Review Article

Non-IgE-mediated cow's milk allergy in breastfed infants

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Introduction

Food allergy is recognized as a growing public health burden. Among different food allergies, cow's milk protein allergy (CMPA) is recognized as a frequently occurring complex food allergy[1-3]. CMPA is defined as an immune-mediated response to proteins in cow's milk that occurs consistently with ingestion[4]. CMPA is most frequently seen during the first few years of life, typically in infancy[1-3]. Infants get exposed to cow's milk proteins (CMPs) via standard infant formulae, when solids containing cow's milk are introduced to the feeding regime or via maternal diet when the baby is breastfed. Thus, CMPA can develop among infants who are exclusively or partially breastfed[5].

Prevalence of CMPA

The estimated prevalence of CMPA varies between 1.9% and 4.9%[6]. The prevalence is higher during infancy and early childhood[2,7], but the perceived prevalence of CMPA is much higher than that confirmed by appropriate laboratory investigations[3]. The incidence of CMPA in exclusively breastfed infants is lower compared to its incidence in formula-fed or mixed-fed infants[5,8,9]. Studies indicate an incidence of CMPA in exclusively breast-fed infants ranging from 0.3% to 0.5%[8,9]. However, there is a lack of data on the prevalence of CMPA in Sri Lanka.

Pathophysiology of CMPA in breastfed infants

At present, the predisposing factors for CMPA are not completely clear. Multiple risk factors involved in the development of CMPA include genetic, epigenetic, and environmental factors, although the underlying mechanisms remain largely undiscovered[2,10].

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CMPA develops as a result of immunological reactions occurring against one or more milk proteins. The main allergens in cow's milk are found in the whey and casein fractions[6]. Whey allergens consist of alpha-lactalbumin, beta-lactoglobulin (BLG), bovine serum albumin and bovine immunoglobulins[6]. Casein allergens consist of four different proteins known as alpha-s1, alpha-s2, beta, and kappa caseins which share similar sequential characteristics[6]. In mothers who consume cow's milk, these allergenic CMPs are absorbed through the gastrointestinal system and then transmitted in human milk[11]. Of the allergenic CMPs, BLG is considered the most important allergen found in breast milk[11,12]. Since BLG is absent in human breast milk, detection of it in levels ranging from 0.9 to 150µg/L indicates dietary origin through maternal cow's milk ingestion[13,14]. Casein has also been found to be important to a lesser extent[12].

Levels of these allergenic proteins in human milk depend on the maternal dietary patterns and their atopic constitution[15]. Levels also vary intra-individually and inter-individually[15]. The variations in allergenic protein levels in human milk partly explain the development of CMPA among exclusively breast fed infants[15]. Early accidental and occasional exposure to allergenic CMPs in maternal milk may initiate sensitization in predisposed individuals. When there is a subsequent exposure to even minute amounts of allergenic CMPs in maternal milk, they act as a booster dose in eliciting allergic reactions. Evidence in favour of sensitization *in utero* is also available. Studies provide evidence that fetal allergen exposure *in utero* via the trans-amniotic route or transplacentally[16] from around 22 weeks of gestation can also result in primary sensitization to allergens[17], leading to CMPA in exclusively breastfed infants.

Exposure to allergenic CMPs leads to a cascade of reactions causing CMPA in a susceptible breastfed baby and induces a diverse range of symptoms and signs. These reactions can be immunoglobulin E (IgE) mediated or non-IgE-mediated[18,19]. In certain individuals, there is a possibility of combinations of these two (mixed IgE and non-IgE-mediated) reactions to the same allergen[20].

Clinical presentations of non-IgE-mediated CMPA in breastfed infants

IgE-mediated CMPA is considered to be an extremely rare manifestation in breastfed infants[21]. Suspected symptoms to the CMPs among breastfed infants are mostly caused by non-IgE-mediated reactions[22]. The onset of symptoms in non-IgE-mediated allergy is usually delayed for hours to days or even a week from the time of exposure to allergens[20]. In contrast to predominant cutaneous or respiratory symptoms in IgE-mediated allergy, non-IgE-mediated allergy symptoms are predominantly gastrointestinal[23]. Apart from that, there can be cutaneous manifestations such as exacerbation of atopic eczema among breastfed infants with non-IgE-mediated CMPA[24].

Table 1 summarizes different clinical presentations of non-IgE-mediated CMPA in breastfed infants[25].

Table 1: ***Clinical presentations of non-IgE–mediated CMPA in breastfed infants***

Mild to moderate non-IgE-mediated CMPA	Severe non-IgE-mediated CMPA
Mostly appear 2-72 hours after ingestion of CMPs	Mostly appear 2-72 hours after ingestion of CMPs
Rare in exclusively breastfed infants	Rare in exclusively breastfed infants
Persistence of symptoms despite first line measures are more likely to be allergy related e.g., reflux	Usually, one or more of the following symptoms which are severe, persistent and treatment resistant will be present. *Gastrointestinal* Diarrhoea, vomiting, abdominal pain, significant blood and/or mucus in stools, irregular or uncomfortable stools ± faltering growth *Skin* Severe atopic dermatitis ± faltering growth
Usually several of the following symptoms will be present *Gastrointestinal* Persistent irritability – 'Colic' Vomiting – Reflux, Gastro-oesophageal reflux disorder Diarrhoea-like stools – abnormally loose ± more frequent Constipation – especially soft stools, with excess straining Abdominal discomfort, painful flatus Blood and/or mucus in stools in otherwise well infant *Skin* Pruritus, erythema, non-specific rashes, moderate persistent atopic dermatitis	

Many clinical syndromes fall under the umbrella term non–IgE-mediated gastrointestinal food allergy including food protein-induced allergic procto-colitis (FPIAP), food protein-induced enteropathy (FPE), food protein-induced enterocolitis syndrome (FPIES), coeliac disease and CM allergy-induced iron deficiency anaemia[26].

FPIAP is a common manifestation of non-IgE-mediated CMPA in exclusively breastfed infants[27], although the exact prevalence is unknown[18]. In FPIAP, oedema and erosions may be noted in the mucosa of the distal sigmoid colon and rectum as a result of cell-mediated immunological reactions[28]. An eosinophilic infiltration of the epithelium and lamina propria may be found in histological investigations[28]. Symptoms of FPIAP typically occur in early infancy, usually with blood in the stool, which may be visible macroscopically or detected microscopically[18,28,29]. Apart from that, diarrhoea and mucus may also be present[27].

FPE usually affects the small intestine. T-cell mediated mechanisms are thought to be responsible for its occurrence and it may present with a patchy distribution, moderate crypt hyperplasia and mild-to-moderate increase in intraepithelial lymphocytes in the small intestine[30]. FPE usually manifests between 2 - 9 months of age and the characteristic symptoms include persistent diarrhoea and failure to thrive[27]. Yet the data on the existence of FPE in breastfed infants is scarce.

Acute FPIES typically presents in infancy[27]. Symptoms begin 1-4 hours after allergen exposure and include repetitive protracted vomiting, lethargy, pallor and diarrhoea. In chronic FPIES, symptoms occur with daily exposure to the allergen. Symptoms include intermittent vomiting, chronic diarrhoea, poor weight gain, and growth faltering[27]. However, FPIES triggered by food protein in breast milk is rare[31]. Characteristics of cardinal non IgE-mediated CMPA associated gastrointestinal allergy syndromes that can appear among breastfed infants are summarized in Table 2[27].

Table 2*: Characteristics of cardinal non-IgE-mediated CMPA associated gastrointestinal allergy syndromes among breastfed infants*

Non-IgE-mediated CMPA	Cardinal symptom	Additional symptoms
FPIAP	Blood in stools	Occasional loose stools, mucus in stools, painful flatus, anal excoriation
FPE	Failure to thrive, diarrhoea	Mucus and bloating, abdominal pain, faltering growth, hypoalbuminaemia
FPIES	*Acute FPIES*: vomiting 1–4 hours after ingestion *Chronic FPIES*: intermittent but progressive vomiting and diarrhoea	*Acute FPIES*: pallor, lethargy, hypovolaemia, hypotension, diarrhoea *Chronic FPIES*: growth faltering

FPIAP: food protein-induced allergic procto-colitis, FPE: food protein-induced enteropathy, FPIES: food protein induced enterocolitis syndrome

Diagnosis and management of CMPA in breastfed infants

The diagnosis of non-IgE-mediated allergy is based on an allergy-focused history[27]. History should be focused on:[6,25,32,33]

- Presenting symptoms, including
  - Age of onset
  - If more than one symptom, the sequence of clinical presentation of each one
  - Speed of onset of symptoms
  - Duration, severity and frequency
- Any personal or family history of atopy or food allergy
- Infant's feeding history – if they were breastfed, formula fed, started on complementary food
- Details of any concern with feeding difficulties and / or poor growth
- Details of previous management if any
- Details of maternal diet when the child is currently breastfed

As a part of the diagnosis and management, it is important to carry out a physical examination as well[23,34]. Findings from both history and examination enable the healthcare professional (HCP) to distinguish IgE-mediated reactions from non-IgE-mediated reactions, to decide on the tests needed to confirm the diagnosis and how to manage the food allergy. Tests for specific IgE antibodies are usually negative and endoscopy guided biopsies also have limited routine use in non-IgE-mediated CMPA. So, they should be restricted to cases that do not respond to dietary elimination or when differential diagnoses are considered[6,27].

The cornerstone for diagnosis of non-IgE-mediated CMPA in breastfed infants is a trial of maternal cow's milk elimination diet for 2 – 4 weeks with resolution of presenting symptoms, followed by reintroduction with symptom recurrence and deterioration unless a convincing history of FPIES or severe reactions were suspected at the beginning[23,25,27]. There has to be a strict elimination of food containing CMPs from the diet of the breastfeeding mother. Ideally it has to be guided by a nutritionist or a suitably qualified HCP[27] to avoid unnecessarily eliminating food allergens that can affect the health of the breastfeeding mother. Reading labels and watching out for hidden ingredients in food should be emphasized. Mothers must be given calcium and vitamin D supplementation during the CMP elimination period[25,27]. Special emphasis has to be made to actively supporting mothers to continue breastfeeding throughout the periods of diagnostic and therapeutic elimination of cow's milk products[25].

Exclusive breastfeeding has to be continued for the first 6-months[25]. Complementary foods can be started at 6-months of age while avoiding cow's milk containing foods. There is no benefit in postponement of the introduction of other possibly allergenic foods for infants[25]. For infants with confirmed CMPA, a cow's milk free diet is recommended until 9 – 12 months of age[25].

Conclusion

Evidence shows that the diagnosis and management of CMPA has room for significant improvement. Significant under-diagnosis, delayed diagnosis, incorrect diagnosis and inconsistencies in the decision to refer or not, were clearly demonstrated in relation to CMPA[35].

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