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Milk Allergy: Significance, Detection, and Management

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Abstract

Milk allergy is a significant public health issue, particularly among infants and young children, with prevalence rates between 2 and 6% in early childhood, declining to 0.1–0.5% in adulthood. It is an immune-mediated adverse reaction to milk proteins, primarily involving immunoglobulin E (IgE)-mediated responses. Symptoms range from gastrointestinal distress and respiratory complications to severe anaphylaxis. The etiology of milk allergy involves genetic predisposition, environmental factors, an immature immune system, and early exposure to formula feeding. Detection methods for milk allergens include skin prick tests, double-blind placebo-controlled food challenges, atopy patch tests, and radio allergosorbent tests. Additionally, analytical techniques, like ELISA, LC-MS/MS, and lateral flow assays are employed for precise allergen identification. Management strategies focus on minimizing milk allergenicity through various processing techniques, such as heat treatment, enzymatic hydrolysis, glycation, lactic acid fermentation, and high-pressure treatment. These methods alter the protein structure to reduce immunogenicity. For individuals with milk allergies, alternative formulas, like soy-based, extensively hydrolyzed, and amino acid-based formulas provide safe nutrition. Regulatory frameworks, including mandatory allergen labeling in many countries, help protect allergic individuals by ensuring transparency in food products. However, India lacks comprehensive allergen labeling except for infant milk substitutes. In conclusion, milk allergy remains a pressing concern, necessitating advancements in detection, processing, and regulatory measures to ensure consumer safety. Ongoing research in allergenicity reduction and improved diagnostic tools will contribute to better management and quality of life for affected individuals.

Keywords: Milk allergy, enzymatic treatment, ELISA, LC-MS, antibody

INTRODUCTION

Food allergies pose a significant global public health issue. The concept of "allergy" was first introduced in 1906 by Austrian pediatrician Clemens von Pirquet. A food allergy is characterized by an abnormal immune response triggered by specific food proteins [1]. In some cases, the immune system, which typically produces antibodies to defend against harmful pathogens, mistakenly identifies these proteins as threats, leading to an adverse reaction. Hippocrates, before 370 BC, was the first to document adverse reactions to milk, noting skin and gastrointestinal issues following its consumption. Approximately five centuries later, Galen of Pergamum, a Greek medical researcher, established a link between these symptoms and milk intake. Food allergies are estimated to affect 1–3% of adults and 4–6% of children under the age of three, with over 70 different foods identified as potential allergens. Adverse food reactions are generally categorized as either toxic or nontoxic [2, 3].

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TYPES OF ALLERGENS

The most prevalent food allergens include eggs, fish, cow's milk, shellfish, peanuts, soy, tree nuts, and wheat. Additionally, cereals, fruits, and vegetables are known to cause allergic reactions, though less frequently. In general, the key food allergens are water-soluble glycoproteins with molecular weights between 10 and 60 kDa, which remain resistant to processing methods, such as heat, acidic conditions, and enzymatic breakdown by proteases. Allergic reactions are categorized into two types: immediate and delayed. In immediate reactions, symptoms develop within minutes or hours of exposure to an allergen, and skin tests typically yield positive results. Conversely, delayed reactions may take several hours or even up to two or three days to appear, with skin tests often showing negative results. Clinical symptoms of food allergies can manifest in various forms, including systemic reactions, such as anaphylaxis, gastrointestinal issues, like vomiting, diarrhea, abdominal pain, and chronic constipation, respiratory problems, such as rhinitis, asthma, and pneumonitis, as well as skin-related conditions like urticaria, eczema, atopic dermatitis, and pruritus [4].

Milk Allergy

Milk allergy is an immune-mediated adverse reaction triggered by milk proteins, often involving interactions between multiple milk proteins that lead to immediate immunoglobulin E (IgE)-mediated responses. It is typically the first food allergy to develop in childhood, as milk constitutes a significant part of an infant's diet. The prevalence of milk allergy is estimated to be between 2 and 6% in young children but tends to decline with age, reaching approximately 0.1–0.5% in adulthood [5].

Research suggests that infants often develop milk allergies because milk is one of the first foreign antigens they consume in significant amounts. Their digestive and immune systems are not yet fully developed, making it difficult to process and tolerate milk proteins. Eliminating milk from the diet helps control inflammation, and over time, oral tolerance can develop, allowing milk consumption without adverse reactions. Epidemiological studies indicate that milk protein allergy is the most common food allergy among infants, with prevalence rates ranging from 2% to 7.5% in population-based studies across various countries [6].

Milk allergies tend to resolve over time, with studies showing that 19% of affected children outgrow it by the age of 4, 42% by 8 years, 64% by 12 years, and 79% by 16 years. Various factors contribute to the development of milk allergy, including genetic predisposition, environmental influences, an immature immune system, an underdeveloped digestive tract, and early exposure to formula feeding. The condition presents a broad range of symptoms, with immediate reactions, such as vomiting, hives, swelling of the lips or eyelids, wheezing, rhinitis, and persistent dry cough. In contrast, delayed symptoms may include dermatitis, diarrhea, iron deficiency anemia, and constipation. Severe allergic reactions, such as anaphylaxis, can be life-threatening and may present symptoms like noisy or difficult breathing, swelling of the tongue, throat tightness, and trouble speaking or a hoarse voice, particularly in young children. Milk is composed of approximately 3–3.5% protein and contains over 25 different proteins, though only a few are known to trigger allergic responses [7]. Clinical challenge tests indicate that individuals with milk allergies typically react to multiple protein fractions, with each allergenic protein containing several epitopes distributed throughout its molecular structure. The variation in protein composition between cow's milk and human milk is believed to contribute to milk allergies in infants. Additionally, human milk has a higher concentration of immunological components, which helps strengthen an infant's immune system and may reduce the risk of developing milk allergies [8].

MECHANISM OF ALLERGIC REACTION

Milk allergy can occur due to the interaction of one or more milk proteins with the immune system, involving various immune responses. Most milk allergies are linked to IgE-mediated reactions. There are four main types of hypersensitivity reactions (I, II, III, and IV), each engaging different immune component. Type I is characterized by anaphylaxis (IgE-mediated), type II involves antibody-dependent cytotoxicity (IgG and IgM), type III is immune complex-mediated, and type IV is delayed hypersensitivity (involving T-cells). Approximately 60% of milk allergies are attributed to the IgE-mediated mechanism. Symptoms associated with IgE reactions typically appear quickly, within 1-2 hours of milk consumption, affecting the skin, respiratory system, gastrointestinal system, and, in severe cases, leading to systemic anaphylactic responses [9, 10].

METHODS FOR DETECTION OF MILK ALLERGENS

The clinical diagnosis of milk allergy can vary significantly due to the wide range of symptoms [11]. Common diagnostic tests include the Skin Prick Test (SPT), Double-Blind Placebo-Controlled Food Challenge (DBPCFC), Atopy Patch Test (APT), Elimination Challenge Test, and Radio Allergo Sorbent Test (RAST) [12, 13]. In addition to these, other analytical techniques, such as ELISA, Rocket Immunoelectrophoresis Test (RIE), LC-MS/MS, and Lateral Flow Kits are also used to detect allergens, each with a specific minimum detection limit for different allergens [14, 15].

MANAGEMENT OF MILK ALLERGY

The management of milk allergy typically involves reducing the allergenic potential of milk proteins through various methods and using milk substitutes. Additionally, it includes controlling allergens at the plant level to prevent contamination [16].

Measures to Reduce Milk Allergenicity

Various efforts have been made to lessen the allergenicity of milk proteins, with several technological processes being applied to improve the use of milk in infant formulas [17–19].

Heat Treatment

Heating milk at 95°C for 60 minutes does not alter the immunoreactivity of casein. However, heating whey proteins between 50 and 90°C increases their allergenicity due to the unfolding of their native structure, which exposes hidden allergenic epitopes. When the temperature exceeds 90°C, the allergenicity of whey protein appears to decrease because of sulfhydryl-disulfide exchange, which promotes conformational changes that can destroy or mask the conformational epitopes on the protein's surface. Heating milk at 120°C for 15 minutes does not impact the antigenicity of casein from cows, buffalo, or goats. Therefore, simple heat treatment is not the most effective method for reducing milk allergenicity [20–23].

Enzymatic Treatment

- *Hydrolysis:* Hydrolysis involves breaking down proteins into smaller proteins or amino acids using enzymes, such as trypsin, protease, pepsin, and chymotrypsin. This process can eliminate conformational epitopes, potentially reducing the allergic potential of the proteins. However, enzymatic digestion may also generate new antigenic substances that could increase allergenicity [23].
- *Cross Linking with Transglutaminase:* The transglutaminase enzyme can bind β-lg and α-la by forming intra- and intermolecular ε-(γ-glutamyl) lysine bonds. For β-lg, transglutaminase-induced polymerization may lower its allergenic potential by concealing its allergenic epitopes, making them unavailable to interact with the immune system.
- *Glycation and Maillard Reaction:* Conjugating β-lg with the oligosaccharide carboxymethyl dextran enhances the emulsifying properties of the protein while reducing its allergenic potential at temperatures between 40°C and 60°C. This effect is influenced by the number of conjugated saccharides, their molecular weight, and the extent of the Maillard reaction [24, 25].
- *Lactic Acid (LA) Fermentation:* Proteolytic enzymes generated during lactic acid fermentation can break down certain allergenic epitopes in proteins, thereby reducing the allergenicity of milk. Fermentation using a combination of *L. helveticus and S. thermophilus* strains reduces the antigenicity of β-lg by 86–95% and α-la by 53–87%.
- *High Pressure Treatment:* When milk is treated with high pressure, ranging from 200 to 600 MPa at temperatures between 30°C and 68°C, the allergenicity of β-lg in the whey can be reduced. However, increased allergenicity can also occur due to the exposure of previously hidden allergenic epitopes within the protein structure.

- *Microwave Treatment:* Microwave treatment speeds up the hydrolysis of β-lg, which helps to reduce its allergenic potential**.**
- *Ultrasound:* Through enhanced hydrolysis, a complete hydrolysate with no allergenicity and a partial hydrolysate with significantly reduced or absent allergenicity can be created [26].

Milk Alternatives

The primary treatment for milk allergies involves strictly avoiding milk and milk-based products to prevent exposure to the allergens. Three types of infant formula – soy, extensively hydrolyzed, and amino acid-based formulas – are suitable for managing milk allergy**.**

MANAGEMENT OF ALLERGEN AT PLANT LEVEL

To manage food allergens at the plant level, several strategies are implemented, including policies and guidelines, supply chain management, staff training, communication, and proper manufacturing practices [27].

Labeling Requirement

According to the Codex Alimentarius Commission, it is mandatory for food labels of member countries to contain the names of common food allergens. Many countries, like Brazil, Chile, and Asian countries, like Malaysia, Japan, China and European Union, have such labeling regulation. In India, there is no mandatory labeling of food allergen specified in the food except for Infant Milk Substitute. The mandatory labeling for allergenic foods for Infant Milk Substitute; Clause 7 of Regulation No. 2.4.1 states – The container of infant milk substitute meant for infants with allergy to cow's/ buffalo's milk protein or label affixed there to indicate conspicuously "HYPOALLERGENIC FORMULA" in capital letters and statement "TO BE TAKEN UNDER MEDICAL ADVICE" [28].

CONCLUSIONS

Allergy has become a significant concern in recent times, with milk being one of the primary food allergens that can trigger allergic reactions in both infants and adults. There are two main types of allergic reactions: immediate and delayed. In milk allergy, IgE plays a crucial role in triggering the reaction. Typically, gastrointestinal and respiratory symptoms are observed. Factors, such as genetics, environmental influences, an underdeveloped immune system, an immature intestinal tract, and early formula feeding contribute to the development of milk allergies. Various methods, including SPT, DBPCSC, and ATP, are used to detect allergies. Processing techniques, like heating, enzymatic hydrolysis, lactic acid fermentation, and certain nonthermal treatments, can effectively reduce the allergenicity of milk proteins by optimizing processing conditions. To enhance consumer protection and improve the quality of life for sensitized individuals, regulations have been put in place, requiring the labeling of potentially allergenic ingredients, including milk.

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