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REVIEW ARTICLE

Cow's Milk Protein Allergy

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Abstract
Cow's milk allergy refers to an immunological reaction to milk protein. It is one of the commonest food protein allergies with an estimated prevalence of 0.5% to 3% at 1 y of life. The disease may be IgE or non-IgE mediated or mixed with a wide range of symptoms often involving multiple organ systems. Gastrointestinal manifestations are common in non-IgE disease and may consist of enteropathy, proctocolitis, colic, reflux-like symptoms, constipation, enterocolitis syndrome and eosinophilic esophagitis. The gold standard for diagnosis remains a double-blind placebo-controlled oral challenge. Specific IgE and skin prick tests may predict severe and persistent disease, and aid in deciding on reintroduction or oral immunotherapy; however, they do not contribute to a definitive diagnosis as they indicate only sensitization. In practice, an elimination diet followed by open challenge under medical supervision is often used for diagnosis except when symptoms are severe such as anaphylaxis. Management consists of the elimination of the allergen with resolution of symptoms between 1-4 wk later depending on the type of allergy. Extensively hydrolyzed and Amino acid formulas are used to substitute milk in infants. Soy-based formulas are often utilized in resource-limited settings. Tolerance to the protein develops over time and periodic reintroduction should be attempted every six months after the initial one year of elimination diet. Oral immunotherapy is a newer treatment technique for IgE-mediated disease. There is no firm evidence on prevention apart from recommending breast feeding in early life along with initiating complementary feeding between 4-6 mo age.

Keywords Cow's milk protein allergy · Food protein allergy · Food protein-induced enteropathy (FPE) · Food protein-associated allergic proctocolitis (FPAP) · Food protein-induced enterocolitis syndrome (FPIES) · Chronic diarrhea

Introduction

Food allergies in children are quite significant in the developed world, affecting 4-8% of under-fives [1]; an increasing awareness in developing regions requires guidance on their accurate identification and management. Cow's milk protein allergy (CMPA) is one of the commonest food protein allergies in children and usually manifests in the first year of life. There are no epidemiological studies to estimate its prevalence from India with literature limited to hospital-based cohorts. Clinical presentation may be quite varied and involves multiple organ systems depending on the mechanism of allergy. A careful history and elimination of the offending food protein with a resolution of symptoms is often the best way to make the diagnosis. In this review, authors summarize the epidemiology, clinical presentation, diagnostic tools, and treatment of cow's milk protein allergy.

Epidemiology

CMPA refers to an immunological reaction to cow's milk. The estimation of the prevalence of milk allergy is complicated by the fact that it may be IgE or non-IgE mediated, and studies estimate its prevalence by different methodologies; for example, using self-symptom reporting, skin prick tests, IgE tests, food challenges and reporting of reactions to cow's milk. CMPA is increasingly being diagnosed in developing regions although it is unclear whether this is just due to increased awareness or an actual increase in incidence. Symptoms of CMPA, especially non-IgE mediated, overlap with common complaints in infancy like excessive crying, regurgitation, skin rashes which makes this condition susceptible to overdiagnosis [1]. Findings from the multicenter EuroPrevall cohort suggest the combined incidence of IgE

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and non-IgE mediated CMPA diagnosed by food challenge over the first two years of life to be less than 1% [2] with another birth cohort reporting incidence of 3.2% [3]. Rates of parental reported symptoms attributed to milk allergy on the contrary are substantially higher, upto 14-25% thus highlighting the importance of oral food challenge in the diagnosis [3, 4].

Clinical Features

The presentation of CMPA depends on the pathophysiology of the underlying allergy i.e., whether it is IgE mediated, non-IgE mediated or a mixed reaction (Table 1). CMPA may also occur in breastfed infants in whom symptoms are triggered by maternal ingestion of cow's milk proteins. Symptoms may develop minutes to weeks after exposure to cow's milk depending on the pathophysiology underlying the allergy.

IgE-Mediated Reactions

These generally occur immediately (within 1 h) but can occur within minutes to <2 h and may consist of symptoms involving skin, respiratory tract, gastrointestinal, neurological and cardiovascular systems with varying degree of severity. The classical oral allergy syndrome (OAS) consists of itching and mild swelling of lips and throat after intake of specific uncooked fruits and vegetables [5].

Non-IgE Mediated Reactions

These are generally delayed and manifest several days after exposure to the allergen (>4 h, usually within 5-7 d). These include the following clinical syndromes;

Food protein-induced enteropathy (FPE) presents in infants with anemia, diarrhea, vomiting, failure to thrive along with malabsorption syndrome [6]. They often have associated eczema and respiratory symptoms. Young infants may present with persistent diarrhea after a seemingly acute episode of enteritis and have an underlying CMPA [7].

Food protein-associated proctitis (FPAP) presents in children under 2 y of age, usually in the first 6 mo of life with rectal bleeding with or without diarrhea or irritability [8]. The children otherwise appear well. Endoscopy may show aphthous ulcers in the rectum and eosinophilic infiltration (>5/high power field). The condition is benign and resolves promptly on milk elimination.

Gastritis and gastroduodenitis may be a symptom in some children and CMPA is a possible cause of hematemesis in infants [9].

Food protein-induced enterocolitis syndrome (FPIES) is often a dramatic presentation of food protein allergy in infants and young children which has acute and chronic forms [10]. *Acute FPIES* presents with vomiting 1-4 h after ingestion of the potential trigger in the absence of classic IgE-mediated skin or respiratory symptoms. The diagnostic criteria for FPIES is described in Table 2 [10]. *Chronic FPIES* results from chronic intermittent exposure to the antigen (such as infant formula). These children present with intermittent vomiting and diarrhea which may be bloody with failure to thrive and in severe cases, dehydration. The symptoms are chronic and intermittent and lack the dramatic acute presentation. While FPIES is a *non*-IgE mediated process, concomitant IgE mediated sensitization to specific food allergens and other atopic features such as eczema are often present.

Mixed (IgE and Non-IgE) Mediated Reactions

Eosinophilic esophagitis (EoE) presents with symptoms of esophageal dysfunction i.e. chest and abdominal pain, vomiting, dysphagia, poor weight gain, reflux-like symptoms and esophageal stricture and may be associated with milk allergy [11]. About 5% of patients undergoing oral immunotherapy for milk allergy may also develop EoE. Endoscopy shows characteristic changes. In cases related to milk allergy, its exclusion causes improvement in symptoms, although usually an empirical six-food elimination diet is attempted.

Some studies assess the gastrointestinal manifestation of CMPA in the Indian setting. Yachha et al. reported CMPA as the cause of malabsorption syndrome in 13% of children

Table 1 Clinical manifestations of cow's milk protein allergy

IgE mediated	Non-IgE mediated	Mixed
Anaphylaxis	Food protein induced allergic proctocolitis (FPAP)	Food protein induced enterocolitis syndrome (FPIES)
Acute urticaria	Constipation	Atopic dermatitis
Oral allergy syndrome	Food protein induced enteropathy (FPE)	Eosinophilic esophagitis
Angioedema	Gastritis/Gastroduodenitis	Eosinophilic enteropathy
Food associated-exercise induced anaphylaxis	Reflux like symptoms, vomiting, feed refusal, dysphagia	
	Contact dermatitis	
	Heiner syndrome	

Table 2 Diagnostic criteria for patients with possible FPIES

Acute FPIES
Major criteria (Mandatory, PLUS)
Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria (≥3 in each episode)
1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency department visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5-10 h) 8. Hypotension 9. Hypothermia
Chronic FPIES
Severe presentation: When the offending food is ingested on a regular basis (e.g., infant formula) • Intermittent but progressive vomiting and diarrhea (occasionally with blood) • Sometimes with dehydration and metabolic acidosis
Milder presentation: Lower doses of the problem food (e.g., solid foods or food allergens in breast milk) • Intermittent vomiting and/or diarrhea • Poor weight gain/FTT • No dehydration or metabolic acidosis

FPIES Food protein-induced enterocolitis syndrome, *FTT* Failure to thrive

below 2 y of age [12]. Poddar et al. evaluated 164 consecutive children with chronic diarrhea and found that 40 (24.5%) had CMPA [9]. The mean age at diagnosis was 17+7.8 mo. Eighty-seven percent had diarrhea with 40% having blood in their stools. One-third had failure to thrive and 10% had a concomitant allergy to soya.

Natural Course of CMPA

The prognosis is generally good with children becoming tolerant to the protein by school age and most by adolescence. A Danish birth cohort reported tolerance in 87% of children at 3 y [13] while an Australian cohort of CMPA patients reported 78% at 6 y. The large multicenter multiregional EuroPrevall study which evaluated a 12049 children birth cohort across Europe reported the resolution of CMPA in 69% of children at 1 y (100% for Non-IgE and 57% for IgE) [2]. This study had significant methodological flaws and most likely underestimated non-IgE gastrointestinal cases of CMPA [14]. Recent studies seem to indicate that a smaller proportion of children achieve tolerance than previously reported with rates of 53-57% at 5 y [15, 16]. Tolerance occurs earlier with non-IgE mediated than those with IgE mediated symptoms and in those who are negative for cow's milk specific IgE. When followed up till adolescence a significant proportion of these children may develop asthma, eczema, allergic rhinitis and allergies to other food items [13].

Diagnosis

The diagnosis of CMPA is complicated by the fact that many symptoms may be non-specific and are shared with other common gastrointestinal and functional disorders.

The cow's milk-related symptom score (CoMiSS) is a symptoms assessment score for CMPA [17]. Its sensitivity varies from 20% to 70% and specificity 54% to 92% making it unsuitable as a stand-alone diagnostic tool, however, it may be useful to raise awareness about the possibility of CMPA as a cause of the infant's symptoms. Since no pathognomonic sign or symptom exists, a comprehensive history and physical examination remains essential. History consists of type of feeding- whether breast fed or formula fed, parental history of atopy, symptoms involving multiple organ systems, temporal relation to cow milk intake and must attempt to rule out common diseases with similar symptoms and establish concurrent conditions.

Specific serum Immunoglobulin E (sIgE) can be measured against whole milk and component proteins of milk such as casein, alpha lactalbumin and betalactoglobulin. While whole milk, casein, alpha-lactalbumin and beta lactoglobulin are major allergens, even proteins such as bovine serum albumin and lactoferrin which are present in small quantities can cause allergy. Only about 26% of cases are mono-sensitized, the majority being sensitized to multiple proteins in cow's milk. The utility of specific IgE in the diagnosis and treatment of CMPA needs to be understood

with nuance. These tests indicate sensitization and do not necessarily predict that the symptoms result from allergies. However, sensitivity to casein, beta lactoglobulin and alpha-lactalbumin is closely related to milk allergy. The sensitivity of sIgE at diagnosis and its persistence indicates a prolonged time to develop tolerance to milk and milk products compared to patients with negative or transiently positive IgE [18]. IgE-positive CMA was also more likely to be allergic to inhaled allergens and other food. Another utility is a prediction of an adverse reaction to oral immunotherapy (OIT). Levels >50 kUA/L have been reported to predict non-tolerance to OIT [19]. Sensitivity to casein at particular cutoffs has been shown to predict children with high anaphylaxis risk [20]. While ordering/interpreting these tests it is important to remember that the method/manufacturer used in practice should be the same one in the publication guiding the clinical decision making [21] as results are not interchangeable.

Skin prick tests (SPTs) can be done with commercial extracts or fresh food. A wheal size of >5 mm (>2 mm in infants <2 y) is associated with higher specificity. The wheal size is significantly larger in children who have persistent disease and hence may be used as a prognostic indicator. Infants who have a negative SPT or sIgE become tolerant to milk much faster. A negative SPT and sIgE also reduce the likelihood of having a severe reaction to milk in an oral challenge test. Children who have early onset symptoms which are severe and likely to be IgE mediated such as angioedema, vomiting and urticaria and have a >7 mm wheal are more than 90% likely to have a positive reaction to an oral challenge and this may be avoided till SPT decreases in size.

None of the available diagnostic tests can prove or disprove a diagnosis of CMPA. The gold standard remains an allergen elimination diet and rechallenge. Clinicians may consider getting specific IgE levels and doing skin prick tests to characterize the course of the illness in the child and possibly guide decisions regarding future rechallenges and treatment with oral immunotherapy.

Diagnostic Elimination Challenge

Guidelines recommend that the diagnosis of CMPA may be made by complete elimination of cow's milk from the diet with resolution in symptoms [22]. In the case of non-IgE mediated symptoms, this may take more than 5 d to happen. The diagnosis may then be confirmed with a supervised oral challenge test. If symptoms do not substantially improve or disappear after elimination, the diagnosis of CMPA is doubtful. However, the "improvement" must be objective and definitive. For example, some parents might report that their child's symptoms of constipation are "much better" after milk elimination but the child remains on laxatives and continues the unnecessary elimination diet. This also raises the issue of overdiagnosis of CMPA. Symptoms such as constipation, diarrhea, colic, gastro-esophageal reflux, blood or mucus in stools, feeding issues and rashes are almost universally cited as indicators of cow's milk allergy. For most infants, these symptoms have no connection with milk allergy and even blood in the stools of infants consuming cow's milk formula is most often not a reproducible cow's milk allergy symptom. Therefore, the symptoms that are suspected to be due to CMPA must be carefully defined and their resolution on milk elimination must be objectively demonstrated before making a diagnosis [23–25].

Food Challenge Test (OFC)

The gold standard for the diagnosis of food allergy is a double-blind placebo-controlled food challenge (DBPCFC). This is time-consuming, expensive, and cumbersome. Therefore, an open food challenge is usually done. In case of non-IgE mediated symptoms, milk is gradually introduced under medical observation for a few hours and the child is sent home on milk. If no symptoms occur in 2 wk, the diagnosis of milk allergy is ruled out. In the case of IgE-mediated allergy, a more strictly supervised challenge with graduated doses of the allergen is conducted while in the hospital. OFC results do not predict the severity of the subsequent reactions [26]. There is no correlation between the eliciting threshold experienced by a child during an OFC and the severity of the reaction upon accidental exposure [27]. Repeat challenges are required to demonstrate tolerance with age and restart the food in the diet.

Endoscopy and biopsy may be required in children presenting with gastrointestinal symptoms as these have a wider differential diagnosis. While these are not necessary for making a diagnosis, endoscopic findings include aphthous ulcers in the rectum in allergic proctocolitis. Biopsy shows eosinophilic infiltration or villous atrophy in duodenal biopsy and eosinophilic infiltration in rectal biopsies.

Treatment

Eliminating cow's milk protein from the diet and its timely and safe reintroduction forms the basis of management. Unlike other allergens, this is challenging since it forms a major part of the nutritional need of the growing infant and inadequate replacement of energy sources and micronutrient supplementation may be detrimental for the infant and the mother. All efforts must be made to promote breastfeeding as the preferred modality of infant feeding.

Table 3 Hydrolyzed and soy-based formulae available in India

Formula	Products	Manufacturer	Remarks	Calories
Soy protein-based	Isomil Zerolac	Abbott Raptakos, Brett	Lactose-free, has sucrose Lactose, sucrose free	65-69 kcal/100 ml
Extensively hydrolyzed	Alimentum Aptamil Pepti	Abbott Nutricia	Lactose-free, casein based, Age <2 y Has lactose, whey based	66-69 kcal/100 ml
AA Formula	Neocate Alfamino	Nutricia Nestle	Contains PUFA, MCT (33-70%) Corn syrup, potato starch	67 kcal/100 ml

AA Amino acid, *MCT* Medium chain triglycerides, *PUFA* Polyunsaturated fatty acids

Breastfed Infants

Breastfeeding continuation should be encouraged after discussion with the family. It presents a unique scenario where the maternal diet should be modified to avoid all products containing cow milk protein (including cheese, yogurt, and butter). Discussion with a dietician is essential to prevent inadvertent exposure to the infant via complementary feeding.

Formula-Fed Infants or Those on Mixed Feeds

Extensively Hydrolyzed Formula

Whey or casein-based extensively hydrolyzed formula (EHF) is considered first-line therapy for formula-fed infants with cow milk allergy [22]. They consist of short peptides (molecular weight of less than 3000 Da) produced after enzymatic breakdown and ultrafiltration of cow's milk protein. About 90% of children with cow milk allergy show a significant response to EHF and these formulae are nutritionally complete and well-tolerated in most children.

Extensively hydrolyzed rice protein-based infant formula (eRHF) may also be used as an alternative with good safety and efficacy where it is available.

Amino Acid-Based Formula (AAF)

These are formulae containing free amino acids which are used to treat infants with a severe allergy to cow's milk protein. These are not used as first-line therapy and are indicated in infants with (i) non-response to EHF when CMPA is still a high clinical suspicion, (ii) life-threatening allergic manifestations such as anaphylaxis, (iii) multiple food allergies. These formulae have a significant cost burden. There are concerns regarding hypophosphatemia with prolonged AAF use; thus, diagnosis and treatment should be considered certain before initiation of AAF [28].

Soy Protein Formulas

Cross reaction to soy protein is seen in 10-15% of these infants, and it is not recommended in infants under 6 mo of age due to safety issues [29]. Better palatability and cheaper cost of soy-based formula especially in resource-limited regions lead to it being an alternative in infants with mild-moderate CMPA. Tables 3 and 4 contain commercially available formulae available in India; and food instructions and precautions to be taken while caring for a child with CMPA [30].

There is limited low-quality evidence on probiotic supplementation [31].

Follow-Up and Reintroduction

Monitoring for the resolution of allergy is essential as most children outgrow the allergy in childhood. The elimination diet should be continued for at least a year in those with IgE-mediated reactions and for 6-12 mo in those with non-IgE-mediated reactions. The child should be assessed for the reintroduction of milk every 6 mo. Infants with IgE-mediated allergy may tolerate cow milk in extensively heated formulations e.g. in baked goods and the intake of such foods can be allowed if it was tolerated regularly in the past. In contrast, strict exclusion of cow milk protein in all forms is recommended in patients with mixed and non-IgE mediated allergy.

Formulae with an intermediate degree of hydrolysis (partially hydrolyzed formula or pHF) are being studied and incorporated into "milk ladders" which can be potentially used for a more controlled introduction of cow's milk and thus improve tolerance [32].

Allergen Immunotherapy (AIT)

Allergen immunotherapy consists of actively introducing small quantities of the antigen to attempt the development of tolerance (desensitization) as opposed to withdrawing it altogether. It is a strategy used for confirmed persistent systemic IgE mediated food allergy and has been used for Cow's milk, Hen's eggs and Peanuts in children. The process is usually initiated at 4 to 5 y of age. The aim is to increase the threshold for clinical reaction to the offending antigen while the child is on AIT.

Table 4 List of safe and harmful foods for infants and children with CMPA

Foods	Safe	Harmful
Milk & milk products	Soya milk, badam milk, coconut milk	Low lactose milk, casein, milk solids, whey, milk fat, lactose **All milk products**: Buttermilk, cream, whipped cream, sour cream, yogurt, ice cream, ice milk, butter, processed cheese, cottage cheese, cream cheese
Cereals	Infant cereals, cooked or dried cereals Macaroni, spaghetti, other noodles Rice and other grains Bread, rolls, buns, biscuits, and cookies Flour (**without** milk or milk products, whey, or casein added)	Infant cereals, dry or in a jar, **which** have milk or milk products Dry cereal All breads, rolls and buns Prepared mixes such as cake, pancake, muffin, biscuits **with** added whey, casein or milk solids Chips **with** cheese, cream, or whey
Proteins	Homemade pulses and meats Dry nuts	Processed, tinned and canned meats, legumes and nuts – read labels for milk proteins
Fats	Margarine, vegetable oils, such as soybean, corn, olive, cottonseed, safflower, and peanut oil, salad dressing (**without** milk products added) Mayonnaise	Milk fat, cream, butter, sour cream, margarine **with** milk, whey, or casein added Salad dressing **with** milk, milk products, yogurt or cheese added
Desserts	Fruit and flavoured ices, gelatine desserts Frozen desserts made with soy protein or tofu Homemade pudding, cakes, pies and cookies made with **milk substitutes** and other safe items Clear candies, chewing gum, baking chocolate and cocoa	Dairy and milk desserts: ice cream, ice milk, yogurt, sherbet, pudding, custard Desserts made **with** caseinate Whipped toppings or liquids that **contain** milk, whey, or cream Frozen desserts, made with **milk or milk products;** Cake, cookie or muffin mixes that contain milk or milk products Candies that do not list ingredients. Also, caramels, butterscotch or any candies such as toffee that **contain** milk, milk products or lactose Cocoa mixes or chocolate syrups **with** milk products Fudge, milk chocolate or yogurt coatings **with** milk fat and/or whey, white chocolate **with** milk or milk products added
Other foods	Tea, coffee, salt, pepper, pure spices and herbs, monosodium glutamate (MSG), pure flavourings, mustard	Flavoured coffees with sodium caseinate Condiments **that contain** cream, lactose, milk or milk products

CMPA Cow's milk protein allergy

The antigen may be given orally or sublingually or both routes (sublingual followed by oral). Data published to date do not allow to recommend a standardized treatment protocol [33, 34] including doses and intervals and measures of effectivity and the major concern is the occurrence of an allergic reaction which may progress to anaphylaxis. It needs to be performed under the close supervision of experienced personnel and with resuscitation facilities after discussion of potential risks and benefits with the family and assessment for contraindications. Long-term outcomes are unclear and further studies are needed.

Prevention- Is It Possible?

A systematic review by Kramer et al. which included evidence from five trials concluded that avoiding the culprit antigen during pregnancy and lactation by modification of the maternal diet was unlikely to reduce the risk of atopy in the newborn baby [35]. Probiotic supplementation antenatally has also not been shown to be of benefit [36]. Timely introduction of cow's milk protein along with complimentary feeding between 4-6 mo of age seems to be the most useful approach with no robust evidence in favor of the delayed introduction of potentially allergenic foods.

Conclusions

Cow's milk is the most common allergen in children. CMPA has an IgE or non IgE or a mixed pathophysiology and may present with a wide spectrum of symptomatology, some of which may mimic common childhood conditions. Caution and careful evaluation is needed to prevent overdiagnosis

and unnecessary elimination diets. Management includes elimination of milk and milk products in the diet, use of appropriate milk substitutes and ensuring adequate growth and nutrition. The choice of substitutes needs individualization considering various factors such as age, severity of symptoms, palatability and cost. Modalities such as allergen immunotherapy may be required for a subset of patients. The majority of children outgrow the condition by 5 y age.

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Declarations

Conflict of Interest None.

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