Narrative Review:
Cow's Milk Protein Allergy in Pediatric Dentistry

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ABSTRACT

Context: Immunological reactions against proteins found in cow's milk (casein and whey proteins) are called Cow's Milk Protein Allergy (CMPA). CMPA has systemic as well as oral symptoms. Also, any casein-containing products used for preventive and therapeutic purposes in dentistry may trigger this allergy. The objective of this compilation is to reveal the importance of CMPA in dentistry by adhering to the literature.

Evidence Acquisition: A literature search was done using PubMed, with focus on articles published in the last 10 years. Searched terms included the following: cow's milk protein allergy, child, pathogenesis, prevention, management, and dentistry.

Results: Oral allergy syndrome and dental erosion caused by gastroesophageal reflux were observed in 40% of patients with CMPA that were detected by the dentists.

Conclusions: Pediatric dentists should be aware of CMPA and pediatricians should be given support in definitive diagnosis of CMPA.

1. Context

Approximately 2000 years ago, Hippocrates reported that cow's milk may cause adverse reactions, such as stomach ache and skin redness (1). Food allergy may affect human life from infancy. Food allergy is defined as a Type 1 hypersensitivity reaction that occurred as a result of abnormal response in the body through specific IgE antibodies being developed against food proteins. If the reaction occurs by immunological mechanisms, it is called "food allergy." If it occurs due to non-immunological mechanisms, it is called "food intolerance" (2). Immunological reactions against proteins found in cow's milk are called Cow's Milk Protein Allergy (CMPA), which was reported in 1901 for the first time (3, 4).

For improving immunity in the newborns, they should be breast-feed during the first 2 years. Breast milk contains many immunologically active cells, immunoglobulin, lysozyme, lactoferrin, cytokine, growth factors, fat soluble vitamins, amino acids, fatty acids, amino sugars and nucleotides. With this digestive protein-carbohydrate-fat enriched content in breast milk, the formation of a flora occurs to support the development of

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baby's digestive system and immune system. It ensures the settlement of beneficial bacteria in intestine and prevents the growth of harmful bacteria. Thus, it is ensured that intestinal cells grow up more healthier with improved mucosal functions (5). In the studies, breastfed children are less likely to contract allergic diseases compared to non-breast-fed children (5, 6). Therefore, given the many other beneficial and protective effects of breast milk, it is recommended that a baby should be breastfeed exclusively for the first 6 months thereafter it should be given supplementary foods in addition to breast milk (6). There are some cases in which babies may not be breastfeed (death of mother, lack of breast milk, or working mothers). In such cases, the infants can be fed with cow's milk instead of breast milk. The aim of this review is to reveal the importance of CMPA in dentistry by adhering to literature.

2. Evidence Acquisition

Literature search was performed using PubMed medical databases. We focused on articles published in the last 10 years. PubMed MeSH terms included milk hypersensitivity/complications, milk hypersensitivity/immunology, milk hypersensitivity/physiopathology, milk hypersensitivity/therapy, milk proteins/adverse effects, immune tolerance, immunotherapy /adverse effects, and child and infant. Keywords were mainly phrases such as cow's milk proteins allergy, cow's milk, food allergy and oral tolerance. Other search terms consisted of food allergy, immune tolerance, and management.

3. Results

3.1. Epidemiology

Food allergy is one of the most common allergic diseases and its prevalence has not been known exactly. In the epidemiological studies conducted, it has been observed that the prevalence of food allergy varies between 5% and 20% (7). The first foreign protein introduced to infants' diet is cow's milk protein. Therefore, it features the most common food allergy among immunological tolerance mechanisms, immature babies and infants and its prevalence is reported to have varied between 2% and 3% (8). The prevalence of CMPA is at a high level in the first year of life; however, it drops below 1% for children who are 6 years of age and over. It was reported that the prevalence of CMPA is 0.5% in babies breastfeed exclusively as a result of transferring of cow's milk protein to breast milk (9). The prevalence of CMPA is reported to have reached up to 50%-74% in babies with the risk of allergy (10).

In Turkey, the number of studies on cow's milk allergy in babies is limited. Dr. Altıntaş et al. reported that the prevalence of CMPA is 1.55% (11). When compared to Western countries, the prevalence of CMPA is considered relatively low in these countries.

3.2. Pathogenesis

Gastrointestinal system has immunological and non-immunological components capable of blocking the foreign antigens and inhibiting them to enter the circulatory system. Antigen-presenting cells are found in reticuloendothelial system and play a role in oral intolerance development. Reticuloendothelial system activating factors increase the activation of such cells and prevent the formation of CD8 (+) cells, thus reducing the development of oral intolerance. The reason of hypersensitivity against foods in infants depends on the excessive levels of protein intake, the low levels of secretory IgA in the gut and the incomplete maturation of gut-associated lymphoid tissues (12). Any failure in the development of oral tolerance results in overproduction of food-specific IgE antibodies. CMPA may occur through IgE and cell. Both mechanisms likely play a role in food allergy (13).

3.3. Factors affecting the development of CMPA

Exposure to food proteins in early infancy may increase sensibility for two reasons. Firstly, mucosal barrier has not fully developed and in this case intestinal absorption of large molecules may increase. Secondly, local and systemic immune response may be undeveloped (14, 15). The high levels of prevalence of CMPA in premature newborns may be explained by the fact that gut permeability allows for absorption of large molecule of cow's milk proteins (16).

There are many factors affecting the CMPA development other than age, such as genetic susceptibility, age to encounter with an allergen (prenatal, postnatal, early or late period), duration and frequency of exposure to allergen, structure of allergen, presence of affecting factors (air pollution, industrial substances, home dusts, pets and smoking etc.), presence of a family history of allergic diseases (especially on the side of mother) and or elevated cord blood IgE levels indicating that the baby is at a high risk (7, 17). These factors are considered to have affected the onset of an allergic disease's symptoms significantly.

The theory upon the increase in allergic diseases has moved away from traditional eating habits with chang-

ing lifestyle in developing countries. The consumption of processed and packaged goods and fast food has increased. This has led to change in the eating habit which is associated with the increase in allergies and allergic diseases (18).

3.4. Cow's milk allergen proteins

CMPA develops against cow's milk proteins. The protein in cow's milk is 20% whey protein and 80% casein protein (19). Casein consists of α-S1, α-S2, β and κ casein proteins. Whey protein consists of β-lactoglobulin, α-lactoglobulin, bovine serum albumin and small amounts of various proteins (lactoferrin, transferrin, lipase, and esterase) (20). Cow's milk has at least 20 protein components which may cause antibody formation in humans (21). Some of them are described as major allergens (especially α-lactalbumin, casein, bovine gamma globulin, bovine albumin, and β-lactoglobulin), and some as minor allergens. Especially β-lactoglobulin, an allergen, is not found in human milk (20). A child allergic to cow's milk may not consume ewe's milk and goat's milk due to possible cross-sensitivity (22). Milk allergens maintain their biological activities even after boiling, pasteurization and evaporation treatments (20).

Milk protein allergens have been examined by Goldman et al. for the first time. A skin test with equal concentrations of purified milk proteins (casein, α-lactalbumin, β-lactoglobulin, bovine serum albumin) was performed on 85 children with known milk allergy. It was found out that 50 children were allergic to milk in the skin test and that 30 of them were not allergic to two or more milk proteins (23). In the second part of the same study, 45 children were given purified milk protein, of which 62% showed allergic reaction against β-lactoglobulin, 60% against casein, 53% against α-lactalbumin, and 52% against bovine serum albumin (24).

Tryptic phosphopeptides bonds found in the structures of α-S1, α-S2 and β caseins ensures easier bonding of phosphate and calcium with casein. In a study, it was reported that calcium bonds more tightly with peptide bonds in the form of phosphoserine commonly found in α-S1 casein and β casein compared to other bonds (25). Consequently, these tryptic peptides play an important role in the caries preventive effect of casein (26).

Although casein fraction contains low level of protein similarities, multiple sensitivity against various casein was observed. Almost all patients are sensitive to α casein (100%) and κ casein (91.7%) (27). Since Beta-lactoglobulin (BLG) is not found in breast milk, it was considered the most important allergen in cow's milk in the past (20).

3.5. Definitive diagnosis of CMPA in pediatric dentistry

A pediatric dentist encounters with a healthy newborn usually in the case of occurrence of natal/neonatal teeth, moniliasis, Early Childhood Caries (ECC) or teething (28, 29). The basic characteristic of the causes of admission is "an apparent restlessness." Besides, another increasingly common health problem disturbing babies is CMPA (30). If parents suppose that the baby restlessness results from a dental condition, they will consult a pediatric dentist. CMPA has systemic symptoms as well as oral symptoms (Figure 1). Oral allergy syndrome is one of the important symptoms of CMPA that should be overemphasized by dentists. The oral allergy syndrome is a type of contact urticaria with symptoms such as lips, tongue, palate and throat itching and angioedema. It may progress and reverse rapidly, besides food skin test is positive (31).

Research shows that 40% of infants are allergic to cow milk that delays increased gastric emptying and symptoms of reflux causing reflux vomiting (32). In recent reviews, a strong association was shown between the prevalence of Gastroesophageal Reflux Disease (GERD) and dental erosion (33). Gastric ingredients of GERD cause erosion due to the characteristic enamel layer. While the critical pH value for the resolution of the enamel layer is 5.5, the pH value of the gastric fluid in the mouth varies between 1 and 1.5. When the enamel is constantly exposed to acidic environment caused by the gastric fluids demineralization takes place on the enamel surface (34).

The erosion of milk teeth becomes more pronounced, especially in young children with increased GERD, which occurs due to the poor muscle control and immature reflux control mechanisms (35). One of these studies reported a strong association with other oral manifestations of GERD in the form of burning mucosal sensation, halitosis, and mucosal erythema (36). GERD can be detected by dentist examination in the early childhood and progression of the disease in the early period can be prevented. Taking preventive measures in terms of oral health is also very important for the patient's awareness in terms of dentistry (37).

In order to make definitive diagnosis, the following questions should be asked: 1. Is there a general restlessness? (If yes); 2. Is there a certain period with increased restlessness?; 3. Is the baby or child given cow's milk or

any cow's milk-based food? (If yes); 4. Is diarrhea or vomiting observed after the baby is given cow's milk or cow's milk-based food?; and finally, 5. Is there a formation of itching, redness in the baby's gum when it is given cow's milk or cow's milk-based food? (Oral allergy syndrome).

If the answers are mainly 'yes', it should be considered that the general restlessness in the baby or child may result from the consumption of milk other than teething or any dental problem. In case of doubt, the patient should be transferred to the allergy department. It is also possible to make the final diagnosis of CMPA by using a detailed medical history, physical examination, skin prick test, specific IgE measurement, removal of food from the diet and food challenge methods (13). Metabolic disorders, anatomic disorders, celiac disease, pancreatic insufficiencies such as cystic fibrosis, fructose intolerance or secondary lactase deficiency, other rare enteropathies and other food allergies, such as eggs, wheat and infections, should be excluded in differential diagnosis of CMPA (2).

3.6. Dental treatment

Although CMPA develops in most children up to 3-4 years of age, sensitivity continues in about 15% of them until the age of 20 (38). CMPA during the same period as the age group at which the grown primary teeth may also affect the restorative treatment selection to be employed by dentists.

Casein, cow's milk protein, is found mainly in milk, cheese and yoghurt. Use of Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) instead of fluoride applications has been increasingly common at the present time. CPP-ACP contained toothpaste and solutions are used in the treatment of incipient enamel lesions (25). Also, CPP-ACP was added to sugarless gum, pastille, glass ionomer cement and resin containing restorative materials as a dental product (39).

In the children at the age group under 6 years having the highest rate of CMPA, casein phosphopeptide-amorphous calcium phosphate is used in order to: Ensure remineralization of white spot lesions; Eeduce colonization of Streptococcus Mutans (SM) in Early Childhood Caries (ECC); Reduce dentin sensitivity of children with primary tooth fluorosis; and Use CPP-ACP containing restorative materials in the cases requiring invasive treatment (40, 41). Pediatric dentist should eliminate the suspicion of CMPA before he or she uses CPP-ACP containing products, especially in children under 6 years. Alternative products should be preferred in children with suspected CMPA.

4. Conclusion

The reason of increasingly common food allergy is the changing lifestyle and eating habits in recent years. If the dentists suspect CMPA in the children as a result of the medical history and physical examination, then one

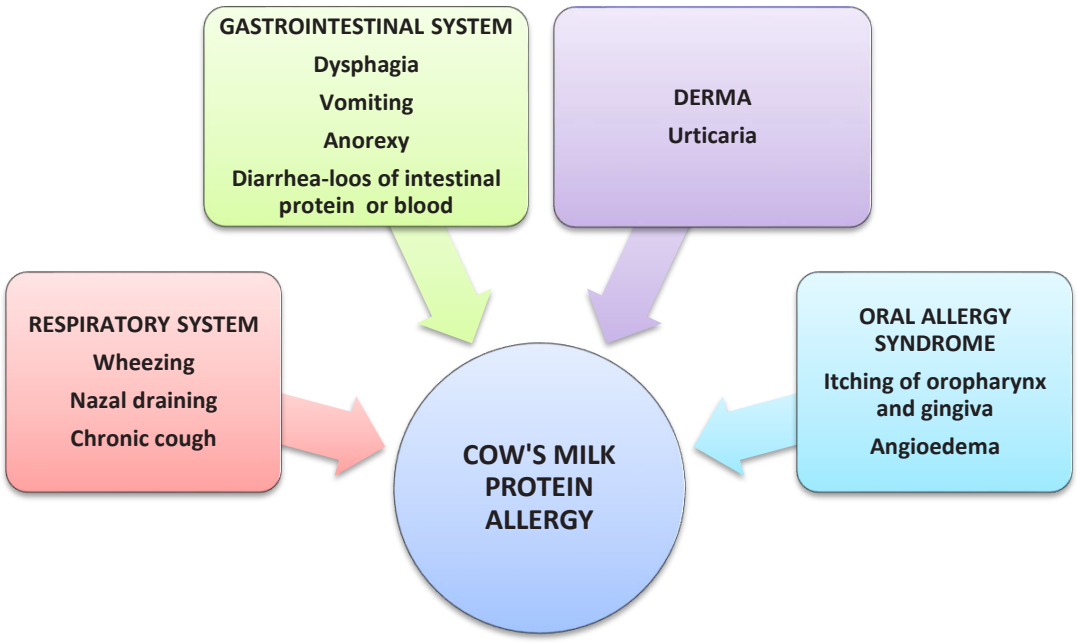

Figure 1. Oral and systemic symptom of cow's milk protein allergy

should consult with a pediatrician. CMPA may be seen during the same period when the primary teeth are fully grown which may also affect the preventive and restorative material selection to be employed by dentists. Dentists should not use any CPP-ACP containing dental products in children with CMPA history or suspected CMPA and family members should be warned against these products accordingly.

Ethical Considerations

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This paper was not extracted from a thesis. It has not got any financial supporters.

Conflict of interest

The authors declared no conflict of interest.

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