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A Comprehensive Review on Milk Allergens

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ABSTRACT

Cow's milk allergens are a predominant source of food allergies worldwide, especially impacting infants and young children. This extensive review offers a thorough analysis of the allergens found in cow's milk, their molecular characteristics, allergic mechanisms, and clinical symptoms. The review investigates. The main milk proteins that trigger allergic reactions, such as caseins and whey proteins. The genetic, environmental, and immunological factors that lead to the development of milk allergies Diagnostic techniques, including skin prick tests, serum IgE tests, and oral food challenges Current treatment approaches, such as avoidance, dietary management, and new therapies like immunotherapy The review further discusses the difficulties in managing milk allergies, particularly concerning infant nutrition and food safety. It emphasizes the necessity for continuous research to enhance the understanding of the pathophysiology of milk allergies and create more effective treatments for individuals affected.

Keywords: Milk, Milk allergens, Milk Proteins, Immunotherapy

Introduction

Milk allergy is a common condition, particularly among infants and small children, in which the immune system reacts excessively to certain proteins found in milk, such as casein and whey. In contrast to lactose intolerance, which results from the body's inability to break down milk sugar, a milk allergy provokes an immune response, resulting in symptoms that can range from mild skin rashes to life-threatening anaphylaxis. Milk allergens are thoroughly researched due to their common occurrence in diets and the potential seriousness of reactions. Around 2-3% of infants around the globe are impacted, with most outgrowing the allergy by the ages of 3 to 5. Nonetheless, some individuals may continue to have the allergy into their adult years. This review intends to present a comprehensive analysis of milk allergens, their effects on public health, diagnosis, management, and emerging therapies. [16][2]

1.Milk allergens

1.1. Definition

Despite continuous conversations, the word "allergy" is still inadequately defined, which creates uncertainty among healthcare providers. Terms such as "allergy," "intolerance," and "hypersensitivity" are frequently misused or regarded as synonymous. Nonetheless, the accepted definition of an allergy pertains specifically to an excessive reaction caused by a particular immune response. Importantly, people who find it difficult to process lactose do not suffer from a lactose allergy, but instead from lactose intolerance, which is a separate condition. [8]

1.2. Milk Allergen Composition

Bovine milk comprises 3-3. 5% protein, which is categorized into two primary groups: caseins (80%) and whey proteins (20%). These proteins possess unique physico-chemical and allergic characteristics. [2] [6]

Caseins
Caseins represent the main portion of milk proteins and are categorized into several families, such as αS1-, αS2-, β-, κ-, and γ-caseins. αS1-caseins are

the most prevalent, making up as much as 40% of the casein fraction. They are made up of both major and minor components that vary in their degrees of phosphorylation. [3] [5] [11]

Whey Proteins

The primary allergenic elements in the whey portion are β-lactoglobulin (β-LG) and α-lactalbumin (ALA). β-LG is the most plentiful protein found in whey, comprising 50% of the overall protein content. It belongs to the lipocalin superfamily and is capable of binding different molecules, including retinol, β-carotene, and fatty acids. ALA is a calcium-binding protein that constitutes around 25% of whey proteins. It plays a vital role in the production of lactose and regulates physiological processes in the mammary gland.[2] [8] [4][9] [12] [16]

1.3.Key differences between caseins and whey proteins:

Caseins exhibit greater hydrophobicity, whereas whey proteins show higher hydrophilicity.

Caseins form aggregates due to anionic regions, which have the ability to chelate metal ions.Whey proteins, such as β-LG, possess a more intricate structure with disulfide bonds and lipid binding functions.

Grasping the composition and characteristics of milk allergens is crucial for creating successful diagnostic and therapeutic approaches. [10] [7] [8]

1.4. Key Cow's Milk Allergens

The main allergens found in cow's milk are proteins present in two primary fractions: casein (αs1-, αs2-, β-, and κ-casein) and whey (α-lactalbumin and β-lactoglobulin). Interestingly, some people may have cross-reactivity with soy protein, especially during non-IgE-mediated allergic responses.

2. Prevalence of Cow's Milk Allergy

The occurrence of cow's milk allergy (CMA) differs considerably based on the diagnostic criteria and the population examined. Estimates fluctuate from Under 1% grounded on oral food challenges, 1-4% per most review articles, As high as 10% stemming from caregiver reports and clinical suspicion.

A 2015 European research identified a diagnosis confirmed by challenge at 0. 54%, displaying considerable variation in non-IgE-mediated allergy among different countries. A recent systematic review placed the self-reported lifetime prevalence of CMA at 5. 7%, while the point prevalence of food-challenge-verified allergy was 0. 3%. In the United States, Food Protein-Induced Enterocolitis Syndrome (FPIES) impacts about 0. 51% of children under 18, whereas Food Protein-Induced Allergic Proctocolitis (FPIAP) may occur in as many as 17% of infants. [15] [7][8] [6]

3.Types of Allergic Reactions

Allergic responses can be generally divided into immune-mediated and non-immune-mediated occurrences. Immune-mediated reactions can be further separated into four key types:

1. IgE-mediated reactions

2. Non IgE mediated reactions

3. Mixed reactions

4. Cell-mediated reactions

In the situation of cow's milk allergy (CMA), non-IgE-mediated mechanisms are the most prevalent cause.

3.1. IgE and Non-IgE-Mediated Allergies

Two main mechanisms clarify allergic reactions to cow's milk and other food allergens:

1. IgE-mediated reactions, which involve the immune system's IgE antibodies

2. Non-IgE-mediated reactions, which do not engage IgE antibodies

Typical symptoms of IgE-mediated CMA include acute hives and swelling. Non-IgE-mediated CMA commonly impacts the skin and gastrointestinal system, with presentations that include:

1. Cow's milk-induced enterocolitis syndrome (affecting the entire gastrointestinal tract)

2. Cow's milk-induced enteropathy (affecting only the small intestine)

3. Cow's milk-induced proctitis and proctocolitis (affecting the rectum and colon)

3.2. Clinical Symptoms of Cow's Milk Allergy

Cow's milk allergy (CMA) mainly impacts infants and young children, with symptoms usually emerging within the initial six months of existence. The majority of affected infants experience symptoms within a week of the introduction of cow's milk proteins into their diet, although some may have reactions earlier or later. Breastfed infants may also experience symptoms if their mothers consume dairy products.

CMA symptoms can affect various organ systems, especially the gastrointestinal tract and skin. Common symptoms consist of:

1. Gastrointestinal issues
2. Skin reactions
3. Allergic shiners (dark circles under the eyes)
4. Mouth ulcers
5. Joint pain and hypermobility
6 Sleep disturbances
7. Night sweats
8. Headaches
9. Bedwetting

Non-IgE-mediated CMA symptoms often manifest with a delay, usually occurring more than two hours after ingestion, impacting primarily the gastrointestinal tract and/or skin.

Conversely, IgE-mediated CMA symptoms, such as hives, angioedema, vomiting, and wheezing, generally arise within minutes to two hours following the ingestion of cow's milk protein. The skin is most often involved, followed by the gastrointestinal tract, and to a lesser extent, the respiratory and cardiovascular systems.

Although most reactions are mild to moderate, life-threatening anaphylaxis can take place in about 1-2% of cases. Cow's milk, together with peanuts and tree nuts, is among the most prevalent foods capable of causing anaphylactic reactions. [6] [8]

3.3. Comparing IgE-Mediated and Non-IgE-Mediated Allergies

Characteristic	IgE – Mediated allergies	Non – IgE – Mediated Allergies
Reaction Time	Symptoms emerge within minutes to 2 hours after exposure	Symptoms arise several hours to days after contact
Severity	Can vary from mild to potentially life-threatening anaphylaxis	Generally mild to moderate reactions
Duration	Symptoms may continue beyond 1 year of age	Symptoms typically resolve by 1 year of age
Diagnosis	Verified through specific serum IgE tests and skin prick tests	Identified through oral challenge assessments

These unique characteristics can assist healthcare professionals in correctly diagnosing and managing IgE-mediated and non-IgE-mediated allergies. [6]

3.4. Other IgE-Mediated Disorder

Alongside cow's milk allergy (CMA), there are additional IgE-mediated disorders, which include:

1.Food protein-induced enterocolitis syndrome (involving the entire gastrointestinal system)

2. Food protein-induced enteropathy (affecting the small intestine)

3. Food protein-induced proctitis and proctocolitis (involving the colon and rectum)

4. Food-induced pulmonary hemosiderosis (Heiner's syndrome)

Mixed IgE- and Non-IgE-Mediated Reactions

Certain conditions feature a blend of IgE- and non-IgE-mediated responses, impacting the skin and/or gastrointestinal system. Examples consist of Allergic eosinophilic gastrointestinal disorders, Atopic dermatitis (eczema)

Outgrowing Cow's Milk Allergy

A majority of children surpass CMA during their early childhood or teenage years. Non-IgE-mediated CMA has a higher chance of being outgrown compared to IgE-mediated CMA. Children exhibiting elevated levels of milk-specific IgE antibodies, numerous food allergies, and/or asthma and allergic rhinitis have a reduced likelihood of outgrowing CMA.

Predicting Tolerance to Cow's Milk

Studies indicate that children with low IgE levels binding to cow's milk and specific IgE binding to particular milk proteins are more inclined to acquire tolerance. Furthermore, milk-specific IgE levels, outcomes from skin prick tests, and the degree of atopic dermatitis can forecast the resolution of CMA within the initial 5 years of life. A web-based tool is accessible to assess the prognosis of children with CMA, though validation studies remain necessary. [8]

4.Symptoms and Diagnosis

Symptoms of CMA, which include anaphylaxis, are non-specific and can result from numerous diseases or allergies, complicating the diagnosis. [8] [13

4.1. Management and Treatment

The objectives of CMA management include:

1. Alleviating symptoms

2. Developing tolerance to cow's milk

3. Promoting normal growth and development

At present, there is no definitive therapy for CMA except for oral immunotherapy (OIT), which may help certain patients achieve tolerance. Typical management entails avoiding cow's milk protein.

Breast milk is the advised first-line management strategy for breastfed infants with CMA. For infants on formula, a cow's milk-based extensive hydrolysate (eHF) is frequently suggested, although some infants might react to residual peptides.

Hydrolysed rice formulas (HRFs) and amino acid-based formulas serve as alternative choices that do not contain cow's milk proteins. [1] [8][18] [13]

5.Diagnostic Methods for Cow's Milk Allergy

The World Allergy Organization (WAO) offers comprehensive guidelines for the diagnosis of cow's milk allergy (CMA) [109]. The diagnosis consists of:

1. Clinical history

2. Diagnostic tests

5.1.1. IgE-Mediated Allergy Diagnosis

Specific IgE antibody assays (e. g., CAP-FEIA System or UniCAP)

Skin prick tests (SPT) for quick detection of sensitization

5.1.2. Non-IgE-Mediated Allergy Diagnosis

Atopy patch tests (APT) to identify delayed responses

Gold Standard Diagnosis

Double-blind placebo-controlled oral food challenge (DBPCFC) to confirm diagnosis

5.1.3. Diagnostic Tests

SPT: SPT is a quick, cost-effective technique for identifying IgE-mediated sensitization

APT: APT is helpful in diagnosing non-IgE-mediated responses, but lacks standardization

DBPCFC: It is the definitive method for diagnosing food allergies, including CMA [7]

6. Future Directions: Immunotherapy and Specific Immunotherapy

Immunotherapy (IT) aims to alleviate allergic symptoms. While IT has an extensive history in treating respiratory allergies, its role in managing food allergies is still developing.

1. Subcutaneous immunotherapy: not advised due to risks of severe reactions

2.Oral or sublingual immunotherapy: possible alternatives

3. Recombinant allergens with diminished allergenic potential: an encouraging strategy

Vaccine Development for CMA

A suggested vaccine comprises recombinant hypoallergenic versions of the primary cow's milk allergens. These versions would preserve T-cell epitopes while being devoid of IgE epitopes, leading to the generation of blocking IgG antibodies.

Caution is necessary to prevent the introduction of new epitopes during the modification of proteins.

Site-Directed Mutagenesis

This method has been effectively utilized on the apple allergen Mal d 1, decreasing its IgE reactivity and allergenic potential.

Importance of Epitope Modification

When altering proteins, it is important to ensure that new epitopes are not introduced. Hypoallergenic molecules that possess T-cell epitopes but lack IgE epitopes are vital for creating specific immunotherapy (SIT) for CMA. Peptides that do not have T-cell epitopes can be associated with a carrier to promote carrier-specific T-cell assistance. T-cell reactive peptides may also be utilized for therapeutic and preventive measures. [7]

7. Challenges in Understanding Cow's Milk Allergy

A major challenge in managing cow's milk allergy (CMA) is the intricate and varied nature of the human immune reaction to cow's milk proteins. At present, no individual allergen or specific structure has been discovered as the main factor behind milk allergenicity.

7.1. Variability in Sensitization

Around 75% of individuals with CMA show sensitization to various proteins, exhibiting considerable differences in the specificity and strength of the IgE response. The most frequently acknowledged allergens seem to be those that are abundantly present in cow's milk, such as caseins, β-lactoglobulin, and α-lactalbumin.

7.2. Future Research Directions

To identify the most clinically significant allergens, comprehensive IgE binding studies must be conducted in large groups of well-characterized CMA patients. Furthermore, it is vital to evaluate the allergenic potential of individual allergen component

7.3. Controversies in IgE Reactivity

There is a persistent discussion about the occurrence of IgE reactivity to specific cow's milk proteins. This could be due to variations in study design, selection criteria, and limited sample sizes. [15]

8. Conclusion:

Cow's Milk Allergy (CMA) is a complicated and multifactorial condition, involving both IgE-mediated and non-IgE-mediated immune responses. It primarily impacts infants and young children, including those who are breastfed and have exposure to dairy products through breast milk. The main allergens that cause CMA are casein and whey proteins, with considerable individual variation in allergic reactions. A precise diagnosis requires a detailed clinical history, diagnostic evaluations, and oral food challenges, since no individual test can definitively verify CMA. The management of CMA mainly consists of avoiding cow's milk and utilizing alternative nutritional formulas, such as hydrolyzed or amino acid-based formulas. Although there is presently no cure, oral immunotherapy (OIT) has shown potential in inducing tolerance in certain patients. Innovative strategies, such as hypoallergenic vaccines and immunotherapy, are being investigated to improve treatment options. The outlook for CMA differs based on the type of allergy, and early diagnosis is vital for effective management. While many children outgrow CMA in childhood, additional research is needed to Identify the most clinically

significant allergens, refine diagnostic approaches and develop effective treatments. The creation of more precise immunotherapies offers hope for enhanced management and possible resolution of CMA in the future.

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