated, non-IgE-mediated and mixed IgE- and non-IgE-mediated [4]. In IgE-mediated CMPA, symptoms can occur immediately and up to 2 h after the ingestion of cow's milk, and can affect the skin, respiratory system, and gastrointestinal tract and cause severe systemic reactions (anaphylaxis) which are potentially life threatening [4,5]. On the other hand, in non-IgE-mediated CMPA the manifestations of the symptoms can be delayed, up to 72 h after the exposure to cow's milk depending on the gastrointestinal symptoms involved. The symptoms are not specific and include colicky pain, persistent gastro-oesophageal reflux, diarrhoea or constipation, blood in stools and exacerbation of eczema [4,5]. These can lead to a diagnosis of allergic proctocolitis, food protein-induced enterocolitis syndrome or eosinophilic gastrointestinal diseases, so it is not unusual to have cases of non-IgE-mediated CMPA being misdiagnosed. The most common confusion is with lactose intolerance, which presents with abdominal pain, bloating, flatulence and diarrhoea but usually without atopic co-morbidities [6]. In addition, CMPA manifests in early childhood [4,5], whilst primary lactose intolerance usually occurs from 3 to 4 years of age and secondary lactose intolerance is transient [7]. Infantile colic can also overlap with CMPA and the incorrect recommendation of colic remedies and anti-colic formulas can delay the correct diagnosis [8].

The first step for the diagnosis is an allergy-focused history which includes the assessment of symptoms, the identification of the different underlying immunological mechanisms, and then linking this to suspected foods [9,10]. For IgE-mediated CMPA, skin prick tests or specific IgE blood tests are useful tools in the diagnostic process. In suspected non-IgE-mediated CMPA, the allergy tests have limited value. The oral food challenge test remains the gold standard for both types of allergy. In some cases, however, it is not performed when there is significant clinical history and laboratory data [11]. The treatment of CMPA is the complete removal of cow's milk from the child's diet, which may in some cases also be required for the breast-feeding mother. Ideally this should be guided by a qualified dietitian [5,12].

In recent years, guidelines on the diagnosis and management of CMPA have been published, with sources including the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [12], the European Academy of Allergy and Clinical Immunology (EAACI) [9], the

Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) [1]. Three guidelines exist in the United Kingdom (UK) which include the National Institute for Clinical Excellence Guidelines (NICE) [5] on food allergy diagnosis and two published guidelines specific for CMPA: one aimed at primary care (Milk Allergy in Primary Care (MAP) guidelines) [13] and the other for secondary and tertiary care, published by the British Society for Allergy and Immunology [14]. Both cover common presenting symptoms and suggest tests and treatment options that should be sufficient to diagnose and optimally manage children with this allergy.

In spite of these guideline documents, significant delays in diagnosis and optimal management continue [15]. This has also been our experience with many parents reporting poor recognition at initial presentation and suboptimal nutritional management. The aim of this survey was therefore to evaluate the experience of CMPA that general practitioners (GPs) have, as the first point of contact for children with suspected allergies in the UK, and to explore the views of parents on the current diagnostic process for CMPA, to enable better management in the future.

2. Methods

Two separate surveys were conducted in June 2014, one for GPs and one for parents. The survey for the GPs was developed by Mead Johnson Nutrition UK and medeConnect (http://www.medeconnect.net/), a leading provider of community-based healthcare research in the UK using both online quantitative and qualitative research methods. The parent questionnaire was developed by Mead Johnson Nutrition UK and Opinion Health (http://opinionhealth.com/about_us), a company that specialises in providing patient insight into healthcare. Both questionnaires were reviewed by Allergy UK (www.Allergy.uk), a leading charity supporting healthcare professionals and patients with food allergies.

GPs who had seen at least one case of a child with CMPA in the past year and parents of an infant diagnosed with CMPA in the past year were eligible to take part in the survey. Ethical approval was not required from the UK ethics authorities as it fell into the category of an anonymous online survey.

The GP survey was distributed online via www.Doctors.net.uk. This site is the largest and most active network of General Medical Council-authenticated doctors in the UK. It is a trusted channel for information, communication and education and is used by more than 40,000 doctors every day. Currently it is the leading channel for communication and research for doctors in the UK. The GPs' survey recorded demographics of the physicians and measured self-reported knowledge on CMPA diagnosis, management and educational needs, and barriers to the diagnosis of CMPA. The questionnaire had 35 questions with both open and closed (categorised) questions.

The second online survey for parents explored similar topics, including the burden to the family, but also contained qualitative data on management experience with CMPA. The survey was sent to everybody that was registered on the database of Opinion Health (www.Opinionhealth.com). The questionnaire was developed to better understand of the role and attitudes of parents in the diagnostic process for CMPA.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21 (Armonk, NY, USA). Descriptive statistics are presented in percentage and figures.

3. Results

3.1. Characteristics of GPs and Parents

A total of 403 GPs completed the survey, and their distribution was from all areas of the UK (Figure 1). Fifty-five per cent were male, 75% graduated between 1990 and 2011 and the majority (67%) of them were experienced GPs. Sixty-two per cent of the GPs (251/403) worked full time and 14% of them had a dietitian associated with their practice. In the 12-month period prior to completing the survey, 52% of the GPs diagnosed ≥ 3 children with CMPA and 65% managed ≥3 cases already diagnosed with this allergy (Table 1).

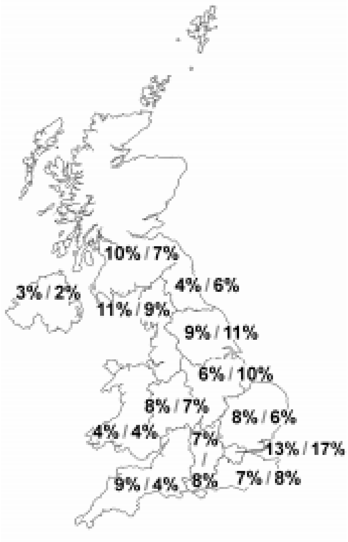

Figure 1. Geographical distribution of participating GPs' practice and parents (%GP/%Parent).

Table 1. Summary of GPs' practice.

Number of Infants <1 Year Diagnosed as CMPA (12 Month Period)	*n*	%
1–2	192	48%
3–4	86	21%
5–10	94	23%
11+	31	8%
Number of Infants <1 Year Treated for CMPA (12 Month Period)	***n***	**%**
None	40	10%
1–2	98	24%
3–4	102	25%
5–10	113	28%
11+	50	12%

A total of 300 parents of infants diagnosed with CMPA completed the second survey questionnaire, of which 206 (68.7%) were mothers and 94 were fathers. Twenty per cent of the parents were aged between 18 and 24 years, with the majority (57%) between 25 and 34 years, and 24% were 35 years old and older. Twenty eight per cent had 1 child, 40% had 2 children and 31% 3 or more children. The parents' distribution was from all areas of the UK (Figure 1).

3.2. Symptom Presentation to Diagnosis: Parents vs. GPs

Parents reported that 49% per cent of the patients presented with symptoms within the first three months of life, and the most common symptoms were colicky pain (60.7%), nausea and vomiting (52%), diarrhoea (51%) and eczema (36%). Similarly, the GPs reported that 72% of children with a suspected CMPA presented to their practice before 6 months of age and their most common symptoms of CMPA included diarrhoea (59%), nausea and vomiting (40%), eczema (31%) and colicky pain (24%) (Figure 2).

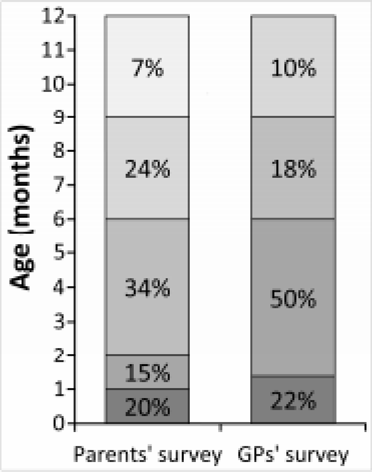

Figure 2. How old the child was during the first appointment with the GP.

In 49% of cases, parents reported that the diagnosis of their child's CMPA occurred within the first 6 months of life and it took on average 10 weeks and a median of four visits to a health care professional before a diagnosis of CMPA was made. In 48% of cases, the diagnosis was made by the GP followed by 21% by paediatricians, 13% by the health visitor and in 5% by a dietitian. Prior to seeking advice from health care professionals, 46% of the parents tried to commence a self-directed elimination diet, 8% used high street tests to "aid" diagnosis and 7% used homeopathy as part of management.

On the other hand, the GP survey indicated that it took a median of 8 weeks to diagnose CMPA but acknowledged that it ideally should take 4 weeks based on current guidelines. When GPs were asked to distinguish between IgE and non-IgE symptoms, 4% of GPs listed anaphylaxis as a non-IgE CMPA symptom. Seventy per cent responded that it was "not necessary to perform any tests" for the diagnosis of CMPA, 17% used specific IgE blood tests and 12% used skin prick tests. When CMPA was suspected, other common conditions considered by the GPs were colic (88%), lactose intolerance (79%), gastro-oesophageal reflux disease (64%) and atopic eczema (78%). The most common medications prescribed by GPs were: emollients (76%), colic relief (*i.e.*, Simeticone) (61%), steroid cream (41%) and antihistamines (27%). Adrenaline auto-injectors were prescribed in 2% of the CMPA children.

Fifty one per cent of GPs consulted the CMPA guidelines, though it was not clear which version was being used, to guide their management, and the same percentage reported going ahead with removing CMP from the infant's diet and prescribing a hypoallergenic formula when this allergy was suspected. However, 45% of infants with this suspected diagnosis were referred to secondary care as part of the diagnostic process.

3.3. Burden of Disease on GPs and Families

Eighty-seven per cent of the GPs found themselves over-stretched in terms of time, resources and costs and 39% said that in the national healthcare system, "the pressure to meet budgets had a negative impact on their ability to treat patients" with CMPA. More than half of them agreed that "the delayed diagnosis of CMPA adds even more pressure to a (national) primary care system already struggling with ever increasing demands", with more than half (53%) stating that they "feel more confident involving secondary care in the diagnosis". Better and faster access to various secondary care specialists is seen as a way of speeding up diagnosis for 31% of the GPs.

The GPs thought that the biggest communication challenges in relation to the parents of children with CMPA were: excessive worry or stress associated with their child's CMPA (79%), unrealistic expectations about their condition and management (61%) and the continued parental request for specific prescriptions of hypoallergenic formulas (60%).

From the parent survey, the significant burden on both parent and child was evident, in particular the length of time to reach a diagnosis which has a negative impact on the child, along with poor sleeping (45%), persistent crying (37%) or abdominal pain (41%). The documented adverse impact on the parents' life included the feeling of exhaustion in 46.7% which was mainly related to lack of sleep, 55.7% had stress or anxiety related to their child's health and 33% of fathers reported a delay in going back to work due to their child's health problems and the time taken to reach a diagnosis of CMPA. The parents mentioned a negative impact on their family life too, with 36.2% stating that they could not enjoy time together as a family and 28% thought their other children got less time and attention.

Parents were also made to feel like they were overreacting, worrying too much about nothing and were not taken seriously in 56% of cases. Forty-six per cent of the parents felt that the amount of time taken to reach the diagnosis of CMPA had impacted the relationship between parents and child, with 16% of fathers and 23.2% of mothers reporting often feeling very irritated and frustrated with the baby and 21% (11.7% of fathers and 25.2% of mothers) felt very low or depressed. Of these 63 parents, 39.7% sought support from a health care professional for feelings of depression.

3.4. Perception of Knowledge/Training by GPs and Parents

The majority of GPs according to this survey were not familiar with the current guidelines for CMPA. Only 13% consider themselves "very familiar" with the NICE allergy guidelines and 6% are following it. Five per cent of GPs reported to be "very familiar" with UK CMPA guidelines and 2% with ESPGHAN guidelines (Table 2).

In the last five years, 69% of the GPs received 1 to 5 h of training in paediatric allergy and 46% rated the training as not effective. The vast majority (82%) of GPs felt they would benefit from further education and support on CMPA. In addition, it was also reported that in 31% of cases, faster access to secondary care for diagnosis or advice would improve the diagnosis. The GPs also highlighted that parents could help speed up the diagnosis of CMPA by filling in a food/symptoms questionnaire (29%), prompting the GP during consultation and being persistent (19%) as well as attending regular appointments and follow-ups (17%).

Table 2. Knowledge of current guidelines on CMPA.

Guideline	Not Aware	Aware but not Read	Somewhat Familiar	Very Familiar/Not Following	Very Familiar/Following
NICE	18%	24%	45%	6%	7%
MAP	55%	23%	17%	3%	2%
ESPGHAN	81%	13%	4%	1%	0%

On the other hand 46% of the parents stated that their GP did not seem to know a lot about CMPA. The survey captured their response and advice to other parents with the following quotes:

- "Go see a doctor, use your instincts and don't doubt yourself!"
- "Push push push until someone takes notice"
- "Keep going back to see professionals and insist on referral to a paediatrician and dietitian."
- "Don't take no for an answer and keep chasing appointments. Do not give up."

4. Discussion

To the best knowledge of the authors, this is the first publication that reports on the journey from diagnosis to management in CMPA as experienced by GPs and parents who have a child with this diagnosis. This study evaluates self-reported knowledge on CMPA, the diagnosis, and treatment and educational needs among GPs in the UK, and it also aimed to establish parents' perceptions and experiences with their own child with CMPA and the burden of the disease on the families. From these results, it is clear that there are significant differences in perceptions between the GP and the parent of the child with CMPA, which is to be expected. In many areas, however, the opposing views highlight shortcomings in medical management and improvements in communication that could ultimately improve the management of CMPA (Figure 3).

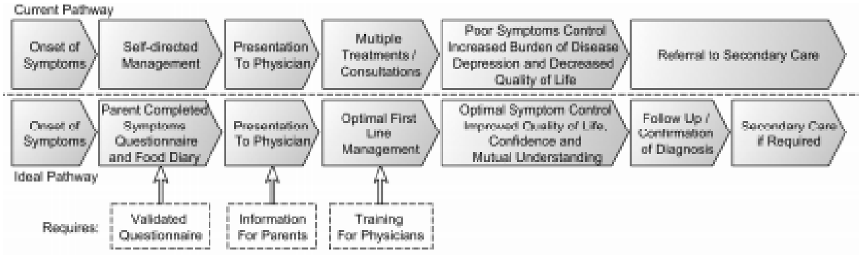

Figure 3. Discord in journey.

The age of presentation of the first symptoms and the visit to their GP correlated between parents and GPs. This confirms the current research that the majority of infants with CMPA will present within the first 6 months of life [16]. Although there is significant overlap in symptom reporting, it is interesting that colicky pain is listed as the most important presenting symptom by parents but not by the GPs. Hill *et al.* [8] highlighted for the first time in 1995 the overlapping disease profile between IgE and non-IgE-mediated allergies, with reflux and colic as part of this overlapping disease. Since then several studies have found that in some children, colic may be related to CMPA [17,18]. In the study by Meyer *et al.* [19], 90% of children that presented with a non-IgE-mediated allergy affecting their gastrointestinal tract had abdominal pain. It is therefore a feature that is commonly described but the severity is difficult to assess for physicians, as it is so subjective. We hypothesise that this survey has highlighted this as a main presenting symptom for parents because colicky pain affects sleep for both child and parents, which can impact family life and the relationship between parent and child.

According to the survey on parents, it took on average of 10 weeks for the diagnosis to be made, whereas GPs estimated this to occur within 8weeks. It is however acknowledged that it should ideally occur within 4 weeks' time. This finding is supported by a study from Sladcevicius *et al.* who showed that it took on average 9 weeks with numerous GP visits in the UK before a child was diagnosed correctly with CMPA [15]. Conversely, a similar study in the Netherlands found that the diagnosis of CMPA occurred there within 4 weeks [20]. This is an important finding that needs to be addressed, as Valentine *et al.* found that the combinations of the symptoms of CMPA with the delayed diagnosis in some cases may affect a family's dynamic and quality of life [21]. In addition there are some studies on IgE-mediated food allergies that showed a significant impact on the parents' life, possibly because of the combination of the child's symptoms, extra-intestinal manifestations (for example poor sleep) [22], the difficulty of getting a quick diagnosis and correct treatment, and the burden and difficulty of following an elimination diet [23]. A delay in diagnosis may also lead to feeding difficulties due to on-going pain associated with feeding, leading to a negative association with the breast or bottle, and may also disrupt early weaning [24,25]. In 2011, Saps *et al.* found that CMPA in early infancy increases the risk of developing functional gastrointestinal disorders in later childhood, such as abdominal pain [26].

The lack of awareness of guidelines on CMPA and the training identified as necessary on this topic has bearing on the recognition and management of this food allergy (Table 3). Our data is supported by a larger study by Hazeldine *et al.* [27] on GPs' perceptions of UK allergy care. More than 50% rated allergy care in primary care as poor and 40% reported that they would benefit from more training. This lack of knowledge was also identified as a barrier for parents (Table 3). Although it may be perceived as a problem unique to the UK as GPs are the first point of contact for the recognition of CMPA, data implies that there are similar knowledge barriers for paediatricians worldwide. Quitadamo *et al.* published in 2014 a result from a survey that evaluated the knowledge about gastro-oesophageal reflux guidelines and found that the majority of the paediatricians were unaware of the 2009 guideline from ESPGHAN and the North American Society for Pediatric, Gastroenterology, Hepatology and Nutrition [27]. In 2014, Maslin *et al.* [28] published a survey on food allergy competencies amongst UK, Australian and USA dietitians, and found a similar trend in physicians with a need to increase their knowledge in different aspects of food allergy diagnosis and management, specifically the areas of developing food challenge protocols and management of feeding problems. As a result, the UK has implemented competency-based training courses on CMPA for dietitians [28]. We believe that such a training program for physicians would benefit and improve diagnosis and management. Whilst awaiting the development of these formal training programs, tools to guide diagnosis may also be useful. A recent tool developed to help GPs with cases of suspected CMPA and/or to evaluate improvement of symptoms is the Cow's Milk-related Symptom Score (CoMiss), published by Vandeplas *et al.* which comprises general symptoms, gastrointestinal, dermatological and respiratory manifestations common to children with CMPA. This tool has not been validated yet but may prove to be useful in primary care [29].

A very important finding of this survey is the impact of the response from the GPs on reported symptoms from parents and on-going management. On the one hand, the GPs found parents to have excessive worry or stress in relation to their child's allergy with unrealistic expectations, but on the other hand, parents did not think they were taken seriously and that they were worrying unnecessarily. This discord may lead to increased worry and stress and may also exacerbate the request for further formula changes as perceived by the GP (Table 3). Many of our parents reported feeling depressed about their child's diagnosis, which has been shown to have impact on communication and also satisfaction with the service. In 2012, Fagnano *et al.* [30] studied parents of children with asthma and the impact of depression on the communication between parents and health care professionals. In that study, 30% of parents had depressive symptoms, and that group was less satisfied with professional visits and felt that their needs were not met.

This study has many limitations. Firstly, a response bias exists, mainly from parents, as those who had a bad experience with their children's diagnosis of CMPA are more likely to participate in such a survey. The second limitation is that it was an online survey distributed via social networks and the questions were self-rated, so some results could be subjective. It is important to highlight that, in the GPs' survey, the responses were more focused on non-IgE conditions and just few a questions targeted IgE-mediated allergies. This was because health economic studies (e.g., Sladkevicius *et al.*) [15] demonstrate that the diagnostic delay is most common in these patients.

Table 3. Summary of suggestions from this survey to improve the diagnosis of CMPA.

Suggested Actions for GPs	Suggested Actions for Parents
Improve listening skills	Develop a symptoms diary that can be taken to the appointment
Allow more time for an allergy-focused history	Develop a simple food diary that can be taken to the appointment
More training on how to recognise and manage	Create awareness that there are guidelines for recognition and management of CMPA
Improve awareness of current guidelines	Create more awareness of CMPA through parent teaching/online training
Development of tools to aid diagnosis and management	Create leaflets with explanation of symptoms/diagnosis/treatment
More access to secondary and tertiary care	

5. Conclusions

This is the first study attempting to establish the experience of both GPs' and the parents' journey from diagnosis to management of CMPA. The difference between parents' and GPs' views on presentation and management of CMPA is notable, which has clinical implications for not only the child but also the family. From this survey, it is clear that GPs require more education on CMPA and also need tools to make this task easier for them. Parents, on the other hand, can also help with this process by improving their knowledge about the condition and making use of tools that they can complete prior to attending an appointment. There is a lack of validated tools to assist with the diagnosis of CMPA, and this survey highlights the need for these to be developed for primary care.

Acknowledgments

This survey was funded by Mead Johnson Nutrition UK. We would also like to acknowledge all parents and general practitioners that participated in this study.

Author Contributions

A.C.L.—involved in data analysis, conceptualising and writing of article; R.M.—involved in data analysis, conceptualising and writing of article; K.A.—involved in data collection and critical appraisal of publication; R.D.—data analysis and article corrections; K.R.—involved in data collection and critical appraisal of publication; H.G.—correction of publication; A.F.—critical appraisal of publication; N.S.—team lead, conceptualising research project and review of article.

Conflicts of Interest

The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results

Abbreviations

CMPA	Cow's milk protein allergy
GP	general practitioner
UK	United Kingdom
NIAID	National Institute of Allergy and Infectious Disease
IgE	Immunoglobulin E
ESPGHAN	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
EAACI	European Academy of Allergy and Clinical Immunology
DRACMA	Diagnosis and Rationale for Action against Cow's Milk Allergy
NICE	National Institute for Clinical Excellence Guidelines
MAP	on food allergy diagnosis, Milk Allergy in Primary Care

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J Pediatr (Rio J). 2014;90(1):16-21

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REVIEW ARTICLE

Eosinophilic colitis in infants[☆]

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Received 10 January 2013; accepted 4 March 2013
Available online 13 October 2013

KEYWORDS
Colitis;
Milk hypersensitivity;
Eosinophils;
Infant

Abstract

Objective: to review the literature for clinical data on infants with allergic or eosinophilic colitis.

Data source: MEDLINE search of all indexes was performed using the words ''colitis or proctocolitis and eosinophilic'' or ''colitis or proctocolitis and allergic'' between 1966 and February of 2013. All articles that described patients' characteristics were selected.

Data synthesis: a total of 770 articles were identified, of which 32 met the inclusion criteria. The 32 articles included a total of 314 infants. According to the available information, 61.6% of infants were male and 78.6% were younger than 6 months. Of the 314 patients, 49.0% were fed exclusively breast milk, 44.2% received cow's milk protein, and 6.8% received soy protein. Diarrheal stools were described in 28.3% of patients. Eosinophilia was found in 43.8% (115/263) of infants. Colonic or rectal biopsy showed infiltration by eosinophils (between 5 and 25 per high-power field) in 89.3% (236/264) of patients. Most patients showed improvement with the removal of the protein in cow's milk from their diet or the mother's diet. Allergy challenge tests with cow's milk protein were cited by 12 of the 32 articles (66 patients).

Conclusions: eosinophilic colitis occurs predominantly in the first six months of life and in males. Allergy to cow's milk was considered the main cause of eosinophilic colitis. Exclusion of cow's milk from the diet of the lactating mother or from the infant's diet is generally an effective therapeutic measure.

Colite eosinofílica em lactentes

PALAVRAS-CHAVE
Colite;
Alergia a leite;
Eosinófilos;
Lactente

Resumo

Objetivo: revisão da literatura sobre dados clínicos de lactentes com colite eosinofílica ou alérgica.

Fonte dos dados: pesquisa no Medline de todas as indexações com as palavras ''colitis or proctocolitis and eosinophilic'' ou ''colitis or proctocolitis and allergic'' entre 1966 e fevereiro de 2013. Foram selecionados todos os artigos que descreviam as características dos pacientes.

Síntese dos dados: foram identificados 770 artigos dos quais 32 preenchiam os critérios de inclusão. Os 32 artigos incluíram o total de 314 lactentes. Conforme as informações disponíveis,

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[☆] Please cite this article as: Lozinsky AC, Morais MB. Eosinophilic colitis in infants. J Pediatr (Rio J). 2014;90:16-21.

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0021-7557
http://dx.doi.org/10.1016/j.jped.2013.03.024

61,6% dos lactentes eram do sexo masculino e 78,6% apresentavam idade inferior a 6 meses. Dos 314 pacientes, 49,0% encontrava-se em aleitamento natural exclusivo, 44,2% recebiam proteína do leite de vaca e 6,8% proteína da soja. Fezes diarreicas foram descritas em 28,3% dos pacientes. Eosinofilia foi encontrada em 43,8% (115/263) dos lactentes. Biópsia retal ou colônica mostrou infiltração por eosinófilos (entre 5 e 25 por campo de grande aumento) em 89,3% (236/264) dos pacientes. A maioria dos pacientes apresentou melhora com a retirada da proteína do leite de vaca da sua dieta ou das suas mães. Teste de desencadeamento com proteína do leite de vaca foi citado em 12 dos 32 artigos (66 pacientes).

Conclusões: colite eosinofílica ocorre predominantemente nos primeiros seis meses de vida e no sexo masculino. Alergia ao leite de vaca foi considerada a principal causa de colite eosinofílica. Dieta de exclusão do leite de vaca da mãe lactante ou da dieta do lactente é uma medida terapêutica geralmente eficaz.

Introduction

The prevalence of food allergy has increased in recent decades, especially in the pediatric population.[1,2] Foods most often related to food allergy are cow's milk, eggs, soy, peanuts, nuts, seafood, and kiwifruit.[2] In infants, cow's milk protein allergy (CMA) is the most common, and usually starts in the first six months of life.

In Brazil, the prevalence of food allergy and the most important types of food allergy are yet to be determined. A study performed in the five geographic regions of Brazil assessed the sensitization of children with atopy, demonstrating that the most sensitizing food allergens were fish, eggs, cow's milk, wheat, peanuts, soybeans, and corn.[3] Among infants, the food that most frequently caused sensitization was cow's milk.[3] It is noteworthy that the presence of sensitization does not mean that the individual will effectively have food allergy.

Based on information from other countries, CMA is the most common type of food allergy in childhood.[4] It affects approximately 3% of children,[5] and its prevalence is higher in the first year of life. An epidemiological study performed in pediatric gastroenterology clinics in several regions of Brazil showed that among 9,478 consultations, 7.3% were prompted by a known or suspected food allergy, and the following were the suspected foods: 77% of cases, cow's milk; 8.7% of cases, soy; 2.7% of cases, egg; and 11.6% of cases, other foods. The analysis of new cases and follow-up allowed for a good estimation of an incidence of 2.2% and prevalence of 5.4% of patients with confirmed or suspected CMA.[6]

CMA should be regarded as an important clinical entity, since that normal infants have high rates of growth and development, and both CMA and the use of inadequate diet substitutes can compromise full growth and development in this important phase of life.[6,7]

Eosinophilic or allergic colitis has been described as a common entity,[5,8] but its exact prevalence is unknown.[4] Walker-Smith, one of the pioneers in the study of gastrointestinal food allergy, stated that, since the last decade CMA has been occurring with different manifestations when compared to those observed in the 1970s and 1980s, when there was a predominance of enteropathy induced by the milk in the infants' diet with infections by enteropathogenic *Escherichia coli*.[9] In this context, the epidemiological study performed in Brazil[6] demonstrated that 20.6% of infants with known or suspected CMA had blood in the stool that might be the result of allergic or eosinophilic colitis.

Eosinophilic colitis is considered one of the presentations of primary gastrointestinal eosinophilic diseases. This group of diseases also includes eosinophilic esophagitis, eosinophilic gastritis, and eosinophilic gastroenteropathy. The differential diagnosis of eosinophilic diseases must include causes that may result in secondary eosinophilic infiltration, such as certain intestinal parasites (*Enterobius vermicularis*, *Strongyloides stercoralis*, and *Trichuris trichiura*) and drugs (carbamazepine, rifampicin, gold, non-steroidal anti-inflammatory drugs, and tacrolimus).[10,11] It is also noteworthy that the clinical picture depends on the predominance of eosinophilic infiltration in the different layers of the intestine, that is, mucosal, muscularis, and serosa layers. There is a high association with atopy at all ages; however, in infants, the connection with food allergy is more frequently established.

Conversely, in adults, in addition to the adverse reaction to foods, other mechanisms lead the treatment to often include medicines in addition to elimination diet. Thus, the term allergic colitis can be used as a second alternative to denominate eosinophilic colitis, in a more appropriate form for infants.[10,11]

Thus, considering the increase in the number of infants with bleeding in the stool associated with CMA and the lack of articles with large samples, a literature review of articles indexed from 1966 to February of 2013 was performed, focusing on clinical and evolution aspects of infants with eosinophilic or allergic colitis.

Methods

A search was performed in the MEDLINE database for all indexed articles containing the words ''colitis or proctocolitis and eosinophilic'' and ''colitis or proctocolitis and allergic'', between 1966 and February of 2013. Publications were considered in the following languages: English, Portuguese, and Spanish. All types of articles were included, as long as they contained the clinical information of the infants with colitis or eosinophilic or allergic proctocolitis.

The abstracts were independently analyzed by two authors who selected articles that had samples or case

Table 1 Demographic and clinical data on allergic or eosinophilic colitis according to the review of published articles.

		Data available in articles	References
Gender	Male	153/248 (61.6%)	11, 13, 15,16, 18-42
	Female	95/248 (38.4%)	
Age at bleeding onset	< 6 months	247/314 (78.6%)	11-42
	≥ 6 months	67/314 (21.4%)	
Type of food	Breast milk	153/312 (49%)	12-42
	Infant formula or whole cow's milk	138/312 (44.2%)	
	Soy formula	21/312 (6.8%)	
Diarrheal stools	Yes	89/314 (28.3%)	11-42
	No	225/314 (71.7%)	

reports of infants (younger than 24 months) whether or not they presented with a clinical picture of elimination of blood in diarrheal stool attributed to colitis or allergic or eosinophilic proctocolitis.

Articles whose abstracts were insufficient to define inclusion or exclusion were read in full. In case of disagreements among the researchers regarding the inclusion of a certain article, information was reassessed until consensus was achieved.

Regarding the selected articles, the following data were evaluated: age and gender of the infant, clinical picture and diet at diagnosis, tests, prescribed treatment, and allergy challenge test was performed.

Results

A total of 770 articles were identified in the initial search, of which 32 were selected according to the predefined inclusion criteria, evaluating 314 infants.[11-42]

According to data shown in Table 1, of the 314 infants, most were male and younger than 6 months. Diarrheal stools were described in 28.3% of patients.

Regarding diet at diagnosis, 153 infants (49%) were exclusively breastfed, and the remaining received cow's milk protein (44.2%), except for 21 infants (6.8%) who received soy-based formula.

Regarding complementary tests, eosinophilia was found in 43.8% (115/263) of infants (Table 2). Sensitization to cow's milk was assessed by skin prick test in 98 patients, and was positive in 10 (10.2%) infants. Specific IgE against cow's milk protein was tested in 91 patients, and was positive in 13 (14.3%).

Of the 314 patients, 225 (71.6%) underwent colonoscopy or rectosigmoidoscopy, which showed areas of friability and erosive lesions of the mucosa. In addition to these patients, 39 underwent rectal biopsy without endoscopic procedure. Thus, biopsies were performed in 264 patients showing eosinophil infiltration (between 5 and 25 per high-power field) in 236 (89.3%) patients. Other histopathological findings were foci of erythema, chronic inflammatory infiltrate with areas of activity (lymphocytes, plasma cells, eosinophils), and signs of degeneration and regeneration of epithelial cells.

Cow's milk protein was removed from the diet of the mother and/or of the infant in most cases, with disappearance of intestinal bleeding.

Allergy challenge tests with cow's milk protein were mentioned in 12 of 32 articles, and were performed in 66 patients. Of these, 47 tests were performed two to three months after diagnosis and start of the elimination diet, and were positive in 34 (72.4%) patients, while 47 other tests were performed after one year of age, and were positive in only 10 (21.2%) patients.

Discussion

Eosinophilic or allergic colitis is a frequent manifestation of CMA in infants, occurring predominantly in males and usually starting in the first six months of life. According to the literature, approximately half of the cases occur during exclusive breastfeeding. Treatment consists of the exclusion of cow's milk proteins from the diet of the lactating mother and/or infant.

The first description of eosinophilic colitis was made by Kaijser in 1937.[43] Allergic proctocolitis was described by Rubin in 1940 and subsequently by Grybosky in the 1960s. They manifest as inflammatory changes of the colon and rectum, secondary to immune reactions triggered by ingestion of food proteins.[44]

Its exact prevalence is unknown. Arvola et al., in 2006, evaluated the cause of rectal bleeding in 40 infants and found an association with CMA through allergy challenge test in 18% of cases.[33] This result differs from the data retrieved by the present literature search, which demonstrated that most patients experienced recovery when submitted to elimination diet excluding cow's milk and dairy products (Table 2). However, it is important to observe that only a small percentage of the articles analyzed mentioned the use of the allergy challenge test to confirm the diagnosis of CMA. According to the data compiled in this article, 72.4% of allergy challenge tests were positive when performed up to two to three months of the elimination diet onset.

Eosinophilic colitis can occur since the neonatal period. In the present review, six reports of eosinophilic colitis in the first week of life were retrieved.[13,25,31,35,39,41]

The main clinical manifestation of the disease is the presence of blood in stool, whether or not associated with diarrheal stools.[44,45] In general, the infant presents no weight loss, impairment of general health status, or changes at abdominal palpation.[5,43] In all descriptions compiled in this article, the clinical manifestation of blood in the stool was reported in all patients, while diarrhea was reported in only 28.3% of cases.

Table 2 Additional tests used for the diagnosis of eosinophilic or allergic colitis according to the literature review.

		Data available in articles	References
Eosinophilia	Present	115/263 (43.8%)	12-23, 25-27, 30-31, 33-39, 41
	Absent	148/263 (56.2%)	
Skin prick test	Positive	10/98 (10.2%)	14, 16, 23, 30, 33, 36, 39, 42
	Negative	88/ 98 (89.8%)	
Specific IgE	Positive	13/ 91 (14.3%)	14-15, 17, 19-20, 23, 31, 33, 37, 38-40, 41
	Negative	78/91 (85.7%)	
Colonoscopy or Rectosigmoidoscopy	Yes	225/314 (71.6%)	11-42
	No	89/314 (28.4%)	
Biopsy - eosinophilic infiltration	Yes	236/264 (89.3%)	11-35, 37-41
	No	28/264 (10.7%)	
Allergy challenge test			12-14, 16, 17, 19, 26, 27, 33,34, 38, 42
After two to three months of elimination diet	Positive	34/47 (72.4%)	
	Negative	13/47 (27.6%)	
After 1 year of age	Positive	10/47 (21.2%)	
	Negative	37/47 (78.8%)	

Several foods have been associated with the development of eosinophilic colitis, but most cases are associated with cow's milk protein.[44] About 50% of cases occur in children on exclusive breastfeeding.[5,44,45] Kilshaw and Cant demonstrated that the presence of β-lactoglobulin can be detected in most samples of breast milk from mothers who consume cow's milk.[46] In the present review, 49% of the described patients were exclusively breastfed. Most articles mention that the process is controlled when the proteins in cow's milk are excluded from the lactating mother's diet. Especially in recent years, studies have identified a subgroup of infants with eosinophilic colitis in the presence of exclusive breastfeeding that did not improve with the exclusion of cow's milk proteins from their mothers' diet.[37,39,47]

Patients with this characteristic have been attended to at this service; however, no data are available on the proportion of infants with eosinophilic colitis during exclusive breastfeeding who do not improve after the exclusion of cow's milk from their mothers' diet.[47] A conducted in Hungary evaluated 34 infants on exclusive breastfeeding with blood in stool caused by eosinophilic colitis. Of the 34 patients, ten had persistent hematochezia when their mothers eliminated cow's milk and egg proteins from their diet. After confirming the diagnosis by colonoscopy and biopsy, breast milk was discontinued and replaced by an amino acid formula. All ten patients improved and showed no recurrence during the 13-month minimum follow-up.[37]

In this circumstance, two hypotheses can be raised: (1) persistence of small amounts of cow's milk proteins in the maternal diet despite the recommendation of elimination diet, considering that it is very difficult for the lactating mother to effectively remove cow's milk proteins from their diet; (2) Allergy to other foods present in the mother's diet that are transported through breast milk, thus raising the suspicion of eosinophilic colitis by multiple food allergies. In this context, a preliminary study performed in Italy[39] evaluated 14 infants with allergic colitis that did not improve after their mothers started having a hypoallergenic diet (free of cow's milk, soy, and egg). The authors performed a skin prick test, specific IgE measurement, and patch test.

All foods tested by the skin prick test and IgE were negative. Conversely, the patch test was positive with their own mother's milk in all cases, with cow's milk in 50% of cases, with soy in 28%, with egg in 21%, with rice in 14%, and with wheat in 7%. Thus, it can be deduced that other foods that were not investigated and that are transported through breast milk could also be responsible for the process of eosinophilic colitis. The results of this article should be interpreted with caution, given the small number of patients and the lack of comparison groups consisting of children with eosinophilic colitis responsive to elimination diet carried out by the mother and another group with normal infants. The main objective of the Academy of Breastfeeding Medicine is to develop protocols for the treatment of diseases that may compromise the success of breastfeeding. Allergic proctocolitis was the subject of one of these protocols.

For cases that did not improve with the exclusion of cow's milk from the mother's diet, the exclusion of other foods (soy, citrus, eggs, peanuts, wheat, corn, strawberries and chocolate) is recommended. They emphasize that such a diet can only be carried out with the supervision of a dietician experienced in the area, to ensure the mother's diet meets her basic nutritional and lactation needs. It recognizes that an infant with more severe eosinophilic colitis that does not respond to an elimination diet conducted by the mother should be fed exclusively on formula adequate for the treatment of CMA.[47] In general, when the allergen is excluded from the mother's diet, the bleeding disappears within 72 to 96 hours, with a maximum waiting period of two weeks.[9,47]

The diagnosis of eosinophilic colitis caused by CMA should be established based on history and thorough physical examination.[5,45] It is important to exclude the differential diagnosis of rectal bleeding, such as infections, necrotizing enterocolitis, intestinal intussusception, and anal fissure.[5,44]

To date, there are no non-invasive tests to confirm the diagnosis. Eosinophilia can be found in approximately 50% of patients with allergic colitis. The skin prick test and measurement of specific IgE against cow's milk can show negative results in infants, as identified in the present review. In turn, the patch test was evaluated in a few studies and, due to the lack of result standardization, it is not recommended to date.[9,45]

The diagnostic confirmation is based on the favorable clinical response by the patient after the start of the allergen elimination diet (cow's milk) and recurrence of bleeding with the reintroduction (allergy challenge test) of cow's milk protein in the diet.[5,44,45] The allergy challenge test is considered the most reliable method for the diagnosis of food allergy.[9] It can be performed in three different ways: non-blind (open), single-blind, and double-blind placebo-controlled test.[9] The two blinded modalities should be used when the clinical manifestations are subjective. In the case of infants, the non-blind allergy challenge test is traditionally recommended.[9,45]

It is noteworthy that only 12 of the 32 articles analyzed in this review sought to confirm the diagnosis with an allergy challenge test. 78.8% of the patients who were submitted to the allergy challenge test after 12 months of age showed negative result, indicating the development of tolerance. Conversely, when the allergy challenge test was performed two to three months after the start of the elimination diet, the diagnosis was confirmed in 72.4% of patients. Thus, when tested, the diagnosis of CMA is confirmed early in most patients, whereas after 12 months, the development of tolerance to cow's milk proteins is usually observed.

Many authors do not use the allergy challenge test to diagnose food allergy, which is the reason for the large discrepancy in reported prevalence and incidence of food allergy. A cohort study that followed 480 children from birth to 3 years of age showed that 28% of parents thought that their children's symptoms could be due to food allergy, especially in the first year of life. Conversely, when the allergy challenge test was performed, the diagnosis was confirmed in only 8% of cases. This result shows the importance of completing the allergy challenge test in the diagnosis of food allergy, avoiding unnecessary costs and maintenance of an elimination diet.[48]

Additionally, the possibility of tolerance development during the interval between the diagnosis and the allergy challenge test cannot be ruled out. In this context, it should be noted that, since the 1990s, the European Society of Pediatric Gastroenterology and Nutrition has considered the non-blind allergy challenge test appropriate for infants, in view of the fact that at this age range the suggestion component induced by the test is virtually nonexistent.[9,49] It should be noted that allergy challenge tests should not be performed if there is risk of anaphylaxis. It is currently recommended to start the test in a hospital environment.[9,45]

The diagnostic workup can be performed by invasive procedures such as sigmoidoscopy and colonoscopy, always associated with local biopsies.

The most common findings are extensive involvement of the rectum and colon mucosa with areas of erosion interspersed with those of normal mucosa. Lymphoid nodular hyperplasia can also be observed. The characteristic histological analysis of food allergy discloses signs of inflammation and eosinophil infiltration in the intestinal mucosa and lamina propria. Although there are controversies, the presence of more than 20 eosinophils per high-power field is generally considered indicative of eosinophilic infiltration. The indication of these procedures should be made considering the clinical characteristics of each particular case.[44,45]

The treatment of eosinophilic colitis consists in the exclusion of the allergen from the diet (cow's milk protein), constituting the ''elimination diet''. In the case of infant formula, which uses cow's milk as basis, its substitution by a formula containing extensively hydrolyzed protein should be recommended.[9] Patients who have not responded well to these should receive free amino acid formula.[9] In cases of exclusive breastfeeding, the mother's diet should exclude cow's milk and dairy foods, and breastfeeding should be maintained.[9,45]

In conclusion, CMA should be considered the main cause of eosinophilic colitis. Tests to assess sensitization to cow's milk do not contribute to establish the diagnosis. Despite the heterogeneity in diagnostic criteria, the infiltration of the rectal mucosa with eosinophils is reported in most biopsies. Exclusion of cow's milk and dairy products from the diet of the mother or infant is an effective therapeutic measure. Allergy challenge test confirmed the diagnosis of CMA in most patients when performed a few weeks after recovery attained through the elimination diet, while tolerance to cow's milk was characterized in most cases with eosinophilic colitis after 12 months of age.

Conflicts of interest

The authors declare no conflicts of interest.

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4. NUTRITIONAL IMPACT OF THE DISEASE AND THE ELIMINATION DIET

This chapter comprises of two sections: the first one (Meyer et al., 2016) focused on the impact of the elimination diet on children's growth before and after commencing it. The second chapter (Meyer et al., 2015) evaluates the children's intake of vitamins and minerals while on an elimination diet for the diagnosis and treatment of non-IgE mediated gastrointestinal food allergies and the current practice of vitamin and mineral supplementation for this group of patients.

The elimination diet is critical for the diagnosis and treatment of non-IgE mediated gastrointestinal food allergies. However, its methodology varies among centres and the severity of the cases. Some teams will initiate a multiple elimination diet with single food reintroduction every four to eight weeks to identify the allergens causing the symptoms. In contrast, others will start with single food elimination (the majority will start with cow's milk) and increase the number of foods progressively until symptom resolution (Meyer R, 2012). The most common foods eliminated during the diagnostic workout have an important contribution to children's diet, and their elimination may have a potential impact on children's growth.

4.1 Growth impact and factors associated

This section includes a publication that describes the changes on children's growth before and after commencing an elimination diet (on a repeated measure analysis) and the associated factors that contribute to growth, like energy and protein intake (Meyer et al., 2016). Even though 131 participants were enrolled on the "Discovering the effect of non-IgE mediated allergies on children and their families" study, data of 130 were analysed in this publication due to availability of growth parameters. Pre-elimination weight and height measurements were taken from clinical notes. The study team took post-elimination measures at the research visit after a minimum of four weeks of an elimination diet.

The mean z-scores for weight-for-age, height-for-age, weight-for-height (< five years old) and body mass index (BMI) before the elimination diet were

-0.203, -0.155, -0.023 and -0.034. The same parameters were evaluated after the elimination diet and the z-scores for weight-for-age, height-for-age, weight-for-height (< five years old) and BMI were 0.008, -0.122, 0.260 and -0.017. There was a statistically significant increase in the weight-for-age after commencing the elimination diet compared to the pre-elimination diet period (p=0.003).

After four weeks of elimination diet it was noted that 9% of the cohort was stunted (low height-for-age), 2.2% of children < five years old were wasted (low weight-for-height) and 5% of children > five years old had BMI less than -2 z-score. Additionally, 2.2% of children < five years old and 10% of children > five years old were overweight.

Before starting the elimination diet, all families received dietetic advice and were asked to record a three-day food after four weeks on the elimination diet for analysis of macronutrient intake. Data of 110 children were included. 68.2% and 50% of children met their requirements for energy and protein intake, respectively. Interestingly, 47.3% of children consumed more than 200% of the reference nutrient intake for protein. Multivariate regression analysis was performed to assess factors that impacted on growth before and after the elimination diet. Vitamin and/or mineral supplements and children that received a higher percentage of energy from protein had a more significant increase on weight-for-age z-scores. Conversely, children that received a higher rate of energy from carbohydrates had on average lower post-elimination height-for-age z-scores. The use of hypoallergenic formulas had a positive impact on weight-for-age, while over-the-counter alternative milk products had a negative impact.

Strengths and limitations

The results of this study are important: I provided evidence that there was an improvement in the weight-for-age and weight-for-height on the four weeks elimination diet. The study has also shown that the improvement was not related to the diet itself (the type of food excluded and the number of foods eliminated), but rather to achieve the energy and protein intake requirements and also linked to the use of hypoallergenic formulas. These findings highlight how important is to give detailed and individualised dietary advice to families before commencing an elimination diet and how this change in clinical practice can impact positively on the growth of children with non-IgE mediated gastrointestinal food allergies.

This study is not without limitations. The main limitation is the absence of a control group of non-allergic children that would allow interesting comparisons between groups (allergic versus non-allergic) in regard to growth and nutrient intake. Another limitation is that weight and height measurements before the elimination diet were collected from clinical notes, and it was not possible to obtain weight and height pre-elimination diet from all the participants. Also, due to study design, no growth measurement was done after four weeks of elimination diet. It would be interesting to have measured it again after two to three months to have a better idea, mainly, of the impact of the diet elimination on the height-for-age.

Publication

1. https://www.ncbi.nlm.nih.gov/pubmed/27418957

Meyer, R., De Koker, C., Dziubak, R., Godwin, H., Dominguez-Ortega, G., et al. (2016) ‘The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies’. *Clin Transl Allergy,* 6(25) pp 1-7. [Online][Acessed on June 2019] DOI:10.1186/s13601-016-0115-x¶

Meyer *et al. Clin Transl Allergy (2016) 6:25*
DOI 10.1186/s13601-016-0115-x

Clinical and
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The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies

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Abstract

Background: Non immunoglobulin E (IgE) mediated allergies affecting the gastrointestinal tract require an elimination diet to aid diagnosis. The elimination diet may entail multiple food eliminations that contribute significantly to macro- and micro-nutrient intake which are essential for normal growth and development. Previous studies have indicated growth faltering in children with IgE-mediated allergy, but limited data is available on those with delayed type allergies. We therefore performed a study to establish the impact on growth before and after commencing an elimination diets in children with food protein induced non-IgE mediated gastrointestinal allergies.

Methods: A prospective, observational study was performed at the tertiary gastroenterology department. Children aged 4 weeks–16 years without non-allergic co-morbidities who were required to follow an elimination diet for suspected food protein induced gastrointestinal allergies were included. Growth parameters pre-elimination were taken from clinical notes and post-elimination measurements (weight and height) were taken a minimum of 4 weeks after the elimination diet. A 3-day estimated food diary was recorded a minimum of 4 weeks after initiating the elimination diet, including also any hypoallergenic formulas or over the counter milk alternatives that were consumed.

Results: We recruited 130 children: 89 (68.5 %) boys and a median age of 23.3 months [IQR 9.4–69.2]. Almost all children (94.8 %) in this study eliminated CM from their diet and average contribution of energy in the form of protein was 13.8 % (SD 3.9), 51.2 % (SD 7.5) from carbohydrates and 35 % (SD 7.5) from fat. In our cohort 9 and 2.8 % were stunted and wasted respectively. There was a statistically significant improvement in weight-for-age (Wtage) after the 4 week elimination diet. The elimination diet itself did not improve any of the growth parameters, but achieving energy and protein intake improved Wtage and WtHt respectively, vitamin and/or mineral supplements and hypoallergenic formulas were positively associated with WtHt and Wtage.

Conclusion: With appropriate dietary advice, including optimal energy and protein intake, hypoallergenic formulas and vitamins and mineral supplementation, growth parameters increased from before to after dietary elimination. These factors were positively associated with growth, irrespective of the type of elimination diet and the numbers of foods eliminated.

Keywords: Growth, Anthropometric measures, Non-IgE mediated allergy, Malnutrition, Nutrients

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Background

It is thought that between 2.2 and 5.5 % of young children in the United Kingdom (UK) suffer from a proven food allergy [1]. However, this data is mainly based on immunoglobulin E (IgE) mediated allergies, with no known population prevalence data for non-IgE mediated food allergies. Non-IgE mediated food allergies include food protein induced gastrointestinal allergies such as proctocolitis, enterocolitis, eosinophilic gastrointestinal disorders, food protein induced enterocolitis syndrome and enteropathy [2, 3]. The pathophysiology and the diagnostic tests differ between IgE and non-IgE mediated allergies, in that the latter requires an elimination diet followed by the reintroduction of allergens to confirm the diagnosis whereas IgE mediated allergies have the benefit of both skin prick or specific IgE tests [4, 5]. The approach to elimination diets vary amongst allergy centres, with some preferring to eliminate all common allergens initially followed by single reintroduction, whereas others commence children on single food eliminations and increase the number of foods eliminated until symptom resolution occurs [6]. Whatever method is used, it can take several months in children with multiple non-IgE mediated food allergies to identify the correct offending allergen(s) through dietary elimination, which may impact on growth.

The most common foods involved in non-IgE mediated allergies affecting the gastrointestinal tract include: cow's milk (CM), hen's egg, soya bean and wheat [3, 6, 7]. Many of these foods, in particular CM, contribute significantly to macro- and micronutrient intake which are essential for normal growth and development, especially during early childhood [8]. Isolauri et al. [9] highlighted poor growth, in particular stunting, as a problem in children on a CM exclusion diet for IgE-mediated allergy. More recently, Flammarion et al. [10] also published growth data on children with IgE-mediated allergy and linked the number of foods excluded to a low weight- and height-for-age (Wtage and Htage) z-score. To date, only one study has been published in a non-IgE mediated population with gastrointestinal symptoms, which found a very high percentage of both wasting [low weight-for-height (WtHt)] and stunting (low Htage) in children [11]. However, this study only reviewed growth in CM allergy and did not focus on other food eliminations; furthermore the growth was not linked to actual dietary intake. Thus, limited information exists on growth in children on elimination diets with food protein induced non-IgE mediated gastrointestinal allergies. We therefore set out to establish the impact on growth before and after an elimination diet in children with non-IgE mediated food allergies affecting the gastrointestinal tract and assessed factors that contributed towards growth.

Methods

Subjects

A prospective, observational study was performed at the tertiary gastroenterology department, from Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK. Parents of children aged 4 weeks–16 years without non-allergic co-morbidities (i.e. cerebral palsy, cardiac disorders) who were required to follow an elimination diet for the diagnosis of suspected non-IgE mediated gastrointestinal food allergies, were approached to take part in the study. Inclusion in the study occurred if after 4 weeks of following the elimination diet, there was an improvement in their gastrointestinal symptoms. This was measured by a repeated likert scale gastro-intestinal symptom questionnaire that has previously been published [12].

Anthropometry

Pre-elimination weight and height measurements were taken from the referral letters, clinical notes and health records, as parents only came in once during the study for assessment, which was after the elimination diet was shown to lead to symptom improvement. At the research appointment, a minimum of 4 weeks after the elimination diet was commenced, weight and height measurements were repeated.

Weight was measured using a SECA (Hamburg, Germany) portable electronic baby (<10 kg), or SECA (Hamburg, Germany) sitting (>10 kg) scales, calibrated as per hospital protocol. Length was measured using a portable recumbent length meter in children under 2 years of age, and a fixed standing height meter in older children (rounded off to the nearest 0.1 decimal). All growth measurements were converted to z-scores using the WHO Anthro (birth—5 years) and AnthroPlus Software (>5–18 years). We assessed the z-scores for Wtage, Htage and WtHt and for children ≤5 years of age and for children >5 years, body mass index (BMI) replaced WtHt in the AnthroPlus Software. We compared the z-scores before and after the elimination diet, where available and assessed the number of children that were stunted (Htage ≤2 z-scores), wasted (WtHt less than or equal to −2 z-score) or overweight (>2 z-score) as defined by the World Health Organisation (WHO) after a minimum of 4 week dietary elimination period [13].

Dietary intake analysis

The parents of all children in this study received dietetic advice with standard diet sheets published by the Food Allergy Specialist Group of the British Dietetic Association at the time of having to embark on the elimination diet. This advice included not only how to avoid allergenic foods, but also individualised information on a suitable hypoallergenic formula (HF)/over the counter milk and supplementation if required as per dietetic assessment. A 3-day estimated food diary (2 week days and 1 weekend day) was recorded a minimum of 4 weeks after initiating the elimination diet. Carers were given detailed instructions on how to complete the diary as accurately as possible, including a portion size guide and a sample menu. HF consumption (including type and volume) and over-the-counter milk alternatives for older children were also documented. Food diaries were discussed with parents and any unclear entries were clarified by the researcher if possible, either at the time of research appointment or by means of telephone communication.

Nutritional intake data was assessed using Dietplan 6 (Forestfield Software Limited, UK). Any foods, in particular specialist foods free from allergens, as well as HF not available on the software database were manually added by the researcher, and product information was obtained from the manufacturer where necessary.

Dietary intake for energy and protein were compared to the UK Dietary Reference Values using the reference nutrient intake (RNI) for protein and estimated average requirements (EARs) for energy [14]. Insufficient intake for protein was defined as an intake <100 % of the lower reference nutrient intake (LRNI—meeting nutrient requirements for 2.5 % of population), sufficient intake was between the LRNI and <200 % of the RNI and excessive intake >200 % of the RNI [14].

For energy intake, the RNI is not used because it represents an excess energy intake for the majority of the population, as highlighted by the Scientific Advisory Committee on Nutrition in the United Kingdom (SACN) [14]. Instead the EAR were used and children consuming below 67 % were classified as low energy intake, between 67 % EAR and 110 % as sufficient intake and excessive intake in this study was arbitrary based on 110 % of the EAR [15].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22 (Armonk, NY, USA). Continuous variables are presented as means with standard deviations or medians with interquartile ranges where appropriate. Categorical variables are presented as frequencies Bonferroni correction was used in univariable analysis. Paired-samples t test was used to compare growth parameters before and after elimination diet and Mann–Whitney U Test was used to compare z-scores between groups of children achieving/not achieving energy intake requirements. Spearman's test was used to check correlation between percentage energy intake from fat, carbohydrates and proteins, and z-scores. Multivariable regression analysis was used to ascertain the association between anthropometrical parameters and the following parameters: macronutrients (i.e. protein, carbohydrate and fat) and vitamin and/or mineral supplementation, consumption of HF and over-the-counter milk alternatives (i.e. oat, rice, coconut or nut milks), food elimination (i.e. CM, egg, wheat, soya) and number of foods eliminated, time between pre- and post-intervention and gastrointestinal symptoms (i.e. diarrhoea, vomiting, feeding difficulties). We accounted for age and gender in the regression model and factors were only included in the regression analysis based on the outcome of univariate analysis. All tests were two-tailed and significance level was set to 0.05.

Results

Subjects

We recruited 131 children in the study and 130 had available growth parameters. Data was obtained from 89 (68.5 %) boys and 41 (31.5 %) girls with a median age of 23.3 months [IQR 9.4–69.2]. In this study 10.8 % were on a HF only, 17.2 % avoided one food, 30.2 % two foods, 15.5 % three foods and 37.1 % eliminated ≥4 foods. Almost all children (94.8 %) in this study eliminated CM from their diet, 74 % also soya with 45.7 and 44.8 % also avoiding egg and wheat respectively. The most frequent combination (30.2 %) of foods eliminated was CM, soya, egg and wheat (with or without other foods) (Fig. 1).

Anthropometrics

The mean Wtage, Htage, WtHt (<5 years of age) and BMI z-scores (>5 years of age) for children after a minimum of 4 weeks elimination was 0.044, −0.186, 0.296 and 0.042. Differences in z-scores before and after intervention were calculated where both measurements were available and are presented in Table 1. There was a statistically

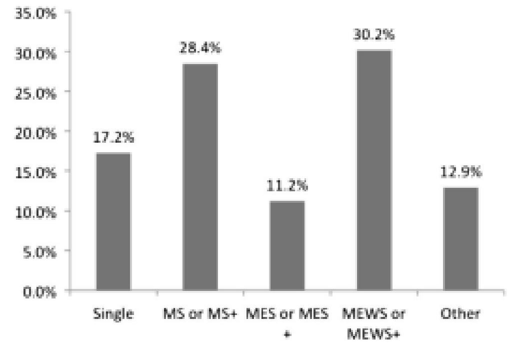

Fig. 1 Combinations of food elimination diets. *MS* milk and soya, *MES* milk, egg and soya, *MEWS* milk, egg, wheat and soya, $^{+}$random additional foods to the list

Table 1 Differences in z-scores for measurements before and after the elimination diet

	N	Before		After		Difference	
		Mean	SD	Mean	SD	Mean	p value
Wtage	88	−0.203	1.147	0.008	1.009	0.211	0.003*
Htage	84	−0.155	1.268	−0.122	1.168	0.033	0.688
WtHt (≤5 years)	56	−0.023	1.246	0.260	1.088	0.282	0.039
BMI (>5 years)	27	−0.034	1.094	−0.051	1.112	−0.017	0.824

significant increase in Wtage z-score (p = 0.003) before and after dietary elimination. Although there was an improvement in Htage z-score from −0.155 to −0.122 this was not statistically significant. After following the elimination diet for 4 weeks, 11/130 (9 %) of children were stunted and 2/90 (2.2 %) children <5 years of age were wasted (z-score less than −2) and 2/40 (5 %) >5 years had a BMI less than −2 z-score. Conversely 2/90 (2.2 %) and 4/40 (10 %) children <5 and >5 years of age were overweight respectively with a WtHt or BMI z-score >2.

Macronutrient intake

Of the 131 patients recruited, 123 had completed food diaries, but only 110 food diaries were included in the data analysis due to some infants being breast fed (difficult to estimate intake on an individual basis) or due to inadequate information on foods or portion sizes. According to our definitions 68.2 and 50.0 % of children met their requirements for energy and protein respectively (Fig. 2). Although not many exceeded their intake for energy (10.0 %), 47.3 % consumed ≥200 % of the RNI for protein. In addition 21.8 % consumed less than the recommended EAR for energy (Fig. 2). In this study, the average contribution of energy in the form of protein was 13.8 % (SD 3.9), 51.2 % (SD 7.5) from carbohydrates and 35 % (SD 7.5) from fat.

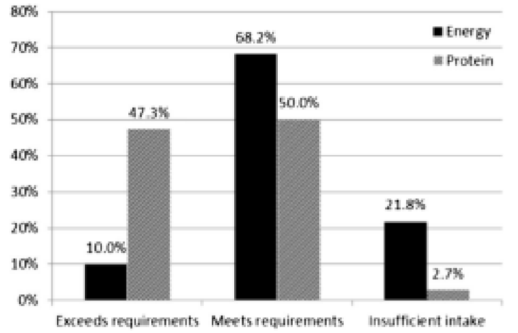

Fig. 2 Percentage of patients with insufficient intake, meeting their requirements or excessive intake

Association between growth parameters and nutritional intake

In this study, 21.8 % did not achieve their EAR for energy versus only 2.7 % not achieving requirements for protein. In fact, 47.3 % exceeded the protein requirements for their age (Fig. 2). We assessed if there were differences in z-scores for all growth parameters between those who achieved and did not achieve sufficient energy intake and did not find any statistical significant association between these (Table 2). This analysis was not performed for protein due to the low number not achieving the protein requirements.

Multivariate regression analysis was performed to assess factors that impacted on the change in growth measurements before and after the elimination diet (Table 3). Table 3 presents these findings, however in summary: those receiving vitamin and/or mineral supplements on average had a bigger increase in WtHt z-score and similarly children that received a higher percentage of energy from protein had on average a bigger rise in WtHt z-scores from before to after the elimination diet. Those achieving EARs for energy had a bigger increase in Wtage z-scores from before to after the elimination diet. Children that received a higher percentage of energy from carbohydrates had on average lower post elimination Htage z-scores.

The presence of a HF impacted positively on both difference in Wtage z-scores and on post elimination Wtage z-scores, conversely over-the-counter alternative milks negatively impacted on the post elimination WtHt z-scores. Children with higher previous WtHt z-score and Wtage had on average lower change in WtHt and Wtage z-scores respectively during the elimination period.

Table 2 Association between energy intake and growth parameters expressed as z-scores

Standard	Insufficient energy intake	Meet or exceeds energy requirements	p value
WtHt	−0.01	0.42	0.82
Wtage	−0.33	0.33	0.07
Htage	−0.35	−0.09	0.18

Table 3 Regression analysis on the association of different factors on growth parameters

Variable	Difference WtHt[a]	Post elim. WtHt	Difference in Wtage[a]	Post elim. Wtage	Post elim. Htage
(Constant)	−1.005	0.592	−0.211	0.94	1.355
Pre elimination z score	−0.272**	0.475***	−0.082*	0.702***	0.654***
Hypoallergenic formula			0.234**	0.458***	
Vitamin/mineral supplements	0.685**				
Energy from protein (%)	0.083**				
Achieving energy EAR			0.197*		
Energy from carbohydrate (%)					−0.026**
Over-the-counter milk		−0.510*			
R^2 (%)	43.4	40.0	18.4	68.9	67.4

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[a] The difference before and after commencing the elimination diet

Children with higher previous WtHt, Wtage and Htage z-scores had on average higher post elimination WtHt, Wtage and Htage z-scores. The following variables were not significantly associated with growth in any of the statistical models: gastrointestinal symptoms, foods excluded (milk, wheat, soya, egg) and number of foods excluded.

Discussion

This study set out to establish growth before and after an elimination diet for presumed non-IgE mediated gastrointestinal food allergies and assessed the impact of macro and micronutrients on these parameters. To the knowledge of the authors this is the first such study focusing on the whole spectrum of non-IgE mediated gastrointestinal allergies and the association between dietary elimination on growth. This study indicated there was an improvement in WtHt and Wtage on the elimination diet, but we found that the elimination diet itself (i.e. CM, soya, egg, wheat) and the number of foods eliminated did not have a positive impact on growth over a 4 week period in our population. However the presence of a HF in addition to achieving energy requirements and percentage protein intake improved the Wtage and WtHt z-score.

In this study stunting was present in 9 % of children after a 4 week elimination diet, but only a very small number of children were wasted (2.2 and 5 %). In the general population the WHO estimates stunting in developed countries to be around 6 % [16]. Flammarion et al. [10] found in an IgE-mediated cohort that 12.1 % of children were stunted and 9.8 % wasted if ≥3 foods were eliminated. Another study performed in Brazil on a non-IgE mediated CM allergic cohort, found much higher levels of stunting and wasting at 23.9 and 8.8 % respectively [11]. The differences in results are most likely related to different populations and also the fact that all of the patients included in our study received individualised dietetic advice using standard diet sheets. Previously published work by Meyer et al. [17] on the nutritional status of children with IgE and non-IgE mediated allergy under dietetic care in the UK have found that 11.9 and 3.7 % were stunted and wasted respectively and that the number of foods eliminated only made an impact on Wtage but not WtHt or Htage. What our current study reinforces, is that in a non-IgE mediated gastrointestinal allergy population on an elimination diet, a significant number of children with this allergy will be stunted irrespective of dietary advice including a suitable HF and vitamin and mineral supplementation [9, 11, 17].

In this study there was an overall improvement in Htage, WtHt, Wtage but only the latter was statistically significant. As there was on average a minimum of 4 weeks between commencing the elimination diet and the research review, there was most probably insufficient time for significant height growth to occur. The average age of our population was around 2 years of age and Himes [18] suggest a minimum time of 52 days in this age group to detect significant changes in height growth. There is concern about short stature in food allergic children, in spite of optimal dietary elimination, which has been highlighted by Isolauri et al. [9] and Meyer et al. [17]. Future studies should aim to review height growth following an elimination diet over a longer period of time to establish the impact of the dietary elimination.

The improvement in WtHt and Wtage found in this study was not associated with the elimination diet itself or the number of foods eliminated. Instead we found that achieving the EAR for energy and the percentage of energy coming from protein (in this study 13.8 %) had a positive impact on Wtage and WtHt. Although it makes sense that better growth is achieved in children that receive their energy requirements, in our study 21.8 % did not achieve the EAR for energy, but seemed to grow well. This is in line with the findings of Flammarion et al. [10] who found that 24 % of children with and 23 % without food allergy also did not achieve their energy requirements, without an apparent impact on their growth. This may be associated with inaccuracies in dietary intake reporting and assessment, however from a clinical perspective our findings still indicate that growth can be improved if EAR for energy is achieved. In contrast to the intake of energy, 47.3 % exceeded their RNI for protein. This is not a novel finding in both food allergic children as well as general paediatric population. Flammarion et al. [10] found in their cohort that the majority of children consumed more than their RNI for protein. The National Diet and Nutrition Survey [19] from the UK also found that in the majority of healthy children, protein contributed around 15 % of energy. Similarly, the European Survey by Lambert et al. [20] established that energy from protein in children from a variety of European countries ranged from 11 to 16.6 %. What is interesting from our study is that protein was positively associated with and improvement in WtHt z-score. The importance of additional protein in catch-up growth has been highlighted by the WHO/FAO/UNO guidelines on protein requirements in 2007 as well as Golden in 2009 [21, 22]. It is thought that up to 15 % of protein may be required in severe stunting [23, 24]. The findings of our study, contribute important information to future dietary management of children with non-IgE mediated food allergies, indicating that a higher level of energy from protein may be required to achieve catch-up in height growth.

In addition to the positive impact of energy and protein, we have also found that the presence of a HF positively impacted on Wtage z-score but not Htage z-score, which is most probably related to there being insufficient time to see changes in height as highlighted above. Conversely, the presence of an over-the- counter milk alternative, negatively impacted on the post elimination WtHt z-score. Over-the-counter milk alternatives (oat milk, rice milk, nut milks) are particularly low in protein and provide on average between 0.1 and 1 g/100 ml of protein, whereas formulas provide 1.6–1.9 g/100 ml of protein (<1 year of age). We hypothesise that the negative impact of these alternative milks is mainly related to the low protein content, as percentage energy from protein has been associated with improved growth. Our group has also recently published the impact of a HF versus over-the-counter alternative on micronutrient intake. We found that micronutrient intake is positively affected by the presence of a HF [25]. This may also affect growth, as in this study the presence of a vitamin/mineral supplement positively impacted on WtHt of these children. We have not been able to isolate specific vitamins or minerals involved, however future studies should assess the impact of vitamin D, zinc, iron and other essential vitamins and minerals on growth.

The limitations of the study include the lack of a control group, which would have enabled a comparison between dietary intake and growth in an allergic and non-allergic cohort. In addition, having a 3 day food diet before and after the elimination diet would have also been beneficial in establishing the impact of nutrient intake on growth. In this study, children were only enrolled after symptom improvement was achieved, which was a major entry criteria for the study, therefore parents were only invited for a growth review after 4 weeks on the elimination diet. This meant that some came a day or two after the 4 week symptom assessment or a week after this. Although this introduces some variation in timing of growth assessment, we believe that this variation in timing would not impact significantly on our growth data. Another limitation of the study is that we did not manage to obtain full growth measurements (weight and height) before and after the elimination diet in all subjects, however we did collect sufficient data to show a significant trend. It would have also been beneficial to have repeated height and weight parameters again 3 months after the elimination diet was commenced to assess the impact on Htage, however this was not possibly with the resources available for the study. In addition, the accuracy of the 3-day food diary needs to be taken into account when interpreting the results. The problems related to accuracy of dietary intake methods have been highlighted by many studies. In our study, we decided on a 3-day semi quantitative food diary, as Lanigan et al. [26] did not find that a weighed record provided a significant benefit over a semi-quantitative diary. In addition a 3-day food diary was chosen instead of a 7 day diary, to reduce the fatigue effect of recording dietary intake for such a long. However, future studies assessing dietary intake my benefit from adding a second dietary intake method to ensure that recorded dietary intake is accurate.

Conclusion

This study has shown that nutritional management of children with non-IgE mediated gastrointestinal food allergies, significantly impacts on growth. In this study patients had improved growth parameters following dietary elimination. This positive impact was related to energy and protein intake, the use of a HF and vitamin and/or mineral supplementation, irrespective of the type of elimination diet and the numbers of foods eliminated. Future studies should aim to recruit a control group to establish whether these findings are unique to children with this type of allergy and assess the impact of the elimination diet over a longer period.

Abbreviations

CM: cow's milk; EAR: estimated average requirements; IgE: immunoglobulin E; Htage: height-for-age; HF: hypoallergenic formula; NHS: National Health

Service; OFC: occipito-frontal circumference; RNI: recommended nutrient intake; SACN: Scientific Advisory Committee on Nutrition in the United Kingdom; UK: United Kingdom; WHO: World Health Organisation; Wtage: weight-for-age; WtHt: weight-for-height.

Authors' contributions

RM—involved in data collection and some dietary analysis, conceptualising and writing of article. CDK—performed majority of data collection and dietary analysis, conceptualising and writing of article. RD—statistical analysis and article corrections. KR—critical appraisal of publication. HG—involved in data collection for the study and correction of publication. GDO—involved in data collection and correction of publication. ALR—critical appraisal of publication. AKS—involved in data collection and correction of the publication. YG—critical appraisal of publication. NS—team lead, conceptualising research project and review of article. All authors read and approve the final manuscript.

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Acknowledgements

We would like to acknowledge all the parents of children with this food allergy who have taken the time to come to our research centre and also fill in the 3-day food diaries.

Competing interests

Funding for this study was obtained through Great Ormond Street Charitable Fund. The authors declared that they have no competing interests.

Availability of data and materials

This is an ongoing prospective study with the population still being followed up. Hence the data is not available. No new software or methods were used for this study.

Ethics, consent and permissions

Ethical approval was obtained from the National Research Ethics Service UK (NRES London—Bloomsbury, NR: 11/LO/1177) for this study. Written consent was obtained for both the study and the publication of the study from parents.

Funding

Funding was obtained from Great Ormond Street Hospital Charity. Once the funding was awarded the funding body was not involved in the design, data collection, data analysis or write-up of this publication.

Received: 15 December 2015 Accepted: 27 May 2016

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4.2 Vitamin and mineral supplementation in non-IgE mediated food allergic children

This section is based on a publication evaluating the current practice of vitamin and mineral supplementation in food allergic children while on an elimination diet, focusing on the impact of this supplementation and also evaluating the prescription rate of supplements for patients who had low vitamin and/or mineral intake based in their diets (Meyer et al., 2015). Previous studies in food allergic children reported low micronutrient intake as the result of the elimination diet, with proper documentation about vitamin D, calcium and omega-3 fatty acids (Sova et al., 2013).

This study's results are part of the "Discovering the effect of non-IgE mediated allergies on children and their families" study. Data on nutrient intake, vitamin and/or mineral supplementation, use of hypoallergenic formula or over-the-counter milk alternatives were collected from a three-day food diary recorded by families after four weeks of the elimination diet. A hundred and ten children had a complete food diary and were analysed. The median age of the cohort was 30 months. All infants that were exclusively breastfed or received two or more breastfeeds per day were excluded from the analysis due to difficulties in estimating individualized consumption. Biochemical markers of micronutrient intake were also collected and analysed when available.

I have analysed dietary adequacy of micronutrients intake without supplements (n=110) and found that no child had vitamin C deficiency. Also, low intake of vitamin B12, B6, thiamine and folate were rare. However, 60% of the children had low vitamin D intake. Low intake of zinc, copper and selenium were also common. From 110 patients, 32 (29%) were taking vitamin and/or mineral supplements, with a mean age of 5.1 years and the majority of them were on over-the-counter milk alternatives. 68% of the patients had a prescriptible supplement. When I evaluate the micronutrient intake from this subgroup of patients, I found that a high number of patients did not achieve their vitamin D dietary requirements. Many children that were identified as having low micronutrient intake for specifics micronutrients (zinc), did not receive an adequate supplement. Moreover, a high percentage of children on supplements exceeded 200% of the reference nutrient intake for vitamin C, vitamin B6, thiamine, folate, selenium and Vitamin A. Only seven (6.3%) children had biochemical markers taken.

This study has shown that 60% of the cohort have low vitamin D intake. This finding is consistent with previous studies in allergic and non-allergic patients (Greer, 2008, Zipitis et al., 2006). Rickets is a concern in the UK and also in many European countries (Goldacre et al., 2014). I also reported a high number of children with low intake of copper, zinc and selenium, which was also demonstrated in previous studies (Ojuawo et al., 1996; Toyran et al., 2012). These micronutrients have an immunomodulatory role in the organism and are essential for children (Kamer et al., 2012).

Strengths and limitations

This study highlights that low intake of vitamins and micronutrients is frequent in children with non-IgE mediated food allergies on an elimination diet and that a high proportion of children do not receive adequate supplementation. The results of this study show how important it is in the clinical practice to take a detailed clinical and food history and also a detailed food diary when evaluating a patient with suspected food allergy. These are essential tools to identify potential micronutrients deficiencies and ally in the prescription of the correct supplement for the patient.

The main limitation of this study is that a three-day diary may not be accurate enough to indicate a vitamin or mineral deficiency, but when analysed correctly can indicate a low intake of micronutrients. Another limitation is that all information analysed in this study was based on parents' documentation, and there is the possibility of a lack of documentation and recall bias of diet components or the use of a supplement. In this case, bias could be related to parents that did not document all supplements their children were on due to concern that the dietitian would request them to discontinue or change it.

Publication

2. https://www.ncbi.nlm.nih.gov/pubmed/25780558

Meyer, R., De Koker, C., Dziubak, R., Skrapac, A. K., Godwin, H., et al. (2015) ‘A practical approach to vitamin and mineral supplementation in food allergic children’. Clin Transl Allergy, 5(11) pp.1-7. [Online] [Acessed on 4th of May 2019] DOI: 10.1186/s13601-015-0054-y

Meyer *et al. Clinical and Translational Allergy* (2015) 5:11
DOI 10.1186/s13601-015-0054-y

Clinical and Translational Allergy

RESEARCH Open Access

A practical approach to vitamin and mineral supplementation in food allergic children

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Abstract

Background: The management of food allergy in children requires elimination of the offending allergens, which significantly contribute to micronutrient intake. Vitamin and mineral supplementation are commonly suggested as part of dietary management. However a targeted supplementation regime requires a complete nutritional assessment, which includes food diaries. Ideally these should be analysed using a computerised program, but are very time consuming. We therefore set out to evaluate current practice of vitamin and mineral supplementation in a cohort of children with non-Immunoglobulin E (IgE) mediated food allergies.

Methods: This prospective, observational study recruited children aged 4 weeks – 16 years, who required to follow an elimination diet for non-IgE mediated allergies. Only children that improved according to a symptom score and were on a vitamin and/or mineral supplement were included. A 3-day food diary including vitamin and mineral supplementation was recorded and analysed using Dietplan computer program. We assessed dietary adequacy with/without the supplement using the Dietary Reference Values.

Results: One hundred-and-ten children had completed food diaries and of these 29% (32/110) were taking vitamin and/or mineral supplements. Children on hypoallergenic formulas were significantly ($p = 0.007$) less likely to be on supplements than those on alternative over-the-counter milks. Seventy-one percent had prescribable supplements, suggested by a dietitian/physician. Sixty percent of those without a vitamin supplement had a low vitamin D intake, but low zinc, calcium and selenium was also common. Of the supplemented cohort many continued to be either under or over-supplemented.

Conclusion: This study has raised the question for the first time, whether clinicians dealing with paediatric food allergies should consider routine vitamin and/or mineral supplements in the light of deficient intake being so common in addition to being so difficult to predict.

Keywords: Dietary adequacy, Elimination diet, Food diary, Non-IgE mediated allergy, Vitamin and mineral supplementation

Introduction

Fundamental to the management of food allergy in early childhood is the total elimination of offending allergens [1]. These often include cow's milk, soya, hen's egg, wheat, fish and nuts; foods which contribute significantly to dietary vitamin and mineral intake [2,3]. Low micronutrient intakes as a result of a dietary elimination have been reported in food allergic children; increasing both the risk of vitamin and mineral deficiency and associated functional morbidity [4-7]. Vitamin D, calcium and omega-3 fatty acids are well documented to be deficient micronutrients in children with IgE-mediated food allergies [8], whilst intakes of trace elements including zinc, selenium and magnesium have been found to be of concern in some non-IgE mediated conditions including allergic colitis and atopic dermatitis [7,9].

A nutritional assessment by a qualified dietitian of the allergic child is now recognised by several international guidelines as essential to ensure dietary adequacy and to support parents in finding suitable alternatives [10-12].

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The ideal dietetic assessment within the time constraints of a consultation should include a growth assessment, biochemical (when available) and dietary intake assessment to guide individualised dietary advice [13]. A dietary intake assessment can be very time consuming and is therefore often limited to a 24-hour recall. These dietary recall methods provide only a snap-shot of intake and are often biased [14,15], but are used in practice because they are quick and easy to do, and they provide the baseline for dietetic recommendations including supplementation of vitamin and/or minerals.

Although dietary intake as assessed by a 3-day food diary or nutritional status measured by blood markers, provide more accurate reflections of usual intake and nutritional status, these also have limitations [16,17]. Food diaries are time consuming and complex and therefore require highly motivated parents with a high level of literacy and understanding to cooperate [15,16]. The limitations for blood markers include nutrient plasma or serum concentrations not being a reliable reflection of intake and tissue stores, requiring a large blood sample from a small child and measurements can be affected by the measuring methods, contamination and health of the child at measurement [16,17]. In practice, blood investigations are mostly not available or results not accessible for the majority of cases at the time of the dietetic appointment. Therefore empirical vitamin and or mineral supplementation is currently based on the type of dietary elimination and intake as assessed during the consultation. We therefore set out to evaluate current practice of vitamin and mineral supplementation in a cohort of children with non-Immunoglobulin E (IgE) mediated food allergies, to assess the impact of micronutrient supplementation on vitamin and mineral intake and also whether those with low intakes based on food intake diaries received supplementation.

Methods

Subjects and study design

A prospective, observational study was performed in the gastroenterology department, at Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK. Ethical approval (number 11/LO/1177) was obtained for this study. Parents of children aged 4 weeks – 16 years, who had no concomitant non-atopic co-morbidities (i.e. Cerebral Palsy), and required to follow an elimination diet for the diagnosis of suspected food protein induced gastrointestinal allergies, were approached to take part in the study. These children were only included if symptoms improved following the elimination diet as judged by a Likert Scale gastro-intestinal symptom questionnaire, that has previously been developed by the same research team [18]. This questionnaire was administered at baseline prior to commencing the elimination diet and again at 4 weeks after commencing the dietary elimination. In addition to this criterion, the cohort we report on was also on a vitamin and/or mineral supplement.

Dietary intake

A 3-day estimated food diary (1 weekend day and 2 week days) was recorded, at a minimum of 4 weeks following the initiation of the exclusion diet. Carers were given detailed instructions on how to complete the diary as accurately as possible, including a portion size guide and a sample menu. Hypoallergenic formula (HF) consumption (including type and volume), milk alternatives (i.e. oat, rice or almond milk) for older children and vitamin and mineral supplements (suggested by dietitian/physician or self-initiated) were also documented. Both over-the-counter and prescribed supplements were further categorised as: calcium, calcium and vitamin D, multivitamin, multivitamin and mineral, iron, and a combination of the aforementioned. All infants that were exclusively breastfed or received ≥ 2 breast feeds per day in addition to their HF were excluded from the dietary analysis, due to difficulties in estimating breast milk consumption in the individual patient. We choose this method, due to studies by Lanigan et al. [19] indicating that a weighed record does not give a significant advantage to an estimated record and also following the study by Ocke et al. [20] indicating a 3-day food dairy being a feasible method in European children.

Food diaries were discussed with parents and any unclear entries were clarified by the research dietitian at the time of the study appointment or by telephone communication after the appointment. The UK Food Portion Sizes published by the Food Standard Agency was used to help guide parents and healthcare professionals in estimating the correct portion size whenever portions needed converting from household measures to grams [21].

Nutritional intake data was assessed using Dietplan 6 Software (Forestfield Software Limited, UK). Any foods, in particular specialist foods free from allergens, as well as HF and vitamin and mineral supplements not available on the software database were manually added by the researcher, and product information was obtained from the manufacturer where necessary.

We assessed the impact of the vitamin and mineral supplements on dietary intake by using the UK Dietary Reference Values in the following way: inadequate intake was defined as achieving less than the Lower Reference Nutrient Intake (LRNI – meeting nutrient requirements for 2.5% of population) and adequate intake as achieving the Reference Nutrient Intake (range between LRNI and excessive intake) [22,23]. There is currently no RNI for vitamin D, for children ≥ 4 years of age in the UK; as a result we used the recommendations from the UK Department of Health which recommended 7 – 8.5 mg for children until 5 years of age and for older children we used 10 ug/day as reference value.

As there is paucity of data regarding Safe Upper Limits for many of the micronutrients in children, we arbitrarily defined excessive intake as more than 200% of the RNI [23].

Biochemical markers of micronutrient intake

We also collected biochemical markers of micronutrient intake, where available, that were performed at Great Ormond Street Hospital for Children, taken within 3 months of the 3 day food diary. As this hospital is a tertiary referral centre, many children may have had biochemical markers of micronutrient intake in their local centres, which we did not have access to.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22 (Armonk, NY). Continuous and categorical data are described respectively as medians and interquartile range, and percentages and rates. In order to establish the impact of vitamin and mineral supplementation on micronutrient intake, food diaries of those children receiving a vitamin and mineral supplement were compared to the Dietary Reference Ranges with and without the supplements. The Pearson Chi-Square test was used to compare the differences in proportions of gender between groups receiving and not receiving VMS; children on vitamin and mineral supplements that were on a HF/over-counter-milk. The Fisher exact test was used to compare rates of dietary eliminations. Mann–Whitney *U* test was used to compare age between groups receiving and not receiving VMS; and to compare RNI intake of vitamin A and vitamin D between children taking different supplements. All tests were two-sided and significance level was set at 0.05.

Results

We recruited 131 children for this study, but 110 children had a complete food diary and of these 29% (32/110) were taking vitamin and/or mineral supplements. The supplemented group included 21 boys (65.6%) and the median age of this group was 5.1 years (IQR: 1.5 to 8.5). Although the proportion of boys was similar in supplemented and un-supplemented group (p 0.916) the age of the supplemented group was significantly higher ($p = 0.005$) than the median age of the group not receiving any supplementation (1.6, IQR: 0.7 to 4.6) [Table 1]. A total of 9/32 children on supplements (28%) were established on a HF, 17/32 (53%) on over-the-counter milk alternatives (i.e. coconut milk, oat milk or rice milk) and 6 (19%) had no cow's milk alternative. We found that children on over-the-counter milk alternatives/no milk replacement were significantly more likely to be on supplements compared to those on a HF in the whole cohort ($n = 110$): 40.4% (23/57) vs. 17.0% (9/53), $p = 0.007$.The majority of children on supplements (68%, $n = 22/32$) had prescribable supplements, consisting of mainly multivitamins, calcium and vitamin D and in two cases an iron supplement. The remaining 12 children (2 overlapped between categories) were taking over-the-counter preparations of multivitamins and also omega-3-fatty acids. Table 2 outlines the type of supplements used. In 23/32 (71%) the suggestion for a vitamin and/or mineral supplement was made by the dietitian/physician, in 6 cases both the dietitian and the parents were involved in choosing the supplement and in 3 children the parents started a supplement without dietetic input. From the cohort on supplements, 14 children were eliminating ≥ 3 foods (cow's milk, soya and gluten/egg/ other), 10 eliminated 2 foods (milk and soya) and 8 excluded 1 food only (i.e. cow's milk). Tables 1 and 2 describe this cohort in further detail, including the elimination diets and the availability of biochemical markers of micronutrient intake blood markers in this cohort.

When we assessed dietary adequacy of micronutrients without a supplement ($n = 110$), based on the definitions outlined in the methodology, we found that no child in the whole group had a deficient vitamin C intake and that low intakes of vitamin B12, B6, thiamine and folate

Table 1 Demographic details, including dietary elimination of the population with and without vitamin supplementation

Description	VMS	Without VMS	p value
Age	5,1 years	1.6 years	0.005**
Male	21/32 (66%)	52/78 (67%)	0.916
Dietary Elimination			
Cow's Milk	6 (19%)	5 (6%)	0.077
Cow's milk and soya	9 (28%)	11 (14%)	0.104
Cow's milk, soya and egg	3 (9%)	5 (6%)	0.689
Cow's milk, soya, egg and wheat/gluten	5 (16%)	9 (12%)	0.544
Other*	9 (28%)	48 (62%)	0.002**

*This group consists of children with other combinations of food eliminations, **$p < 0.01$.

Table 2 Dietary supplementation and biochemical markers of micronutrient intake of the group of children receiving supplements

Description	Patient numbers
Type of Supplement (some may have multiple supplements)	
Calcium	5
Calcium and vitamin D	4
Multivitamin (containing vitamin D)	15
Multivitamin and Mineral	8
Therapeutic iron	2
Other	5
Supplement initiated by:	
Dietitian/Physician	23
Dietitian and parent	6
Parent	3
Biochemical markers of micronutrient intake: (some children had multiple biochemical markers taken)	
Total available	7
Iron profile	7
Selected vitamins	2
Selected trace elements	3
Deficiencies:	
Iron	2
Zinc	1

were rare (Table 3). The dietary intake also revealed that in the whole group 60% (66/110) had a low vitamin D intake and that low zinc, copper and selenium were also seen in some patients (Table 3).

We then assessed dietary intake in those children with a supplement (n = 32) and whether those who had a low micronutrient intake also received appropriate vitamin and/or mineral supplementation. Our data suggests that although 25 children did receive a supplement with vitamin D, only 18/66 (27%) from the cohort with insufficient intake, were correctly identified as requiring this supplement and 10 of those receiving the supplement continued to not achieve their vitamin D requirements. We also found that 22 children had a low zinc intake however only 2/22 of this cohort was given a supplement containing zinc. Similarly, from the whole cohort 10 were identified as having a low calcium intake according to the food diary, but from this group only 3 children received a calcium supplement. However, 15 (18 in total) other children with an adequate calcium intake, were given a calcium supplement (Table 3), which is a similar trend for other vitamins and minerals.

Many children had an intake with supplementation exceeding 200% of the RNI for vitamin C, vitamin B6, thiamin, folate, selenium and vitamin A. In fact we found that of the 22 patients on a supplement containing vitamin A, 59% (n = 13) had intakes exceeding 200% of the RNI. We compared intake of Vitamin A for children who took a specific supplement known to be higher in vitamin A (Dalivit™, Boston Healthcare Limited) versus any other

Table 3 Overview of the vitamin and mineral supplementation: deficient intake in the whole cohort and those that received supplementation and the impact of the supplementation on dietary adequacy

Nutrient	Total number of children receiving supplements for each micronutrient	Deficient intake without VMS (whole cohort)	Deficient patients who were taking VMS[§]	>200% RNI with VMS	Adequate intake* with VMS	Intakes < LRNI with VMS
Vitamin C	23	0% (0/110)	N/A (0/0)	96% (22/23)	4% (1/23)	0% (0/23)
Vitamin A	22	10% (11/110)	9% (1/11)	59% (13/22)	41% (9/22)	0% (0/22)
Niacin	21	8% (9/110)	22% (2/9)	62% (13/21)	38% (8/21)	0% (0/21)
Vitamin B6	21	2% (2/110)	0% (0/2)	95% (20/21)	5% (1/21)	0% (0/21)
Thiamin	18	2% (2/110)	0% (0/2)	89% (16/18)	11% (2/18)	0% (0/18)
Calcium	18	9% (10/110)	30% (3/10)	44% (8/18)	50% (9/18)	6% (1/18)
Vitamin B12	17	1% (1/110)	100% (1/1)	94% (16/17)	6% (1/17)	0% (0/17)
Riboflavin	16	6% (7/110)	14% (1/7)	63% (10/16)	38% (6/16)	0% (0/16)
Vitamin D	25	60% (66/110)	27% (18/66)	16% (4/25)	44% (11/25)	40% (10/25)
Folate	12	3% (3/110)	0% (0/3)	67% (8/12)	33% (4/12)	0% (0/12)
Iron	10	7% (8/110)	0% (0/8)	40% (4/10)	60% (6/10)	0% (0/10)
Zinc	7	20% (22/110)	9% (2/22)	14% (1/7)	86% (6/7)	0% (0/7)
Copper	5	10% (11/110)	0% (0/11)	20% (1/5)	80% (4/5)	0% (0/5)
Selenium	3	11% (12/110)	0% (0/12)	67% (2/3)	33% (1/3)	0% (0/3)

*Children that had > LRNI and < 200% of RNI were classified as having adequate intake.

[§] This is the number of children from the whole cohort that had a deficient intake and were on a VMS.

form of Vitamin A supplementation. Children who received this supplement with vitamin A had significantly higher percentage RNI intakes of Vitamin A (505% RNI vs. 218% RNI, $p = 0.014$). Similarly, children who received Dalivit™ had higher RNI intake of vitamin D (205% RNI vs. 78% RNI, $p = 0.036$).

Four children received high doses of iron; however 2 of these had diagnosed iron deficiency anaemia, so were expected to receive therapeutic dosages.

Discussion

This study found that almost 30% of children from the whole cohort of children with non-IgE mediated food allergies received vitamin and/or mineral supplementation. The mean age of our supplemented cohort was over 5 years with more children receiving a vitamin and/or mineral supplementation when they were on alternative over-the-counter milks (i.e. coconut, oat or rice milk) which are nutritionally not complete [24]. The higher age of the supplemented group is to be expected as a significant number of children in our cohort were below 2 years and on a HF that contain significant amounts of vitamins and minerals [22].

The use of complementary and alternative medicine, including vitamin and mineral supplementation in atopic dermatitis is known to be commonplace in this population [25]. Studies by Johnston et al. [25,26] investigating the use of parent directed dietary elimination for atopic dermatitis, found that 40% of children were on vitamin and/or mineral supplements and that this is more common than in non-atopic children (24%). The key difference between our study and those published on atopic dermatitis were that all of our patients had an individualised dietetic review, whereas in the study by Johnston et al. [24], only 51% had consulted a dietitian. The primary role of the allergy dietitian is not only to discuss elimination of food allergens, but most importantly to suggest food alternatives that replace the nutrients eliminated which would include a HF and other nutritious foods [27].

Not surprisingly, 75% of children on supplements avoided ≥ 2 food allergens, with cow's milk and soya and a combination of cow's milk, soya, egg, wheat and others being the most common foods eliminated. It is known that children with multiple food allergies are at a higher risk of poor growth and a deficient vitamin and mineral intake [4,28]. What is of concern is that from our study many children who were identified by a 3-day food diary as having a low intake for certain micronutrients, did not receive a supplement, whereas others received excessive amounts of micronutrients. For example 11 patients from our whole cohort had a deficient vitamin A intake, but only 1 of these received a supplement containing vitamin A; conversely, 21 children with sufficient vitamin A intake, received a supplement containing vitamin A. This has resulted in 59% of our cohort receiving > 200% of the RNI for vitamin A. This occurrence can easily be explained by the UK government prescribable multivitamins which always contain vitamin A. As vitamin D is a commonly reported deficiency in the allergic cohort, all patients that require vitamin D, will therefore automatically receive vitamin A as well [5]. The question is whether the excessive vitamin A intake through supplementation is harmful for the allergic child. In 2003 "tolerable upper limits" for 1–3 year olds of various vitamins and minerals were published by the Scientific Committee on Food in Brussels. In this report the upper limit for vitamin A for this age was set at 800 ug RE/day, which would be 200% of the RNI for this age [29]. Similarly the Upper Safe Limits set by the Institute of Medicine is set at 600 ug/day for 1–3 year olds and 900 ug/day for 4–9 year olds [30]. However, no observed adverse effects have been reported for intakes up to 6000 ug/day and it is thought that only a chronic dose of 10–20 times the normal dose would lead to toxicity [30]. Levels therefore reported in our study would certainly not lead to toxicity. Excessive intakes of water soluble vitamins like vitamin C, B vitamins and folate are common and rarely are of significant concern, unless the child has reduced fluid intake, abnormal metabolism or metabolic defects [15].

From the whole cohort (supplemented and unsupplemented), 60% of children had a low vitamin D intake, which is not a surprising finding as 52% of those were not on a HF and it is thought that on average only 10% of the daily requirements for vitamin D are contributed by food in older children who are not on breast milk/formula [31,32]. What is of concern in this study is that only 27% of our population with a low dietary intake for vitamin D were identified as at risk and provided with a supplement that contained vitamin D. A recent study by Goldacre et al. [33] indicated that rickets in England is now at its highest in five decades and is not limited to specific ethnic groups, a concern that is reflected in many European countries. Current recommendations in the UK suggest the use of a multivitamin with vitamin D if volume of formula is below 500 ml or if a child is breastfed [34,35]. However, there are no recommendations for vitamin D specifically for children with food allergies, in spite of this being a commonly reported deficiency in this population [36,37].

In this study we also identified children with low intakes of copper, zinc and selenium, which are not commonly associated with IgE-mediated allergies. Deficiencies and low intakes of these minerals have been documented in children with atopic dermatitis and non-IgE mediated gastrointestinal allergies [7,9]. Only 19% of our cohort received supplements with zinc and selenium and none with copper. Meyer et al. [38] has highlighted low intakes of these trace minerals, in particular in children who are not on a hypoallergenic formula. These micronutrients have an important immunomodulatory role and need to be taken into account when assessing dietary intake also in allergic children [39].

Although a low dietary intake may assist in identifying children at risk of a deficiency, it is known that certain nutritional blood markers may be more sensitive and specific in identifying true deficiency. From our cohort only 7 children had biochemical markers of micronutrient intake available to guide dietitians in their supplement recommendation. The reality therefore is that the dietitian will have to rely on dietary intake and foods eliminated from the allergic child's diet to guide a vitamin and/or mineral supplementation regime. The validity of dietary intake assessment through food records, 24 hour recalls and food frequency questionnaires has been debated by many studies and have significant limitations on an individual level [16]. A systematic review in 2009 on dietary assessment methods for micronutrient intake in infants and children found that a weighed dietary record was more accurate than a food frequency questionnaire for vitamin and mineral intake [16]. In clinical practice however, these are rarely available to a dietitian at the time of the appointment, are time consuming to complete for parents, and for dietitians to analyse [17]. As clinical time constraints are increasing and the child's nutritional safety is paramount, this study has raised the question for the first time, whether dietitians and clinicians dealing with paediatric food allergies should consider routine vitamin and/or mineral supplements in the light of deficient intake being so common, especially for vitamin D, calcium, zinc and selenium and toxicities (if supplemented within the RNI/RDA) being theoretical rather than of clinical significance.

The limitations of this study are linked to the dietary assessment methods, the analysis program as well as the low number of children on supplements. A 3-day estimated food diary may not be the most accurate dietary assessment method to reflect usual intake. However, in the absence of a validated food frequency questionnaire for allergic children and also the ability to take repeated 24 hour recalls, which would have been affected by the atopic disease process itself, a 3-day food dairy was the best choice. In addition, a 3-day food diary suggest low intake, but certainly would not indicate a vitamin or mineral deficiency. Future studies should aim to assess the association between dietary intake methods and actual deficiencies in the food allergic population. In addition, it may be that parents did not document all the supplements their child was on, due to a concern that the dietitian would request them to discontinue or change the supplements. Due to no RNI being available for vitamin D > 4 years of age we also had to use a cut-off of 10 ug/day for children older than 5 years. This reference value may have elevated the number of children with deficient intake, as it is generally used as an aim value for adults. In addition whilst the dietary analysis program calculates vitamin D intake from the diet, it cannot account for the contribution of sunlight (Zipitis et al. [32]). In this study only 32 children out of 110 that had vitamin/and or mineral supplementation. Although this can be perceived as a low number, we do believe that in spite of this, the study is important in highlighting the difficulties dietitians have in predicting which child requires supplementation of vitamins, minerals or both, and opens the debate to routine supplementation of allergic children irrespective of their food allergy.

Conclusion

This study investigates the current practice in a tertiary gastroenterology centre of vitamin and/or mineral supplementation in children with non-IgE mediated allergies on an elimination diet. It is the first study that highlights the difficulties in making a decision in regard to appropriate dietary supplementation based on the information a dietitian has during their clinic appointment. We have highlighted that there is a significant discrepancy between children identified with a low intake through a 3-day food diary and those receiving a micronutrient supplement. In the light of vitamin and mineral deficiencies being common in the food allergic cohort, future studies should be performed to assess the impact of routine vitamin and mineral supplementation in children with food allergies using both nutritional blood markers and dietary intake methods.

Abbreviations

HF: Hypoallergenic formula; IgE: Immunoglobulin E; NHS: National Health Service; RDA: Recommended dietary allowance; RNI: Recommended nutrient intake.

Competing interests

Funding for this study was obtained through Great Ormond Street Charitable Fund. None of the authors have any competing interests related to this publication.

Authors' contributions

RM – Involved in data collection and some dietary analysis, conceptualising and writing of article; CDK – Performed majority of data collection and dietary analysis, conceptualising and writing of article; AKS – Involved in data collection and correction of the publication; RD – Statistical Analysis and article corrections; KR – Critical appraisal of publication; HG – Involved in data collection for the study and correction of publication; ACL – Critical appraisal of publication; NS – Team lead, conceptualising research project and review of article. All authors read and approved the final manuscript.

Acknowledgements

This study was funded by the Great Ormond Street Children Hospital Charity. We would also like to acknowledge all parents and children that participated in this study and took the time to fill in the 3-day food diary.

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Received: 24 November 2014 Accepted: 23 February 2015

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5. THE IMPACT OF NON-IGE GASTROINTESTINAL FOOD ALLERGIES ON THE QUALITY OF LIFE OF CHILDREN AND THEIR FAMILIES

The fifth chapter of this thesis focuses on two publications. The first one reports the parent's perception of the impact of non-IgE mediated gastrointestinal food allergies on the quality of life of their children (Foong et al., 2017). The second publication reports the impact on the quality of life of families with children diagnosed with non-IgE mediated food allergies (Meyer et al., 2017). Both publications are derived from the "Discovering the effect of non-IgE mediated allergies on children and their families" study.

It has been reported in the literature that the diagnosis of food allergies during infancy can cause a significant psychological and emotional burden on children and their families when compared with children without food allergies (Morou et al., 2014; Primeau et al., 2000). The impact on the quality of life of children suffering from IgE-mediated food allergies and their families is well studied and documented, including validated tools and specific food-allergic health-related quality of life (HRQoL) questionnaires (DunnGalvin et al., 2008; Muraro et al., 2014a). Conversely, there is a paucity of data and no validated tool to evaluate the impact on the quality of life of children with non-IgE mediated gastrointestinal food allergies and their families (Nowak-Wegrzyn et al., 2015).

In the first publication (Foong et al., 2017), I analysed the impact of non-IgE mediated gastrointestinal food allergy on the quality of life of affected children aged two to 16 years old. The team and I have used the Pediatric Quality of Life Inventory (PedQL^{TM}) (Varni et al., 2004), which is a validated questionnaire for parental proxy use for children aged above two years (Varni et al., 2015). The PedQL^{TM} scores out of a 100, and a lower score represents a worse quality of life. It evaluates five different domains: nursery (two to four years old) or school (≥ five years old) functioning, emotional functioning, physical functioning, social functioning and psychosocial functioning, The results from our cohort were compared to three published cohorts of children (norm data, functional abdominal pain and IgE-mediated peanut allergy) who had their quality of life evaluated by the same tool (Eiser and Varni, 2013; King et al., 2009; Youssef et al., 2006).

Parents of 52 children with non-IgE mediated gastrointestinal food allergies completed the PedQL^{TM}. The mean total score of the cohort was 75.43 (SD 13.82). Multiple linear regression was conducted, and the factors that were significantly associated with worse quality of life within our cohort were the number of foods excluded and the presence of nasal congestion. When the results were compared with the norm data cohort, I found that our cohort had a significantly worse quality of life in the physical (*t*(25)= -2.36, p= 0.03), psychological (*t*(25)= -2.20, p= 0.04), and emotional (*t*(25)= -2.62, p= 0.02) domains, and also overall (*t*(25)= -2.12, p= 0.04). When the results were compared with the functional abdominal pain cohort, I found that our cohort had a significantly better social functioning but a significantly worse emotional functioning. The third comparison of our results was with an IgE-mediated cohort. No significant differences were found in the overall quality of life and the majority of the domains, with the only significant difference being the non-IgE mediated cohort showing a worse physical function.

The second publication of this chapter reported the impact on the quality of life of parents of children diagnosed with non-IgE mediated gastrointestinal food allergies (Meyer et al., 2017), using the Family Impact Module of the Pediatric Quality of Life (PedQL FIM^{TM}) (Varni et al., 2004). The questionnaire has 36 questions divided into eight domains: physical functioning, emotional functioning, social functioning, cognitive functioning, communication, worry, daily activities, and family relationships. The parents reply to the question on a 5-score Likert scale (0= never a problem; 4= always a problem) and then each score is reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better functioning and less negative impact.

In this study, the results from our cohort were also compared with those of historical cohorts, children with sickle cell disease and families of children with intestinal failure (Panepinto et al., 2009; Sanchez et al., 2013). These cohorts were chosen as they represent families with children diagnosed with chronic illness, with the severity of symptoms varying from mild to severe. The team and I found that the total mean PedQL FIM^{TM} score in our cohort was 57.43 (SD 22.27). All domains were affected; however, the most affected ones were daily family activities, and parents were distraught. Multiple linear regression was used to determine which factors were more related to a worse quality of life for the families, and it was found that a higher number of foods eliminated, a higher symptom severity, younger age and presence of nasal congestion had a significant negative impact on the quality of life of the families.

When the results were compared with the sickle cell historical cohort (Panepinto et al., 2009), I found that our cohort had significantly worse scores in all domains. Moreover, when the results were compared to the intestinal failure cohort (Sanchez et al., 2013), our cohort had a lower mean score in all domains, with physical, emotional and worry domains being significantly lower.

Strengths and limitations

Both studies have a substantial clinical impact, as they were carried out to better understand the impact of non-IgE mediated gastrointestinal food allergies on the HRQoL of children and their families, which will lead to better care and support by the health care professionals for those children and families. The first study highlighted that the main domains that are affected in the children's lives are the physical, emotional and psychosocial. Those are mainly linked to the delay in diagnosis, emotional distress related to environments involving foods or associated symptoms. From the second publication, our data indicate that families in our cohort have a poor quality of life in all domains of the validated questionnaire. They are particularly affected in daily activities as well as physical and emotional functioning (Meyer et al., 2017). These often start with poor symptom recognition and delay in diagnosis. When diagnosed, symptom management can often impose further stress. Parents also report significant worry about their child. The fear of accidental exposure and therefore the burden of planning meals, sourcing free-from foods, ensuring that foods are not contaminated and often trusting others to keep to the dietary elimination, is significant (Rouf et al., 2012). The studies have shown that are important implications upon the physical, psychological and emotional domains for the child and the family, as the disease brings a routine change for the whole family, including careful preparation for daily activities. It also generates a high level of anxiety and frustration related to the fear of accidental exposure to the allergenic food and severity of the reaction; also difficulties accepting feeling different from one's peers. Both studies brought valuable clinical knowledge to clinicians, showing that it is essential to give advice and support to children and their families in early stages of the disease to reduce the impact and the burden in their lives.

Both studies have limitations. The main limitation of the first publication is that part of the "Discovering the effect of non-IgE mediated allergies on children and their families" cohort was excluded from this study as the parent proxy PedQL^{TM} is designed for children older than two years of age. The PedQL^{TM} has not been specifically validated for non-IgE mediated gastrointestinal food allergies. Nevertheless, it has been designed to be used in all types of paediatrics diseases. The main limitation of the second publication is similar to the reported above, and it includes the fact that the questionnaire is a generic tool but has never been validated specifically for non-IgE mediated food allergies. Also, the PedQL FIM^{TM} was validated for children older than two years of age, and we have used it in a younger cohort. The PedQL FIM^{TM} has nonetheless been used in many cohorts younger than two years old in the literature.

Publication

1. https://www.ncbi.nlm.nih.gov/pubmed/27992662

Foong, R. X., Meyer, R., Godwin, H., Dziubak, R., Lozinsky, A. C., et al. (2017) 'Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies'. Pediatric Allergy and Immunology, 28(3) pp. 251-256.

2. https://www.ncbi.nlm.nih.gov/pubmed/28261374

Meyer, R., Godwin, H., Dziubak, R., Panepinto, J. A., Foong, R. M., et al. (2017) ‘The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies’. World Allergy Organ J, 10(1):8 pp. 1-8 [Online] [Acessed on 4th of April 2019] DOI: 10.1186/s40413-016-0139-7

Pediatric Allergy and Immunology

ORIGINAL ARTICLE **FOOD**

Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies

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To cite this article: Foong RX, Meyer R, Godwin H, Dziubak R, Lozinsky AC, Reeve K, Knibb R, Shah N. Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies. *Pediatr Allergy Immunol* 2017: **28**: 251–256.

Keywords
non-IgE-mediated allergies; quality of life; gastrointestinal allergies; paediatrics

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Accepted for publication 14 December 2016

DOI:10.1111/pai.12689

Abstract

Background: Food allergy can have a significant impact on health-related quality of life (HRQoL). Parental proxy questionnaires are commonly used when children are too young to complete questionnaires themselves. Little data are available on HRQoL in children with non-IgE-mediated gastrointestinal food allergy (GIFA). The aim of this study was to evaluate HRQoL in these children by parent proxy.
Methods: A cross-sectional questionnaire study was conducted with children aged 2–16 years with confirmed GIFA. Parents of these children completed the Pediatric Quality of Life Inventory (PedsQL™) and the family impact module of the PedsQL. The PedsQL scores were compared to two published cohorts: functional abdominal pain (FAP) and IgE-mediated food allergy.
Results: Fifty-two parents of children with GIFA completed the PedsQL™ parent proxy. The GIFA cohort had significantly better overall HRQoL compared with the FAP cohort, but lower emotional functioning scores. The GIFA cohort also had poorer physical QoL compared with the IgE cohort (all $p < 0.05$). The more foods excluded, comorbidity of nasal congestion, abdominal pain, back arching, the persistence of flatus and gastrointestinal symptom severity after elimination diet were related to poorer QoL in this non-IgE cohort. Regression analyses showed that number of foods and nasal congestion significantly predicted total QoL score as perceived by parents.
Conclusions: This study has shown that different areas of HRQoL of children with GIFA are affected compared with children with FAP or IgE-mediated food allergy, highlighting the need for a specific GIFA HRQoL questionnaire to better understand the impact on these children.

Background

The impact of immunoglobulin E (IgE)-mediated food allergy on children and their families, particularly for health-related quality of life (HRQoL), has been well documented (1–3). Studies have shown that food allergies can cause significant psychological and emotional burden on children and their families compared with children without food allergy (1, 4). Valentine and Knibb, for example, showed that children with food allergies had difficulties with school lunches and experienced restrictions on favourite foods and carrying medication had a negative influence on HRQoL (5). Parents reported lower HRQoL with regard to shopping and concern over the health of their child compared with parents of children without food allergy (5).

Specific food-allergic HRQoL questionnaires have now been validated for IgE-mediated food allergy. These comprise questions such as food anxiety, social and dietary eliminations and the emotional impact on parents and their children (6–8). There is, however, a paucity of data assessing the impact on children's HRQoL in non-IgE-mediated gastrointestinal food allergies (GIFAs) (9, 10). The European Academy of Allergy and Clinical Immunology have acknowledged that a validated tool to measure HRQoL in this group of children is required and the tools available for children with IgE-mediated food allergy are not suitable for those with GIFA (7).

Studies using more generic HRQoL measures have been used. For example, Klinnert et al. (11) looked at family HRQoL in children diagnosed with eosinophilic oesophagitis, a GIFA condition, using a generic pediatric QoL questionnaire (PedsQL) and found that these children and their families reported a diminished HRQoL compared with healthy individuals, with lower scores in the children with increased severity of symptoms and number of foods eliminated (11). Meyer et al. (12) looked at the impact of GIFA on the family (using the family impact module [FIM] PedsQL™ questionnaire) and showed that this was worse compared with families of children with chronic diseases such as sickle cell disease and intestinal failure.

Children with GIFA are usually young and present with symptoms in infancy. Parental proxy questionnaires are commonly used when children are too young to complete questionnaires themselves. The aim of this study was to better understand the HRQoL of children with GIFA through assessment by parental proxy and comparison with published data on HRQoL of children with IgE-mediated food allergy and children with functional abdominal pain (FAP) (13, 14).

Method

Design

A cross-sectional questionnaire study was carried out at Great Ormond Street Hospital, London, United Kingdom, from December 2011 to November 2013. Ethical approval was granted for the study (NR11/LO/1177), and all parents gave written informed consent.

Participants and procedure

Parents of children aged 2–16 years were approached to take part in the study where an elimination diet had improved child's symptoms of GIFA. This included children with eosinophilic gastrointestinal disorders, allergic dysmotility disorders and food protein-induced enterocolitis. Symptom improvement was established using a previously published questionnaire that ranked gastrointestinal symptoms according to a Likert scale (Appendix S1). This questionnaire was initially completed in clinic at the start of the elimination diet (baseline) and then sent by post at 4 and 8 weeks during their elimination diet and completed via phone interview (15). Data on the assessment of symptom improvement have been published in further detail by Lozinsky et al. (16). Once symptom improvement was seen on the elimination diet, parents were sent the Pediatric Quality of Life Inventory (PedsQL™) proxy questionnaire and the FIM of the PedsQL™ (17) by post. A research appointment was scheduled for researchers to answer any questions about the questionnaire content. Subsequent home food introductions have occurred in all children but this work is yet to be published. Children with non-allergic comorbidities and those who did not have any symptom improvement during the elimination diet period were excluded.

Materials

The PedsQL™ has been validated for parental proxy use in children aged above 2 years (15). It is scored out of 100 and a higher score represents a better QoL. The FIM PedsQL™ Questionnaire (17) assesses the impact on the HRQoL of the family as a whole (see Appendix S2 for full details of the scales used).

Comparison groups

Our data were compared to three published control groups who had also used the Parental Proxy PedsQL™ tool to assess HRQoL. The first comparison was made with our cohort to published norm data for this scale (18). The other two groups were children with FAP (mean age = 11.2 years) (13) and those with IgE-mediated peanut allergy (mean age of children = 9.8 years; fathers' mean age = 45.33, s.d. = 4.42; mothers' mean age = 42.59, s.d. = 4.46) (14). FAP was chosen as it is a gastrointestinal disorder which can present with similar symptoms to GIFA (i.e., abdominal pain) and both can take time to diagnose which is likely to have a significant impact on HRQoL. The IgE group was selected because of the similarities to GIFA, such as food avoidance, difficulties experienced in social situations involving food and anxiety around food exclusions, in spite of the more acute onset of peanut allergy. Comparisons with this group were conducted with non-IgE children aged 5–12 years only to ensure age groups of the two cohorts were comparable.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 22 (Armonk, NY, USA). Data were checked for skew and kurtosis and were within acceptable levels for normal distribution. One-sample *t*-tests were run to look at differences between PedsQL™ scores for the GIFA group and norm data. Between-subject *t*-tests were used to compare PedsQL scores between children with GIFA and the cohorts of children with IgE-mediated food allergy and FAP. The study had 94% power to detect medium effect sizes for one-sample *t*-tests, 50% power for comparisons with the IgE-mediated group and 75% for comparisons with the FAP group. Pearson's correlations were conducted to measure the relationship between Parent Proxy PedsQL™ scores and FIM PedsQL™ scores. A multiple linear regression model was run to assess the relationship between PedsQL™ scores for parents of children with GIFA (outcome variable) and variables that were significantly associated with this measure. All tests were two-sided, and significance level was set to 0.05.

Results

A total of 66 children aged 2–16 years were identified with GIFA, of which 52 parents consented to participate and completed the PedsQL™ proxy questionnaire and the FIM. The questionnaires were mainly completed by mothers ($n = 43$, 82.7%), three (5.8%) by fathers and six (11.5%) did not specify which parent completed the questionnaire. Demographic data and GIFA characteristics of the children are described in Appendix S3. Over 50% of the patients had up to three foods eliminated, and the most common combination of foods eliminated was cow's milk, egg, soya and wheat (26.9%) or cow's milk and soya (26.9%). Of the cohort, 61.5% had at least one comorbidity, with nasal congestion (67.3%) being the most prevalent.

Comparisons between GIFA group PedsQL scores, FIM scores and norm data for the PedsQL

The mean total parental proxy PedsQL™ score for the GIFA cohort was 75.43 (s.d. = 13.82) with the lowest mean score seen in the domain of emotional functioning (mean = 67.72, s.d. = 19.58; Table 1). In comparison with norm data for the PedsQL™, the GIFA cohort had significantly worse physical ($t(25) = -2.36$, p = 0.03), emotional ($t(25) = -2.62$, p = 0.02), psychosocial ($t(25) = -2.20$, p = 0.04) and total QoL ($t(25) = -2.12$, p = 0.04; Table 1). Poorer parent-rated HRQoL for the child was significantly related to poorer family related QoL (r = 0.58, $p < 0.001$).

Table 1 Proxy PedsQL™ scores of children with gastrointestinal food allergy in different domains and norm data

	Non-IgE cohort			Norm data
	N	Mean	s.d.	Mean
Nursery functioning (2–4 years)	16	72.40	19.65	N/A
School functioning (≥5 years)	33	73.18	18.06	78.19
Emotional functioning	51	67.72	19.58	81.04*
Physical functioning	51	77.56	16.12	84.37*
Social functioning	52	83.85	15.07	86.82
Psychosocial functioning	52	74.94	14.43	82.11*
Total Score	52	75.43	13.82	82.79*

*$p < 0.05$.

Comparisons between GIFA, IgE and FAP cohorts

Overall HRQoL and social functioning QoL were significantly better in the GIFA cohort compared with the FAP cohort; however, the GIFA cohort had significantly worse HRQoL scores for emotional functioning (Table 2). In comparison with the IgE cohort, there were no significant differences in overall HRQoL, but the GIFA group had significantly poorer QoL for physical functioning (Table 3).

Relationships between GIFA characteristics and quality of life

Univariate analysis showed that the parental proxy total PedsQL™ scores for children with GIFA were significantly related to the number of foods excluded (r = −0.38, p = 0.006) and scores for gastrointestinal symptoms (r = −0.32, p = 0.021), abdominal pain (r = −0.28, p = 0.043), back arching (r = −0.40, p = 0.003) and flatus (r = −0.28, p = 0.047) after commencement of the elimination diet. Children with nasal congestion had significantly poorer total QoL (n = 35, mean=72.84, s.d. = 14.96) compared with children with no

Table 2 Comparison of quality of life between the gastrointestinal food allergy cohort and the FAP cohort

	Non-IgE-mediated cohort			Functional abdominal pain cohort				
	N	Mean	s.d.	N	Mean	s.d.	Mean difference	p-value
N	Mean	s.d.	N	Mean	s.d.			
School (≥5 years)	33	73.18	18.06	65	72.2	15.80	−1.0	0.78
Emotional	51	67.72	19.58	65	75.20	18.10	7.5	**0.04**
Physical	51	77.56	16.12	65	76.94	11.80	−0.7	0.80
Social	52	83.85	15.07	65	67.10	12.30	−16.8	**<0.001**
Psychosocial	52	74.94	14.43	65	§	§	§	§
Total average	52	75.43	13.82	65	70.10	7.90	−5.3	**0.01**

§–Assessment not performed in functional abdominal pain (FAP) by Youseef et al. (13) Significant p-values ($p<0.05$) are highlighted in bold

Table 3 Comparison of quality of life between the gastrointestinal food allergy cohort aged 5–12 years and the IgE cohort

	Non-IgE-mediated cohort			IgE-mediated cohort				
	N	Mean	s.d.	n	Mean	s.d.	Mean difference	p-value
Physical	26	77.37	15.08	44	89.92	11.41	12.55	**<0.001**
Emotional	26	70.96	19.65	44	70.45	19.37	−0.51	0.92
Social	27	82.96	15.83	44	81.93	15.67	−1.03	0.79
School (≥5 years)	27	72.78	18.83	44	77.50	19.30	4.72	0.32
Psychosocial	27	75.49	15.65	44	76.93	16.20	1.44	0.72
Total average	27	76.01	14.40	44	81.27	13.58	5.26	0.13

Significant p-values ($p<0.05$) are highlighted in bold nasal congestion (n = 17, mean=80.75, s.d. = 9.40), (t (46.47) = 2.32, p = 0.025).

When examining relationships between GIFA characteristics and subscales of the PedsQL, there were significant correlations between the number of foods excluded and social (r = −0.39, p = 0.005), nursery-related (n = 16, r = −0.74, p = 0.001) and psychosocial (r = −0.33, p = 0.018) QoL. Severity scores for gastrointestinal symptoms after commencement of the elimination diet were significantly related to physical (r = −0.44, p = 0.001) and psychosocial (r = −0.28, p = 0.046) QoL. Children with nasal congestion had significantly poorer psychosocial QoL (n = 35, mean = 72.07, s.d. = 15.30) compared with children without (n = 17, mean = 80.75, s.d. = 10.55; t(43.85) = 2.41, p = 0.020). Nursery-related QoL was also negatively correlated with the child's age (n = 16, r = −0.60, p = 0.013).

Multiple linear regression analysis was conducted with variables that were significantly associated with QoL. The model was significant (F(6, 45) = 3.37, p = 0.008) and explained 31% of the variance ($R^2 = 0.31$; Adj $R^2 = 0.22$) in total PedsQL™ HRQoL scores. Factors that had a significant negative impact on the PedsQL™ total scores were the number of foods excluded and nasal congestion (Table 4).

Discussion

This study set out to understand the impact of GIFA on the HRQoL of children as reported by the parents. When compared to the norm data, our cohort had significantly worse total HRQoL scores especially in the physical, emotional and psychosocial functioning domains.

When the GIFA children were compared to the IgE-mediated cohort, there were no significant differences in overall HRQoL; however, our cohort had poorer physical QoL. This may be due to the gastrointestinal symptoms that accompany GIFA including extra-manifestations such as pain, hypermobility and fatigue (19), which can significantly impair QoL that are not common in nut allergies. In our univariate analysis, persistent flatus following an elimination diet was significantly related to QoL in our cohort, although this association disappeared in the regression analysis possibly due to this variable being unable to explain any more variance in QoL over and above that of the number of foods and nasal congestion. Lozinsky et al. (16) found that 26% of participants had flatus as a symptom on dietary elimination. It therefore seems a persistent symptom that could affect QoL through discomfort, pain and poor sleep (16). There is paucity of data on the impact of flatus on HRQoL in GIFA although in our experience parents reported night waking was common with painful passage of flatus. In an adult study where 71% had flatulence, the presence of gastrointestinal symptoms was reported to have a negative impact on HRQoL (20). In a study by Abaci et al., mothers of infants with infantile colic defined as unexplained, inconsolable crying often accompanied with flushing of the face, drawing-up of the legs and passing of gas reported poorer HRQoL especially in the domains of physical and social functioning (21). Our results also showed a significant negative impact on physical functioning in association with the severity of gastrointestinal symptoms (i.e., abdominal pain, back arching, flatus) post-elimination diet.

Emotional functioning was reported as the domain of HRQoL that parents felt their children with GIFA were most affected by and scores were significantly poorer than norm population data and children with FAP. Although not previously described for GIFA, feelings of anxiety and worry in children with food allergy have been well documented, with several studies on children with IgE-mediated peanut allergy reporting lower emotional health scores compared with children without food allergy (1, 14, 22). Poorer emotional HRQoL may be related to the children with GIFA experiencing emotional distress related to environments involving food or associating symptoms (i.e., abdominal pain, vomiting) with eating specific foods. Delays in diagnosis due to the absence of diagnostic tests for GIFA, which can lead to prolonged symptoms, may also have an impact on the emotional psychological health of children.

Emotional functioning can also be affected by quality of sleep or sleep deprivation (23). Previous studies with children affected by other atopic conditions (e.g., asthma, eczema) have shown that there is an increase in nocturnal awakening and disturbed sleep (24, 25). Poor sleep has been reported in approximately one-third of patients with GIFA (19), which can impact their emotional health. Over half of our cohort had nasal congestion, which can be a manifestation of allergic

Table 4 Regression analysis to examine associations between non-IgE characteristics and total PedsQL scores

	Unstandardized coefficients		Standardized coefficients	95% Confidence intervals	
Predictors	B	s.e.	Beta	Lower	Upper
Number of foods excluded	−2.34	0.90	−0.33**	−4.15	−0.52
Gastrointestinal symptom	0.21	0.55	0.09	−0.89	1.32
Abdominal pain	−3.42	4.41	−0.12	−12.31	5.47
Back arch	−6.78	5.82	−0.18	−18.50	4.93
Flatus	−6.00	5.12	−0.22	−16.30	4.32
Nasal congestion	−8.03	3.70	−0.28*	−15.49	−0.57

*p < 0.05; **p < 0.01.

rhinitis (26). This comorbidity may have an effect on sleep, which could explain the lower scores we found in these children; however, this link requires further research.

Eliminating multiple foods was found to have a negative correlation with HRQoL in our cohort, which has also been reported in children with IgE-mediated food allergy (2). It has been shown that anxiety increases in children if food elimination includes two or more foods (27) and this could have contributed to the poorer emotional HRQoL seen in our cohort.

We found that poorer HRQoL in the child was related to a bigger impact on the whole family. This is a similar finding to that of Greenhawt et al. (28) where the HRQoL of carers of children with food protein-induced enterocolitis syndrome (FPIES), a type of GIFA, was compared to carers of children with IgE-mediated food allergies. Although they used a different questionnaire (Food Allergy Quality of Life – Parental Burden [FAQL-PB] Index), they found that carers of children with FPIES reported significantly worse QoL compared with those of children with IgE-mediated food allergy but also that the FAQL-PB scores correlated strongly with PedsQL-FIM scores.

Limitations

This study had several limitations. Firstly, GIFA was diagnosed following symptom improvement after an elimination diet but was not confirmed with a follow-up re-introduction challenge. Therefore, it is not a challenge-proven diagnosis. Secondly, the parent proxy PedsQL™ is designed to be used in children aged at least 2 years. In our cohort, there were a number of children who were <2 years old and as there was no tool available to assess their QoL, they were excluded. There was also no prospective control group available for us to compare our data to. Although the PedsQL™ is designed to be used for all types of diseases, it has not been specifically validated for parent proxy use for children with GIFA. GIFA can often start in infancy; thus, developing a tool that allows for more specific GIFA disease-specific questions is important, but validating it for use by parents for younger children, unable to complete questionnaires themselves, is also necessary.

Another limitation is that we used two historical comparison groups in our study where the children had different diseases and were recruited and interviewed by researchers differently. Although we tried to find cohorts that had some effects of QoL that would be similar to children with GIFA, all chronic diseases have unique clinical features that can directly impact HRQoL and trying to make comparisons between diseases that are potentially different can be challenging. We also had very few fathers take part in our study and future work should consider encouraging more fathers to give their views about the impact on QoL.

Due to the small sample sizes, our study was underpowered to detect small effects and there may be more differences between these groups than we have been able to find. In contrast to this, there is also the risk that we have made a type I error and reported false-positive differences due to the number of tests we ran. As this is the first study to report on the impact of GIFA on QoL in comparison with other similar chronic conditions, we felt it important to report all differences found so that future research can build upon these findings in robust and properly powered studies.

Conclusions

This study has found that parent-reported HRQoL of their children with GIFA was worse compared with a normal population. However, when compared to children with IgE-mediated allergy or FAP, only the domains of physical and emotional functioning, respectively, were significantly worse. The number of foods excluded, severity of gastrointestinal symptom scores and the presence of nasal congestion had a significant negative impact on total HRQoL score. Proxy parental HRQoL scores are useful; however, the development of a questionnaire that allows for specific assessment of children with GIFA of all ages is needed to better understand the impact of this disease on children's lives.

Declaration of funding

This study was funded by a charitable grant from Great Ormond Street Hospital Charities.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Gastrointestinal Symptom Questionnaire using Likert Scale from the study "Discovering the impact of non IgE-mediated gastrointestinal food allergies in children and their families".

Appendix S2. Further description of the two questionnaires used.

Appendix S3. Table of descriptive statistics of the GIFA cohort.

Meyer *et al. World Allergy Organization Journal* (2017) 10:8
DOI 10.1186/s40413-016-0139-7

World Allergy
Organization Journal

ORIGINAL RESEARCH **Open Access**

The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies

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Abstract

Background: The impact on health related quality of life (HRQL) has been well studied in children with Immunoglobulin E (IgE)-mediated food allergy. However limited data exists on related quality of life (QOL) of families who have a child suffering from food protein induced non-IgE mediated gastrointestinal allergies. We aimed to establish the QOL of families with children at the beginning of following an elimination diet for non-IgE mediated gastrointestinal food allergies.

Methods: A prospective, observational study was performed. Parents of children aged 4 weeks–16 years who improved after 4–8 weeks of following an elimination diet for suspected non-IgE mediated allergies were included. The Family Impact Module (FIM) of the Pediatric Quality of Life (PedsQL™) was used and we compared our data to two historical cohorts: one with sickle cell disease and another with intestinal failure.

Results: One hundred and twenty three children with a median age of 20 months were included (84 boys). The total FIM Score was 57.43 (SD 22.27) and particularly low for daily activities and worry. Factors that impacted significantly included age ($p < 0.0001$), number of foods excluded ($p = 0.008$), symptom severity ($p = 0.041$) and chronic nasal congestion ($p = 0.012$). Children with non-IgE mediated food allergies had worse scores in all domains ($p < 0.0001$) compared to sickle cell disease and worse physical ($p = 0.04$), emotional ($p = 0.04$) and worry ($p = 0.01$) domains compared to intestinal failure.

Conclusions: This study found that parent QOL and family functioning was worse in those families who had a child on an elimination diet for non-IgE mediated allergies compared to those with sickle cell disease and intestinal failure, highlighting the impact this disease has on families.

Keywords: Non-IgE mediated allergies, Gastrointestinal allergies, Quality of life, Family impact score

Background

The prevalence of food allergy in children ranges between 3 and 7%, with the majority of allergies caused by cow's milk, hen's egg, soya bean, wheat, peanut, tree nuts, fish and shellfish [1–3]. Current nomenclature classifies food allergies as either Immunoglobulin E (IgE) mediated, non-IgE or a mix of IgE and non-IgE mediated [4]. Food allergies affecting the gastrointestinal tract are mainly non-IgE mediated, but can also present with mixed symptoms. The most common reported symptoms include: diarrhoea, constipation, vomiting, severe abdominal pain, feeding difficulties and growth faltering [5]. In addition to the gastrointestinal symptoms, extra-intestinal manifestations including joint pain, lethargy and also severe sleep disturbances due to abdominal discomfort, are common [6]. The combination of aforementioned symptoms in addition to the burden and cost of the elimination diet may impact significantly on family life [7].

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The impact on health related quality of life (HRQL) in children suffering from IgE-mediated food allergies and its effect on their families has been well studied [8–10].

Primeau et al. [11] indicated significantly more disruption in the familial/social dimension in families with a peanut allergic child, compared to parents of children with rheumatological disease. Similarly Sicherer et al. [12] also found an increase in emotional impact on parents and limitation on family activities in their cohort of IgE-mediated food allergic children. Particular mothers seem to be affected with higher levels of stress and anxiety [13]. In 2014 the European Academy for Allergy and Clinical Immunology (EAACI) published a position statement guiding the use of HRQL questionnaires in food allergic patients and their families [8]. The Food Allergy Quality of Life – Parent Burden questionnaire has been validated for IgE mediated, but not for non-IgE mediated allergies affecting the gastrointestinal tract [14]. The EAACI position statement highlighted the fact that there were only validated disease specific HRQL and family burden assessment tools for IgE-mediated food allergies and that there was a need for further studies to establish the burden of non-IgE mediated allergies and to develop new questionnaires. To date, the only data published on the family burden in non-IgE mediated allergies is the study by Klinnert et al. [7] on families with children with Eosinophilic Oesophagitis (EoE), a mixed non-IgE and IgE-mediated condition and Greenhawt et al. on Food Protein Induced Enterocolitis Syndrome (FPIES) [15]. Both studies indicated a significant impact on daily functioning of families in a variety of domains [7, 15]. Studies have also shown that having a child with chronic gastrointestinal pain or inflammatory bowel disease impacts significantly on family life [16, 17]. Limited data exists on the family impact of the whole spectrum of protein induced gastrointestinal non-IgE mediated allergies, which comprises a variety of diagnoses including proctocolitis, food protein enterocolitis syndrome, food protein induced dysmotlity, enteropathy and eosinophilic gastrointestinal disease. In our experience, it is in particular the initial period following diagnosis, where the burden is greatest on families. We therefore set out to establish the QOL of families with children at the beginning of following an elimination diet for non-IgE mediated gastrointestinal food allergies. We hypothesized that the families QoL would be much worse than families who have children with other chronic disease.

Methods

Subjects and procedure

A prospective, observational study was performed at the tertiary gastroenterology department, from Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom (UK). Ethical approval was obtained for this study (Nr 11/LO/1177) from the NRES London-Bloomsbury Committee and only children with parental consent took part in this research project. Parents of children aged 4 weeks – 16 years without non-allergic co-morbidities (i.e., cerebral palsy, cardiac disorders) who were required to follow an elimination diet for the diagnosis of suspected non-IgE mediated food protein induced gastrointestinal allergies were approached for the study. The foods chosen for elimination was individualised, based on an allergy focused history performed by the gastroenterologist and also considered the success/failure of any previously eliminated foods. The elimination diet was managed by a specialist paediatric allergy dietitian, using the standard British Dietetic Association Diet sheets for specific food allergens. As we wanted to capture quality of life early at diagnosis, the inclusion in the study occurred if, after 4–8 weeks of following the elimination diet, there was an improvement in their gastrointestinal symptoms. This was measured by a repeated Likert scale gastrointestinal symptom questionnaire that has previously been published [18]. Children for this study were classified as non-IgE mediated allergy based on the success of the elimination diet and not on endoscopic evidence, as the majority did not undergo an endoscopic procedure, which is not routine practice in the UK. We also did not classify children into categories of food protein induced enteropathy, food protein induced enterocolitis syndrome, food allergic dysmotlity or proctocolitis as in the first 4–8 weeks diagnosis is still established and the groups would be too small for statistical sub-analysis. We also collected data on atopic co-morbidities, including asthma, hayfever, atopic dermatitis and have included nasal congestion under this category, as our previously published work showed this a common complaint from parents [5].

We used the Family Impact Module of the Pediatric Quality of Life (PedsQl™) published by Varni et al. [19], that has been designed for use both as an adjunct to the existing PedsQL™ measurement scores or as a standalone assessment tool from 2 to 18 years of age. Permissions had been granted for the study to use this questionnaire from the Mapi research trust (http://www.mapi-trust.org/). The PedsQL Family Impact Module™ (FIM) [Version 2] questionnaire has been validated to measure impact for families with children ≥ 2 year of age. Although children in our allergic cohort were expected to be younger than 2 years of age, many previous studies have used the FIM in younger cohorts, including the publication by Sanchez et al. [20] that we used as historical control for this study [20–23]. In addition, using this module enabled us to compare our data to other cohorts. The FIM consists of 36 questions grouped into sections of Physical Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Communication, Worry, Daily Activities and Family Relationships. Parents answered the questions on a 5 score Likert scale (0–4) where 0 means: "it is never a problem" and 4 means "it is almost always a problem". Each score was then transformed into 0–100 scale in a following way: 4 = 0, 3 = 25, 2 = 50, 1 = 75, 0 = 100. If a parent scored more than half of questions in a section then an average score was calculated accounting for missing data. Average score of all questions represents Total Score. Parent QOL Summary Score is an average of scores from Physical, Emotional, Social, and Cognitive Functioning sections. Family Summary Score is an average of scores from Daily Activities and Family Relationships.

There are no cut-off values set for what is interpreted as "poor" QOL for families as reply to questions are subjective and depend on parental perception of their QOL. However, for the purpose of the study, all patients that had a PedsQL FIM™ score < 30 were contacted by the researchers and offered additional support.

Parents were sent the PedsQL FIM™ questionnaire and the research nurse assessed that all questions were completed at the time of the research appointment, which occurred 4–12 weeks after commencing the elimination diet. We compared our data to two historical control groups that fit the criteria of a chronic health related problem [22]. We obtained permission from Panepinto et al. [24] to use group mean scores from their PedsQL FIM™ from children with sickle cell disease (45.5% mild and 54.5% severe disease). Similarly, using the same questionnaire, we compared our results to those with intestinal failure (average bowel length 30 cm ±24) published by Sanchez et al. [20]. These two groups were chosen primarily because of available data using the same PedsQL FIM™ and because sickle cell disease represented a chronic disorder with milder symptoms whereas the children with intestinal failure were parenteral/enteral nutrition dependent with chronic symptoms and therefore embodied the severest end of spectrum of gastrointestinal disease.

Statistical analysis

Descriptive statistics and logistic regression were done in IBM SPSS Statistics for Windows, Version 22 (Armonk, NY) and *t*-tests were done in R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Two sided *t*-test was used to compare PedsQL FIM™ mean scores between food allergic group and sickle cell disease group. The same statistical technique was used to compare the intestinal failure to the allergic group, but we matched the ages and used only data of children < 7 years as Sanches et al. [20] only included children below this age (in three categories 1–12 months, 13–24 months and 2–6 year). A multiple linear regression model was used to assess the relationships between PedsQL FIM Total Score and number of foods excluded, the gastrointestinal symptoms score (taken from Likert scale questionnaires after 4–8 weeks from beginning of the elimination diet) and atopic features accounted for age (in years) and gender. Only variables which were significant were included in the model. Significance level was set to 0.05.

Results

We identified 252 children with suspected non-IgE mediated gastrointestinal food allergies between December 2011 and November 2013 that were eligible for inclusion in the study. Ninety-one patients were excluded because they did not want to partake in the study, were unable to attend/not reachable or had non-atopic co-morbidities. Therefore 161 children were enrolled in the study, of which 30 patients did not improve on the elimination diet and consequently were excluded. Eight parents did not complete the PedsQL FIM™, therefore we analyzed questionnaires of 122 children. This cohort included 84 boys (68.3%) and the median age of the whole cohort was 20 months [IQR: 9 to 67.5]. Table 1 summarises the patient demographics, including the number and type of elimination diets implemented. The majority of children were on multiple exclusions, with milk, egg, wheat and soya being the most common combination. Gastrointestinal symptoms and the improvement of symptoms following the elimination diet have been reported in a previous publication [18]. In addition, 86% had at least one atopic co-morbidity, with persistent nasal congestion being the most commonly reported.

In 111 (90.2%) of subjects, the mother filled in the questionnaire and 3 (2.4%) were completed by fathers. In 9 (7.3%) cases, parents did not indicate who was filling in the questionnaire. Due to the small number of fathers completing the questionnaire, we were not able to perform any statistical analysis on the differences in perceived QOL of the family between parents. The total average PedsQL FIM™ Score was 57.43 (SD 22.27) and while all domains indicated a poor QOL the impact of non-IgE mediated food allergies seemed to particularly affect daily family activities most and parents were very worried (Table 2).

Multiple linear regression analysis was performed to ascertain the impact on families QOL (Total Average) of the following factors: gender, age, number of foods excluded, atopic co-morbidities (asthma, eczema and nasal congestion), persistent nasal congestion and gastrointestinal symptoms (individual and total score of symptoms) present after dietary elimination. The

Table 1 Patient demographics

Variable	Data
Number of patients	123
Gender	84 boys (68.3%)
	38 girls (31.7%)
Age	20 month [IQR: 9 to 67.5]
Number of foods eliminated	
1	29 (23.6%)
2	33 (26.8%)
3	16 (13%)
4	23 (18.7%)
≥5	22 (17.9%)
Type of elimination[a]	
HF Only	14 (11.4%)
MES or MES+	11 (9%)
MEWS or MEWS+	33 (26.8%)
MS or MS+	30 (24.4%)
Other	15 (12.2%)
Single	20 (16.3%)
Atopic co-morbidities	
Eczema	60/122 (49%)
Asthma	36/122 (30%)
Allergic Rhinitis	25/122 (20%)
Nasal congestion	85/122 (70%)
At least one atopic feature	105/122 (86%)

[a] HF – hypoallergenic formula, MES – milk, egg soya, MEWS – milk, egg, soya, wheat, MS – milk, soya

factors that impacted significantly ($p < 0.05$) on the families QoL included age ($p < 0.0001$), number of foods excluded ($p = 0.008$), total symptom score ($p = 0.041$) and nasal congestion ($p = 0.012$); implying that the higher number of foods excluded, the higher symptom severity, the younger age and the presence of nasal congestion negatively impacted QoL of families.

Table 2 FIM in children with non-IgE mediated food allergy on QoL in different domains

	Number	Mean	Std. Deviation
Total Score	123	57.43	22.27
Parent QoL	123	58.95	23.25
Family Functioning	122	57.96	25.26
Physical Functioning	122	55.43	26.89
Emotional Functioning	123	55.72	24.13
Social Functioning	123	62.21	27.72
Cognitive Functioning	121	63.33	24.57
Communication	123	58.54	29.15
Worry	123	50.17	24.33
Daily Activities	122	48.84	31.84
Family Relationships	121	63.43	26.01

When comparing the family impact on QOL between our cohort and the patient group with sickle cell disease, we found that children with non-IgE mediated food allergies had worse scores in all domains. The difference was greatest in emotional and cognitive functioning and daily activities (Table 3). Similarly, when comparing our cohort to children with intestinal failure, we found that in all domains the mean score was lower in children with non-IgE mediated food allergy, but only the physical, emotional and worry domains achieved statistical difference (Table 4).

Discussion

This study sets out to establish the impact of QOL on families with children who have non-IgE mediated food allergies affecting the gastrointestinal tract based on an elimination diet with symptoms improvement. The study aimed to capture the early impact of this food allergy on the QoL of families, who have often waited for months for a diagnosis.

In this study, we found that the average total PedsQL FIM™ score was worse than both intestinal failure and sickle cell disease. Our data indicates that families in our cohort are particularly affected in daily activities as well as physical and emotional functioning. Additionally the parents report significant worry about their child. Sources of stress for families of healthy children include the difficulties of feeding young babies, sleep issues, infant crying and social isolation [25–27]. Many of these aforementioned stresses are also experienced by parents of children with non-IgE mediated allergies, in addition to children struggling with sleep due to abdominal pain and feeding difficulties [28, 29]. The poor physical and emotional functioning of parents of children with non-IgE mediated allergies often starts with poor symptom recognition and delay in diagnosis [30], and when diagnosed, symptom management can often impose further stress. The mainstay for treatment for this allergy is an elimination diet that needs to be monitored and strictly adhered to. The fear of accidental exposure and therefore the burden of planning meals, sourcing free-from foods, ensuring that foods are not contaminated and often trusting others to keep to the dietary elimination, is significant [29]. Although this allergy is non-IgE mediated and parents do not need to worry about anaphylaxis, an inadvertent exposure to an offending allergen can lead to worsening of symptoms that can take a couple of days to weeks to improve [18]. Similar areas, affecting functioning of families of children with other chronic diseases, including diabetes and cancer have also been documented [22, 30].

Table 3 QoL differences between children with Sickle Cell Disease and Non-IgE mediated allergy

	Sickle cell disease cohort		Non-IgE mediated Cohort		Mean difference	Statistical significance
	Mean	Std. Deviation	Mean	Std. Deviation	Between cohorts	*p* value
FIM Total Score	73.2768	18.39831	57.43	22.27	−15.8468	<0.0001
FIM Parent QOL	73.9996	18.70280	58.95	23.25	−15.0496	<0.0001
FIM Family Functioning	74.3541	22.25948	57.96	25.26	−16.3941	<0.0001
Physical Functioning	66.8246	22.96708	55.43	26.89	−11.3946	0.0011
Emotional Functioning	75.6744	20.96464	55.72	24.13	−19.9544	<0.0001
Social Functioning	80.2517	23.16745	62.21	27.72	−18.0417	<0.0001
Cognitive Functioning	76.0460	23.02157	63.33	24.57	−12.7160	0.0001
Communication	77.5709	23.72894	58.54	29.15	−19.0309	<0.0001
Worry	65.7270	26.32828	50.17	24.33	−15.5570	<0.0001
Daily Activities	69.7133	26.80064	48.84	31.84	−20.8733	<0.0001
Family Relationships	77.3271	23.67000	63.43	26.01	−13.8971	0.0001

Worry is a common emotion documented in particular in families of children with IgE mediated peanut allergy, due to the fear of their child dying [9, 11]. From our study, we do not know the exact reasons for the increased worry, but in EoE the worry is specifically related to medical management, problems with adherence to the diet, having diarrhoea/vomiting in front of other children and long term uncertain prognosis [31]. In the QoL study on FPIES, parents scored in particular high on concerns about nutrition, meal preparations, the child's health and others not appreciating the severity of reactions [15]. In addition to this, we suspect that parents worry about the uncertain prognosis and often express their concern about their child deteriorating to where they were before the diagnosis/elimination diet and also the long term impact of medication used for management. In particular, mothers seem to be more affected when their child has a chronic disease. Greene [32] indicated that mothers of children with recurrent abdominal pain displayed greater anxiety, depression and somatization, which was also found in mothers of peanut allergic children [9]. Ninety-percent of our questionnaires were filled in by the mothers and we can therefore not rule out that perception of family impact is worse for the mothers than the fathers also in non-IgE mediated gastrointestinal allergies.

We have also found that the more foods that are eliminated the worse the impact on family QOL. This is not surprising at all, as the more foods are eliminated the more limited the commercial food choices are resulting in an increased need for home prepared foods. This also has a significant impact on social activities for both the child and the parent (i.e., what they can eat at a birthday party and eating out), in addition to the emotional well-being [31].

In 86% of our cohort, at least one co-morbidity (i.e., asthma, eczema, rhinitis and chronic nasal congestion) was present, which can impact on QOL irrespective of the presence of food allergy. Using regression analysis, we found that chronic nasal congestion was the only co-

Table 4 QoL differences between children with intestinal failure and non-IgE mediated allergy

	Intestinal failure		Non-IgE mediated cohort			Between cohorts	Statistical significance
	Mean	St Dev	*n*	Mean		mean difference	*p* value
TOTAL Average	61.3	17.32	100	53.92	21.86	−7.38	0.1332
Average QoL	63.48	15.64	100	55.07	22.58	−8.41	0.0931
Physical	62.34	17.83	99	50.56	25.79	−11.78	0.0401*
Emotional	64.13	19.23	100	53.05	23.98	−11.08	0.0409*
Social	60.05	26.96	100	57.96	27.63	−2.09	0.7431
Cognitive	66.96	21.78	100	60.13	24.26	−6.83	0.2176
Communication	64.49	26.97	100	54.08	28.17	−10.41	0.1099
Worry	61.74	21.25	100	47.91	24.3	−13.83	0.0132*
FAMILY Average	57.61	20.09	99	54.95	25.76	−2.66	0.6442
Daily Activities	46.38	29.92	99	44.02	31.36	−2.36	0.7436
Family Relationships	64.35	20.69	98	61.53	27.18	−2.82	0.6419

* $p < 0.05$

morbidity that significantly impacted on QOL. Eczema, hayfever and asthma, where present did not impact on the QoL of families. Interestingly nasal congestion has been found in 72% of children < 2 years of age with cow's milk protein allergy in a study by Paddack et al. [33], which is similar to our findings. Nasal congestion affects both feeding coordination and sleep, both of which are important for maintaining the QOL of families.

The study results also indicated that it is not one symptom but the sum total of gastrointestinal symptoms (including the perceived severity) that impacts family QOL. Again this is not a surprising finding as studies on EoE have found QOL correlates with the severity of symptoms [7].

We hypothesised that the PedsQL FIM™ Score would be worse in our cohort than children with other chronic diseases [9, 10]. This hypothesis was proven correct in all domains of QOL when comparing our data to families of children with sickle cell disease. In the sickle cell cohort, 56% had severe sickle cell disease, but data on management was not available. Parents of children with this disease live in the fear of an acute sickle cell crisis, that may present with a vaso-occlusive or haemolytic crises affecting all organs and sepsis. However, patients with sickle cell disease also develop frequent and recurrent painful episodes throughout life, that worsen with age, thereby exhibiting chronic symptoms which are also seen in young children with non-IgE mediated gastrointestinal food allergies [18]. Nevertheless we suspect that the worse FIM scores of our non-IgE mediated cohort can be explained by the allergic group requiring a food elimination diet [12], sleep being affected with ongoing symptoms and the uncertain prognosis as non-IgE mediated gastrointestinal allergies remains poorly understood. Rouf et al. [29] found that mothers with food allergic children adjusted over time to develop strategies to overcome the emotional and practical challenges presented. However, in children with non-IgE mediated gastrointestinal allergies, the goal post for management and prognosis is constantly changing (i.e., can present with vomiting but then develop constipation later), thereby making it difficult to develop strategies to overcome emotional challenges [34].

We also compared our cohort to a group of children with intestinal failure aged between 6 months – 7 years (mean age 2.3 years) that are stable and dependant on either parenteral or enteral nutrition (56% had gastrostomies) [20]. The impact on families with artificial nutritional support is significant, as it entails frequent night-time feeding, concern about maintaining a sterile environment to prevent often life threatening infections and regularly requires procedures for re-inserting lines and changing gastrostomies. Similar to our cohort, this group would be dependent on optimal nutritional management to control symptoms and social and family life would be impaired due to the dependence on artificial nutrition. Although intestinal failure represents an extreme gastrointestinal condition, we were surprised to see that even compared to this group physical and emotional functioning, as well as worry about their child as significantly lower. Although there are no studies that explain this finding, we would hypothesise that this may be related to the knowledge of progression in disease with intestinal failure, where healthcare professionals understand the seriousness of the condition and there is a significant amount of research and support associations to help families, which is not yet the case for non-IgE mediated gastrointestinal allergies.

This study has several limitations. The first is related to the PedsQL FIM™ questionnaire itself; that it is not specific for families with children with non-IgE mediated food allergies [8, 35, 36]. Although the FIM has been used as means of assessing the impact on the family and measurement of self-reported functioning in the family, we are unable to assess the impact of the food allergy itself. The advantage however to using this generic tool is that we were able to compare this to other diseases [37–39]. In addition, the PedsQL FIM™ has been validated for children 2–18 years of age and we have used it in a younger cohort. Although this questionnaire has been used by many studies in children < 2 years of age, this limitation needs to be taken into account. It may also be perceived as a limitation of the study that inclusion of patients occurred based on symptom improvement following an elimination diet, rather than a formal challenge procedure. We wanted to establish QoL of family early on as this is when we have observed it to be the worst. All patients had subsequent home reintroductions of foods, however if we waited for these to occur, there would have been a delay of several months and QoL improves with time. Another limitation is the control groups, which were both historical and therefore not specifically selected as a control group for this study. In addition significant age differences exist between the sickle cell cohort and our patient group, which may have biased the data. The timing of completing the QOL questionnaire may also be a limitation. Parents completed the questionnaire 4–12 weeks after a successful elimination diet which may have affected scoring as coping skills often improve with time.

Strengths of this study include providing for the first time an indication of the burden for families of children with non-IgE mediated gastrointestinal allergies compared to other chronic diseases. It also highlights the specific domains of concern for families, namely worry, physical and emotional functioning. This knowledge can already impact on the advice and support given to families of children in the early stages of diagnosis when an elimination diet is initiated, when it is likely to impact most.

Conclusion

This study has found that the QoL of parents and family functioning was worse in children on an elimination diet for non-IgE mediated gastrointestinal allergies compared to sickle cell disease and they also had worse scores in emotional and physical domains and worry than parents/families of children with intestinal failure. We found that the symptom severity, the number of foods avoided and also the presence of chronic nasal congestion impacts on QoL of families. We have highlighted with this study the impact this allergy has on families, which may help to inform clinical services with putting in place appropriate advice and support structures.

Abbreviations

EoE: Eosinophilic Oesophagitis; FPIES: Food protein induced enterocolitis syndrome; HRQL: Health related quality of life; IgE: Immunoglobulin E; PedsQL FIM: Pediatric quality of life family impact module; QOL: Quality of Life

Acknowledgements

We would like to acknowledge all the parents of children with this food allergy who have taken the time to come to our research centre and also fill in the QOL questionnaires.

Funding

This study was funded by a charitable grant from Great Ormond Street Hospital Charities.

Authors' contributions

RM Study design, planning and write up of publication. HG Data collection, planning and write up of publication. RD Data analysis and critical review of publication. JP Contribution of sickle cell data and critical review of publication. RF Critical review of publication. MB Critical review of publication. ACL Critical review of publication. KR Critical review of publication. NS Study design and critical review of publication. All authors read and approved the final manuscript.

Competing interest

The authors declare that they have no competing interests.

Consent for publication

Consent for publication has been obtained from parents when informed consent was received.

Ethics approval and consent to participate

Ethics approval was obtained for this study from the NRES London Bloomsbury National Research and Ethics Society of the UK (Nr 11/LO/1177). All patients in this study have had signed consent from their parents/guardian.

Data analysis

Statistical analysis methods are described in the text – no further statistical results are available.
No data is available for public access as this is an ongoing prospective cohort.

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Received: 11 September 2016 Accepted: 22 December 2016

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6. CONCLUSIONS AND FUTURE PERSPECTIVES

6.1 Brief summary of the thesis

This thesis set out to investigate diverse aspects of non-IgE mediated gastrointestinal food allergy in children utilising a publication approach. The thesis's introduction argued for the importance of this study by considering research studies and evidence already completed and the aspect that required exploration. The following four chapters considered the publications around this study, in a progressive manner, showing the building of knowledge to ensure the research for this thesis was systematic and robust. This final chapter will now consider its key contributions to knowledge, limitations and implications for policy and practice

6.2 Key contribution

The series of studies included in this thesis have significantly advanced the knowledge about the relatively recently described clinical condition of non-IgE mediated gastrointestinal food allergies. For the first time, it has become apparent that the necessary amount of time that is required for the elimination diet in order to diagnose the majority of patients with non-IgE mediated gastrointestinal food allergies is four weeks, which previously varied widely in the literature and was based on experts' opinion.

The results of this study have been well disseminated in the paediatric gastroenterology community. It has been awarded Editor's choice of Pediatric Allergy and Immunology journal (Issue August 2015) and the results were also presented in the European Society for Paediatric Gastroenterology Hepatology and Nutrition annual meeting. Professor Katie Allen (2015:presentation), an Australian leading consultant also presented the study's results during the 2015 congress of the European Academy of Allergy and Clinical Immunology.

The team I worked alongside with at the Great Ormond Street Hospital have utilised the findings of this study and have now embedded it in clinical practice as a tool in the diagnosis process of children with suspected non-IgE mediated gastrointestinal food allergies since 2015. Also, now in Australia I have disseminated the knowledge of my findings to the allergy team at the Royal Children's Hospital and to the Monash Medical Centre who are in the process of reconsidering their practice on the basis of these findings.

Additionally, this thesis demonstrates that a detailed medical and food history and an individualised dietary advise can lead to an improvement of growth parameters of the affected children, supporting the importance of a multidisciplinary team in the treatment of children with this condition. The impact of non-IgE mediated food allergies on the quality of life of affected children and their parents has been quantified, demonstrating the burden of this increasingly diagnosed public health issue.

Another knowledge gap that has been addressed in this thesis was the reporting on the significant low intake of vitamin and micronutrients that occur in non-IgE mediated allergic children, highlighting the importance of taking a comprehensive medical and nutritional history, as well as supplementing micronutrients accordingly. The perception of the disease by parents and by general practitioners is remarkably different. Separate education programmes for both parents and health professionals on the front line who often have the first contact with the patient are fundamental to tackle this problem optimally.

6.3 Implications for police and practice

The findings of the studies included in this thesis have the potential to change clinical practice. Important ground educational work with families and GPs will be crucial to avoid delay of diagnosis and its long-term nutritional and growth consequences. With the evidence from this thesis, guidelines should now be able to take into account the suggested time of elimination diet of four weeks, as well as vitamins and nutrients supplementation as appropriate.

A recommendation has been put in for change in guideline for Monash Medical Centre - Monash Health and this will impact on allergists practice in Victoria – Australia. Also, as discussed above (6.2), the findings have now been out into practice at the Great Ormond Street Hospital.

6.4 Limitations

It is essential, however, to acknowledge the limitations of the included studies. The main limitation was that these clinical studies had an observational cohort design and lacked a control group. Inherently, it is possible that there were unknown confounding factors that could not be adjusted for in the analysis stage. Another important limitation is the absence of a food challenge after four to eight weeks of the elimination diet in order to conclude the diagnostic gold standard process. Nonetheless, a randomised controlled trial with a no-treatment or placebo group would have been impractical, if not unethical.

The evaluation of mineral and vitamin deficiency was based on a three-day dairy documented by parents. This dietary assessment method may not the most accurate due short time frame, lack of documentation and recall bias of the diet components. Nevertheless in the absence of a validated food frequency questionnaire for allergic children, the three day diary was the best choice for the study as when analysed correctly can point towards low intake of vitamins and micronutrients if present.

The analysis of the impact of the disease on quality of life relied on a Likert scale and parents' perception of signs and symptoms. This could have been influenced by recall bias due to varying severity degrees and timing of diagnosis. The Likert scale utilised is a well-established and validated tool and designed to be used in different types of paediatric disease. However, the severity of the disease itself is also likely to play a significant role on the quality of life, and there is a lack of qualitative research on parents' opinion using validated instruments and in-depth interviews.

6.5 Future Studies

Future studies will be important for this group of patients as there is much more to understand and investigate non-IgE mediated gastrointestinal food allergies in infancy and childhood. Identifying reliable diagnostic tests for the diagnosis of non-IgE mediated food allergies is essential to decrease the delay in the diagnosis process, to reduce the number of consultations in the primary care settings and to improve the quality of life of children and their families. Research focusing on the improvement of knowledge and development of tools for health care professionals and families are also essential to reduce the burden of the disease in both groups.

Studies evaluating new treatment options for food allergy are also important and necessary, as the diet elimination presents multiple challenges for patients, families and health care professionals. Recently, oral immunotherapy has been studied as a potential treatment for IgE-mediated allergies (Nurmatov et al., 2017). It involves administering gradually increasing amounts of food allergen under medical supervision, with possible outcomes of developing desensitisation or tolerance to the food allergen (Nurmatov et al., 2017). To date, nothing similar has been studied for non-IgE mediated gastrointestinal food allergies.

Population-based studies, as well as genetic association studies, will be important to better understand the aetiology of food allergies, which ultimately lead to personalised treatment options choice. Identifying the risk factors for the disease and measures to prevent or decrease the prevalence in the long term is also important as food allergy is one of the diseases of the century and its incidence is still rising.

For a more profound knowledge of the disease leading to a better understanding of diagnosis and treatment options, studies of larger cohorts are necessary. Those should focus on finding diagnostic tests to facilitate the diagnosis of non-IgE mediated gastrointestinal food allergies and on other treatment options, including medications for the most severe cases.

6.6 Conclusions

The prevalence of food allergy in the paediatric population is increasing in the last decades, and it is recognised as a significant public health problem.

Non-IgE mediated gastrointestinal food allergies are an important form of food allergy in infancy and childhood with a high prevalence.

The diagnosis and treatment of non-IgE mediated gastrointestinal food allergies remain a challenge.

The "Discovering the effect of non-IgE mediated allergies on children and their families" is a landmark study in the paediatric food allergy field. There was a big gap of knowledge regarding non-IgE mediated gastrointestinal food allergies in childhood. This well-designed study investigated and elucidated some important characteristics and clinical features of this group of patients. Its impact is reflected in the number of publications derived from the results of this cohort, the large number of citations and the potential impact in clinical practice worldwide as much more is known about this condition.

The main finding of this study is that elimination diet of four weeks is enough for the diagnosis in the vast majority of the patients with suspected non-IgE mediated food allergies. I also reported, for the first time, the burden of this disease for children and their families.

Further research is warranted to improve the diagnostic process and treatment of non-IgE mediated gastrointestinal food allergies in infancy and childhood. Studies investigating preventative measures for the development of food allergies in childhood are also essential in the future.

APPENDIX

A. *Aims, studies and articles characteristics*

Aims	Studies	Articles	Characteristics
1. Prospectively investigate the required length of elimination diet to achieve symptom improvement	1. Discovering the effect of non-IgE mediated allergies on children and their families	1. Lozinsky, A. C., Meyer, R., De Koker, C., Dziubak, R., Godwin, H.,. (2015b) 'Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies'. *Pediatric Allergy and Immunology,* 26(5) pp. 403-408.	**Prospective Observational Study** **Funding**: Charitable grant from Great Ormond Street Hospital Charities
2. A) To evaluate the knowledge of GPs about diagnosis and management of CMPA and to compare with parents views and opinions; And B) To better understand diagnosis tools, treatment and tolerance in infants diagnosed with eosinophilic colitis	2. UK CMPA cohort	2. Lozinsky, A.C., Meyer, R., Anagnostou, K., Dziubak, R., Reeve, K., et al. (2015a) 'Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents'. *Children,* 2(3) pp.317-329.	**Survey based study** **Funding:** Mead Johnson Nutrition UK
	3. Systematic review	3. Lozinsky, A. C. & Morais, M. B. (2014) 'Eosinophilic colitis in infants'. *Jornal de Pediatría,* 90(1) pp.16-21.	**Systematic review** **Funding**: none
3. Evaluate possible impacts of the elimination diet on growth and nutrients deficiencies	1. Discovering the effect of non-IgE mediated allergies on children and their families	4. Meyer, R., De Koker, C., Dziubak, R., Godwin, H., Dominguez-Ortega, G., et al. (2016) 'The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies'. *Clin Transl Allergy,* 6(25) pp 1-7. [Online][Acessed on June 2019] DOI:10.1186/s13601-016-0115-x	**Prospective Observational Study** **Funding**: Charitable grant from Great

Aims	Studies	Articles	Characteristics
		5. Meyer, R., De Koker, C., Dziubak, R., Skrapac, A. K., Godwin, H., et al. (2015) ‘A practical approach to vitamin and mineral supplementation in food allergic children’. Clin Transl Allergy, 5(11) pp.1-7. [Online] [Acessed on 4th of May 2019] DOI: 10.1186/s13601-015-0054-y	Ormond Street Hospital Charities
4. Analyse the potential impact of non-IgE mediated gastrointestinal allergies on the quality of life of the affected children and their families	1. Discovering the effect of non-IgE mediated allergies on children and their families	6. Foong, R. X., Meyer, R., Godwin, H., Dziubak, R., Lozinsky, A. C., et al. (2017) ‘Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies’. Pediatric Allergy and Immunology, 28(3) pp. 251-256. 7. Meyer, R., Godwin, H., Dziubak, R., Panepinto, J. A., Foong, R. M., et al. (2017) ‘The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies’. World Allergy Organ J, 10(1):8 pp. 1-8 [Online] [Acessed on 4th of April 2019] DOI: 10.1186/s40413-016-0139-7	**Prospective Observational Study** **Funding**: Charitable grant from Great Ormond Street Hospital Charities

B. *Number of citations per article included in the thesis*

Reference	**Number of citations**
Lozinsky, A. C., Meyer, R., De Koker, C., Dziubak, R., Godwin, H., et al. (2015b) 'Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies'. *Pediatric Allergy and Immunology,* 26(5) pp. 403-408.	**24**
Lozinsky, A.C., Meyer, R., Anagnostou, K., Dziubak, R., Reeve, K., et al. (2015a) 'Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents'. *Children,* 2(3) pp. 317-329.	**17**
Lozinsky, A. C. & Morais, M. B. (2014) 'Eosinophilic colitis in infants'. *Jornal de Pediatría,* 90(1) pp.16-21.	**47**
Meyer, R., De Koker, C., Dziubak, R., Godwin, H., Dominguez-Ortega, G., et al. (2016) 'The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies'. *Clin Transl Allergy,* 6(25) pp 1-7. [Online][Acessed on June 2019] DOI:10.1186/s13601-016-0115-x	**18**
Meyer, R., De Koker, C., Dziubak, R., Skrapac, A. K., Godwin, H., et al. (2015) 'A practical approach to vitamin and mineral supplementation in food allergic children'. Clin Transl Allergy, 5(11) pp.1-7. [Online] [Acessed on 4th of May 2019] DOI:	**21**

Reference	Number of citations
10.1186/s13601-015-0054-y	
Foong, R. X., Meyer, R., Godwin, H., Dziubak, R., Lozinsky, A. C., et al. (2017) 'Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies'. Pediatric Allergy and Immunology, 28(3) pp. 251-256.	**2**
Meyer, R., Godwin, H., Dziubak, R., Panepinto, J. A., Foong, R. M., et al. (2017) 'The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies'. World Allergy Organ J, 10(1):8 pp. 1-8 [Online] [Acessed on 4th of April 2019] DOI: 10.1186/s40413-016-0139-7	**9**

C. My contribution to each publication

My contribution to the Discovering the effect of non-IgE mediated allergies on children and their families study includes overall coordination of data collection, statistical analysis and writing of the manuscripts.

In the study performed outside the Discovering the effect of non-IgE mediated allergies on children and their families project, my contribution included the study design and a significant proportion of data collection, statistical analysis and writing of the manuscripts.

My contribution for each publication is summarised in the following Table.

Reference	**Collection of data**	**Writing of manuscript**	**Statistical analysis**	**Study design**
Lozinsky, A. C., Meyer, R., De Koker, C., Dziubak, R., Godwin, H., et al. (2015b) 'Time to symptom improvement using elimination diets in non-IgE-mediated gastrointestinal food allergies'. *Pediatric Allergy and Immunology,* 26(5) pp. 403-408.[†]	**70%**	**80%**	**10%**	**50%**
Lozinsky, A.C., Meyer, R., Anagnostou, K., Dziubak, R., Reeve, K., et al. (2015a) 'Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents'. *Children,* 2(3) pp. 317-329.[§]	**80%**	**80%**	**30%**	**50%**

Reference	**Collection of data**	**Writing of manuscript**	**Statistical analysis**	**Study design**
Lozinsky, A. C. & Morais, M. B. (2014) ‘Eosinophilic colitis in infants’. *Jornal de Pediatría,* 90(1) pp.16-21.[⌘]	**80%**	**80%**	**70%**	**50%**
Meyer, R., De Koker, C., Dziubak, R., Godwin, H., Dominguez-Ortega, G., et al. (2016) ‘The impact of the elimination diet on growth and nutrient intake in children with food protein induced gastrointestinal allergies’. *Clin Transl Allergy,* 6(25) pp 1-7. [Online][Acessed on June 2019] DOI:10.1186/s13601-016-0115-x[¶]	**50%**	**50%**	**10%**	**50%**
Meyer, R., De Koker, C., Dziubak, R., Skrapac, A. K., Godwin, H., et al. (2015) ‘A practical approach to vitamin and mineral supplementation in food allergic children’. Clin Transl Allergy, 5(11) pp.1-7. [Online] [Acessed on 4th of May 2019] DOI: 10.1186/s13601-015-0054-y.[¶]	**50%**	**50%**	**0%**	**60%**
Foong, R. X., Meyer, R., Godwin, H., Dziubak, R., Lozinsky, A. C., et al. (2017) ‘Parental perception of their child's quality of life in children with non-immunoglobulin-E-mediated gastrointestinal allergies’. Pediatric Allergy and Immunology, 28(3) pp. 251-256.[†]	**60%**	**50%**	**10%**	**50%**
Meyer, R., Godwin, H., Dziubak, R., Panepinto, J. A., Foong, R. M., et al. (2017) ‘The impact on quality of life on families of children on an elimination diet for Non-immunoglobulin E mediated gastrointestinal food allergies’. World Allergy Organ J, 10(1):8 pp. 1-8 [Online]	**60%**	**50%**	**0%**	**60%**

Reference	Collection of data	Writing of manuscript	Statistical analysis	Study design
[Acessed on 4th of April 2019] DOI: 10.1186/s40413-016-0139-7 *				

Scientific Journal	Impact factor for 2017
† Paediatric Allergy and Immunology	4.137
§ Children	Not available – open access
⌘ J Pediatr (Rio J)	1.690
¶ Clinical Translation Allergy	3.539
* World Allergy Organization Journal	5.676

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