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Case Report

Int J Clin Pediatr. 2020;9(3):98-102

Challenges and Pitfalls in the Diagnosis and Management of Non-IgE Cow's Milk Protein Allergy: Two Cases

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Abstract

As the incidence of cow's milk protein allergy (CMPA) has increased in the last decades in both breastfed and formula fed infants, possible pitfalls in its diagnosis and management are also increasing. This is especially evident in non-IgE milk allergy due to the considerable delay between the appearance of clinical symptoms after ingestion of the allergen, and the non-specific gastrointestinal symptoms that characterize it. The misdiagnosis could often be combined with inappropriate use of either partially hydrolyzed or amino acid-based infant formula for the management of symptoms. The aim of the paper is to present two cases to illustrate common pitfalls in diagnosis and management of CMPA with divergent gastrointestinal syndrome manifestations: food protein-induced allergic proctocolitis and food protein-induced enterocolitis syndrome, in an effort to increase awareness of these conditions and to guide clinicians in day-to-day practice when facing suspected cases of CMPA.

Keywords: Cow's milk protein allergy; Non-IgE-mediated; Food protein-induced enterocolitis syndrome; Food protein-induced allergic proctocolitis; Extensive hydrolysate formula

Introduction

The incidence of cow's milk protein allergy (CMPA) has increased in both breastfed and formula fed infants [1]. In developed countries, it is estimated that the incidence of CMPA in infancy is approximately 2-3% [2]. CMPA is underpinned by a maladaptive immune response to cow's milk proteins (CMPs) and can manifest through IgE-mediated or non-IgE-mediated pathways, or a mixture of both [1].

Unlike IgE-mediated reactions where symptoms typically occur within minutes, up to 1 - 2 h after exposure to CMPs, in non-IgE-mediated cases, the clinical symptoms may occur from a few hours or up to several days after ingestion, in addition to lack of specific symptoms [3]. A detailed history and elimination of CMP from the diet remains the cornerstone of accurate diagnosis when an allergy is suspected. A subsequent oral food challenge (OFC) or re-introduction of CMP is necessary to confirm this suspicion [4]. Once a diagnosis of CMPA has been established, strict elimination of CMP from the patient's diet may be recommended for certain periods of time. This time frame is dependent on the clinical syndrome by which non-IgE-mediated CMPA presents. In addition, non-IgE-mediated food allergic disorders with gastrointestinal symptoms such as food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE) and food protein-induced allergic proctocolitis (FPIAP) are relatively uncommon in infants and young children, but are likely under-diagnosed [5].

Strict elimination of CMP is usually required for 6 - 9 months in FPIAP and 12 - 18 months in FPIES, hence significantly impacting family's quality of life. Ultimately, accurate diagnosis will help to minimize the number of infants subjected to unnecessary elimination diets on one hand and under-diagnosis on the other [3].

The aim of the report is to present two clinical cases illustrating common pitfalls and challenges associated with the diagnosis and management of non-IgE CMPA with unspecific gastrointestinal symptoms/signs (Table 1) [3, 6, 7]. Each case will be presented starting with symptoms, diagnosis and management followed by discussion on the pitfalls. Increased awareness of these conditions can be extremely useful for the practicing clinician faced with suspected CMPA.

Case Reports

Case 1

A 2.5-month-old girl on standard cow's milk formula since the age of 4 weeks, presented with two episodes of mucus and flakes of blood in her stools. She was otherwise thriving with good appetite and weight (75th percentile of WHO Growth Chart), and no signs of atopic dermatitis. She was delivered by cesarean section (breech position) at term (39 weeks gestation) without any perinatal problems (Apgar score: 9, birth weight: 2.950 kg, head circumference: 35.8 cm and birth length: 50.2

Manuscript submitted May 11, 2020, accepted June 19, 2020
Published online June 30, 2020

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doi: https://doi.org/10.14740/ijcp375

Table 1. Common Gastrointestinal Symptoms/Signs of Non-IgE CMPA in the First Year of Life

Mild to moderate symptoms/signs	Severe symptoms/signs
Irritability, vomiting, food refusal or aversion, diarrhea, constipation, abdominal discomfort, painful flatus, blood and/or mucus in stools in an otherwise well infant.	Diarrhea, vomiting, abdominal pain, food refusal or food aversion, significant blood and/or mucus in stools, irregular or uncomfortable stools, with or without faltering growth, pallor, lethargy, hypotonia, hypovolemia, hypotension, hypoalbuminemia, failure to thrive.

CMPA: cow's milk protein allergy.

cm). She was the outcome of the first pregnancy of a 27-year-old teacher following an assisted conception (*in vitro* fertilization). She had mixed feeding from the first day of life and breastfeeding was discontinued at the age of 4 weeks. There was no family history of allergic disease. No laboratory tests were performed for this case.

The infant's parents were informed by the pediatrician that their child suffered from a common mild allergy to cow's milk protein called FPIAP without performing further investigations. The parents were asked to avoid dairy products and beef in the infant's diet for 12 months, and a partially hydrolyzed formula (pHF) was prescribed as a milk substitute. The infant continued to have blood-stained stools in the following 2 weeks and was seen in the pediatric allergy clinic at the age of 3 months. An extensively hydrolyzed milk formula (eHF) was then prescribed for 4 weeks and the infant's symptoms resolved. The diagnosis of FPIAP was confirmed by re-introduction of the standard cow's milk formula and the recurrence of blood in stools. The eHF and avoidance of dairy products was continued up to the age of 10 months when CMP was re-introduced into the infant's diet without any problems. During this whole period, her growth curves remained within normal.

Case 2

A 5-month-old girl who was exclusively breastfed, developed 3 - 4 episodes of vomiting approximately 3 h after feeding with a standard cow's milk formula. She fell asleep and woke up 3 h later without any symptoms and in a very good mood. The mother gave breastmilk for the next couple of feeds and the infant was fine. The family doctor suggested over the phone to try the formula at home again the following morning. Approximately 2 h after formula administration, the infant developed multiple episodes of vomiting and became pale and lethargic. She was transferred to the accident and emergency department and managed with intravenous fluids. She was admitted to the pediatric ward and subsequently diagnosed with acute FPIES without performing an OFC. An eHF was given supplementary to breastmilk which was well tolerated. During this whole period, her growth curves remained within normal.

She was normally delivered at term (40 weeks gestation) without any perinatal problems (Apgar score: 10, birth weight: 3.150 kg, head circumference: 36.5 cm and birth length: 51.4 cm). She was the outcome of the second uncomplicated pregnancy of a 31-year-old nurse following a normal conception. Her older brother suffered from egg allergy and her father had asthma.

Discussion

Pitfalls in the diagnosis and management of case 1

Although the clinical history is strongly suggestive of FPIAP, the diagnosis in this case was not objectively established by the pediatrician as this case was then referred to specialist allergy clinic. A 2 - 4 weeks elimination diet of CMP followed by re-introduction should have been performed to confirm the diagnosis, as suggested by most international guidelines [8-10]. Resolution of symptoms through CMP elimination and subsequent recurrence with re-introduction establishes CMPA diagnosis and rules out other possible triggers [4].

FPIAP, previously known as allergic or eosinophilic proctocolitis, often causes rectal bleeding in otherwise healthy infants, as outlined in the case above. This transient and benign condition typically occurs in the first weeks of life and often resolves by late infancy. It is characterized by inflammation of the distal colon in response to food proteins such as CMPs and soy, through a mechanism that does not involve IgE antibodies. Blood tests for specific IgE to CMP and/or skin prick tests to establish FPIAP diagnosis are not highly sensitive when IgE-mediated reactions are not suspected based on clinical history [7]. Atopy patch tests are also not indicated due to lack of standardization. Endoscopy should be performed only in severe cases when a differential diagnosis is suspected [7].

In daily practice, many pediatricians rely on positive fecal occult blood testing to diagnosis FPIAP leading to over- and misdiagnosis. As the presence of blood and mucus in an infant's stools may occasionally be related to other causes (e.g. viral infections, vaccinations, antibiotics), it is critical to follow the elimination/re-introduction process to confirm CMPA. The possibility of over-diagnosis, leading to unnecessary elimination of cow's milk and dairy products in diet may also affect the late development of tolerance or prolonged allergy to CMP in the infant.

Management of FPIAP relies on dietary restriction of CMPs. Beef avoidance is unnecessary unless symptoms develop with its introduction into the infant's diet. In the presented case, avoidance of CMP was suggested for 12 months. This is usually not necessary for more than 6 - 9 months as most infants become tolerant by 1 year old. For formula-fed infants, a pHF such as that proposed, is not indicated in the management of FPIAP as per recommendations from several established guidelines (Table 2) [8-12]. Most patients respond to an eHF, whereas an AAF is rarely required.

For breastfed infants with FPIAP, elimination of the offending food from the mother's diet usually results in gradual

Table 2. Therapeutic Formula Options for Signs and Symptoms Relating to Food Allergy or Intolerance

Signs and Symptoms	Australia [10]		DRACMA [11]		ESPGHAN [12]	
	First choice	Second choice	First choice	Second choice	First choice	Second choice
FPIAP	eHF	AAF			eHF	AAF
FPIES	eHF	AAF	eHF	AAF	eHF	AAF
Eos eso	AAF		AAF		AAF	
Immediate FA	eHF/soy[a]	AAF/eHF	eHF	AAF/soy	eHF	AAF
Atopic eczema	eHF/soy[a]	AAF/eHF	eHF	AAF/soy	eHF	AAF
Urticaria			eHF	AAF/soy	eHF	AAF
Constipation due to suspected CMPA			eHF	AAF		
Heiner syndrome			AAF	eHF		
Gastrointestinal syndromes related to suspected CMPA	eHF/soy[a]	AAF/eHF	eHF	AAF	eHF	AAF

[a]If infant is older than 6 months. Adapted from Reference [8], ©2017 by the author. CMPA: cow's milk protein allergy; AAF: amino acid formula; DRACMA: Diagnosis and Rationale for Action against Cow's Milk Allergy; eHF: extensively hydrolyzed formula; Eos eso: eosinophilic esophagitis; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition; FA: food allergy; FPIAP: food protein-induced allergic proctocolitis; FPIES: food protein-induced enterocolitis syndrome.

resolution of symptoms and allows for continued breastfeeding [7]. Occasionally, an eHF or AAF may be warranted temporarily to resolve the bleeding within 48 - 72 h of the allergic trigger [13, 14]. Up to 20% of infants who are breastfed will have spontaneous resolution of bleeding without changes in the maternal diet [13, 14]. If an infant was previously breastfed exclusively and the symptoms developed after the introduction of cow's milk formula as supplementary milk, the mother does not usually need to avoid cow's milk and dairy products in her diet.

Pitfalls in the diagnosis and management of case 2

The crucial pitfall in this case was the lack of acute FPIES diagnosis suspicion by the family doctor. His suggestion to retry the milk formula at home instead of in a controlled environment resulted in a potentially life-threatening situation for the infant due to its high risk for hypovolemia and shock [15].

Acute FPIES is considered a rare condition, with an estimated cumulative incidence in infants of 0.015-0.7% [13, 15]. Chronic and atypical FPIES are less common and the underlying pathophysiologic mechanisms remain obscure. Although any food can induce FPIES, rice, oats, cow's milk, soy, fish and egg are common triggers in infancy [14]. Most patients will become tolerant to the offending food by school age [14].

As exemplified in this case, the dominant symptom was vomiting, which presented repetitively 2 - 3 h after the ingestion of CMP. Vomiting may be a common feature of other acute pediatric conditions including gastroenteritis and sepsis. Diagnosis of FPIES is challenging and may be missed because of its delayed onset of symptoms after food ingestion, and the lack of specific allergic skin and respiratory symptoms [14]. Acute FPIES is characterized by repetitive, projectile vomiting 1 - 4 h following ingestion of the offending food, which can be accompanied by other symptoms/signs such as lethargy, hypotonia, marked pallor, dehydration, hypotension, hypothermia, diarrhea and metabolic derangements [14].

In 2017, international consensus guidelines aimed to standardize the diagnosis of acute FPIES, to avoid inappropriate diagnosis through a system of major and minor criteria [16]. However, their validity has recently been questioned as patients with milder or more severe phenotypes of FPIES from different geographical regions might not be captured based on this criterion [17]. Currently, no accurate diagnostic biomarkers exist. Diagnosis remains mainly clinical and relies on the ability of healthcare professionals to suspect FPIES based on clinical history. In unclear cases, an OFC performed in a controlled environment by experienced personnel could confirm diagnosis. The management of FPIES is based on avoidance of the offending food in diet (CMP in the presented case), prompt treatment of accidental exposures and periodic re-evaluation (every 12 - 18 months) with controlled OFC to assess the development of tolerance [15].

Appropriate fluid replacement is the cornerstone of acute management. Ondansetron may be administered to reduce vomiting but should be avoided in infants less than 6 months old and patients with a history of heart disease [15]. Intramus-

cular adrenaline is not indicated. After review of the acute episode, education on the clinical features and management of acute FPIES should be provided to the parents or patients if they are old enough to understand [13]. In terms of breastfeeding, most infants with FPIES can tolerate the incriminated allergen through breastfeeding and hence, there is no need for avoidance of the allergen in maternal diet [18]. Continued breastfeeding should be encouraged [13].

Another common pitfall in the first-line nutrition management of FPIES is the use of AAF in non-breastfed infants (Table 2) as milk substitute for prolonged time. For most children with FPIES, an eHF will be sufficient to resolve symptoms of allergy [19]. However, there is a subset of children where an AAF may be warranted [15]. The judicious use of an AAF is heavily debated as it presents a significant economic burden to parents and/or the healthcare system. Literature recommends the use of AAF for the following presentations or conditions: 1) Symptoms are not fully resolved on eHF or if the eHF is not tolerated; 2) Faltering growth or failure to thrive; 3) Multiple food eliminations; 4) Eosinophilic esophagitis; 5) Severe eczema and/or complex gastrointestinal food allergies or 6) Symptoms persist on breastfeeding [20]. It is important to remember that the goal of allergy management should be to help build oral tolerance. This is challenging with AAFs as they do not contain peptides to educate the immune system. Protein hydrolysates could modulate the immune system whilst providing a safe solution for the management of non-IgE CMPA [21].

Conclusions

Non-IgE-mediated CMPA with gastrointestinal symptoms can have delayed and heterogenous manifest ranging from mild/moderate to severe cases. Diagnosis is challenging and relies on the ability of healthcare professionals to suspect non-IgE CMPA based on extensive medical history. Elimination of CMP in diet and its subsequent re-introduction or an OFC in controlled environment may be necessary to confirm this suspicion. Increased awareness of clinicians dealing with possible CMPA is paramount in avoiding pitfalls.

The mainstay of its management involves the elimination of CMP from the infant's diet for prolonged time, and periodic re-evaluation to assess tolerance acquisition depending on the clinical phenotype of CMPA. Educating parents and patients is important to ensure the offending food is avoided. Due to the potential severity and varied practices in CMPA management, a multidisciplinary approach involving caregivers, specialized nurses, pediatricians, allergists, gastroenterologists and dieticians is crucial. Breastfeeding should be encouraged, and CMP avoidance is not usually necessary in maternal diet. Most mixed-fed infants would tolerate an eHF as milk substitute. AAF may not be the first choice for nutrition management of the gastrointestinal-related symptoms of CMPA due to its lack of capabilities to build tolerance and high cost burden. Nutrition management of food allergy should follow the recent paradigm shift in allergy prevention: away from passive food avoidance towards a more personalized approach ultimately aiming at tolerance building.

Acknowledgments

The authors thank Ms Katie Qiof MIMS Pte. Ltd for providing medical writing support which was funded by Friesland Campina, Singapore.

Financial Disclosure

No financial grant was provided for Nicolaos Nicolaou and Amir Latiff for the development of this manuscript.

Conflict of Interest

Urszula Kudla and Leilani Muhardi were employees of Friesland Campina at the time of manuscript submission.

Informed Consent

The informed consent was not obtained from the patients/parents as these are common cases that present in the allergy clinic. There is no information provided in the manuscript that can be linked to the patient in the case.

Author Contributions

NN provided the cases. NN, AL, UK and LM provided extensive inputs on the development and finalization of the writing. All authors have read and approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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