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The challenge of cow milk protein allergy ☆

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Abstract

Hypersensitivity to cow milk proteins is one of the main food allergies and affects mostly but not exclusively infants, while it may also persist through adulthood and can be very severe. Different clinical symptoms of milk allergy have been established. The diagnosis of milk allergy differs widely due to the multiplicity and degrees of symptoms, and can be achieved by skin or blood tests. Cow milk contains more than 20 proteins (allergens), that can cause allergic reactions. Casein fractions and β-lactoglobulin are the most common cow milk allergens. Human milk is free of β-lg, similar to camel milk. On the contrary, β-lg is a major whey protein in cow, buffalo, sheep, goat, mare and donkey milk. Caseins in milk of the different species differ in fraction number, amino acid composition, and their peptide mappings. β-Casein is the major fraction in goat casein, which is similar to human casein and different from cow casein. The peptide mappings of goat α-la and β-lg are completely different from those of cow milk. Different procedures can reduce the allergenicity of cow milk proteins by heat or enzymatic treatment to some degree. Allergies to milk proteins of non-bovine mammals have also been documented due to cross-reactivity between cow milk proteins and their counterpart in other species, and even between goat and sheep caseins. Genetic polymorphisms of milk proteins play an important role in eliciting different degrees of allergic reactions. Goat milk lacking α-s1-casein, which is the main casein in cow milk, is less allergenic than goat milk with α-s2-casein, which is more typical for many goat breeds. Several studies have reported real and dramatic benefits from using goat, camel, mare or even soy milk as alternatives in cases of cow milk allergy and they can be considered hypoallergenic. However, therapeutic benefits vary with the degree of severity of the allergy and may be only around 60% of all cases, since other studies revealed allergenicity to occur also for any of those other milks.

Keywords: Cow milk allergy; Goat milk proteins; Sheep milk proteins; Allergenicity; Human milk substitutes

1. Introduction

Milk is a biological fluid designed to contain all nutritional requirements of a specific mammalian newborn; therefore, the composition of milk differs by the needs of the neonate of different species. For example, human milk is the most fit food for human infants, but when breast-feeding is not available, cow milk is usually used as a substitute for human milk. This substitution can lead to nutritional and immunological problems, such as allergy to cow milk proteins.

2. Definition of cow milk allergy (CMA)

The word allergy means an altered or abnormal reaction. Such a reaction may occur when there is contact between a foreign protein "an allergen" and body tissues, that are sensitive to it. The allergy may reach the tissues by direct contact with the skin or mucous membranes or through the blood stream after absorption. Allergic reactions have been classified into two types:

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(1) The immediate reaction type in which the allergic manifestations occur within hours of the patient coming in contact with the allergen and often within seconds or minutes; in this form of allergy skin tests are nearly always positive.
(2) The delayed reaction type in which manifestations may not appear for many hours or even for 2 or 3 days; in this type skin tests are usually negative.

Cow milk allergy is clinically an abnormal immunological reaction to cow milk proteins, which may be due to the interaction between one or more milk proteins and one or more immune mechanisms, and resulting in immediate IgE-mediated reactions. On the other side, reactions not involving the immune system are defined as cow milk protein intolerance.

CMA occurs in some infants after ingestion of an amount of cow milk. In some cases allergy to goat and sheep milk or cheeses made from them has also been recognized (Dean et al., 1993; Wuthrich and Johansson, 1995; Umpierrez et al., 1999; Pessler and Nejeat, 2004). CMA is generally more serious in early infancy (Hill and Hosking, 1996; Jarvinen et al., 2002).

3. Incidence of cow milk allergy

Cow milk is one of the most common food allergies in children. Although most children out-grow CMA by the age of 4 years, some retain the allergy for life. CMA may occur in adults usually involving immediate allergic reactions or eczema. The incidence of CMA ranges from 0.3 to 7.5% in population-based studies in different countries (Goldman et al., 1963; Gerrard et al., 1973; Ghosh et al., 1989; Dean, 1995; Motrich et al., 2003). The wide range in these estimates may be due mainly to different diagnostic criteria in addition to other factors such as race, age of the tested patients, type of infant feeding, as well as the duration of observations (Taylor, 1986).

4. Clinical manifestation of CMA

Symptoms of CMA can appear immediately or start several hours or even days after the intake of moderate to large amounts of cow milk or its infant formula. A wide spectrum of clinical manifestations has been recorded with CMA including gastrointestinal, respiratory, cutaneous as well as systemic anaphylactic symptoms (Fig. 1). Clinical symptoms involve immediate or delayed reactions operating separately or together (Bahna and Gandhi, 1983a; Amon et al., 1999; Drouet et al., 1999). Immediate reactions are mainly IgE-dependent, leading to cutaneous, intestinal or respiratory

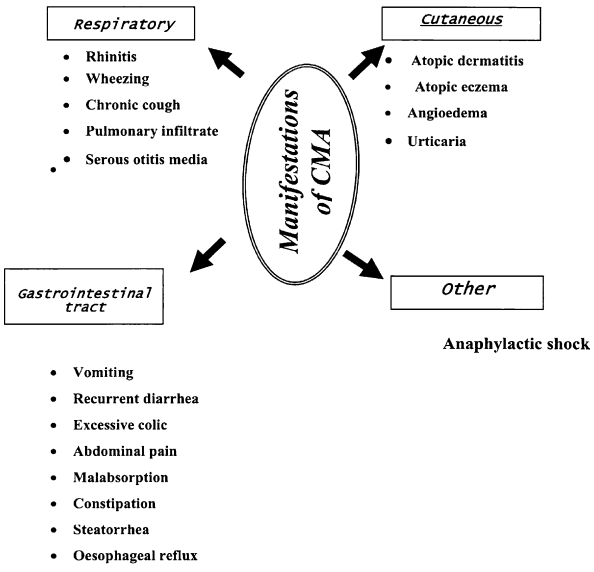

Fig. 1. Manifestations of CMA (Taylor, 1986; Host, 1994; Amon et al., 1999; Drouet et al., 1999; Majamaa et al., 1999; Heine et al., 2002; Hidvegi et al., 2002).

symptoms and in some cases to anaphylactic reaction (Sicherer, 2000). Delayed reactions happen after T-cell dependent mechanisms and can be operative both at the skin and the intestinal level (Taylor, 1986). The most frequent symptoms among the common manifestations of CMA are gastrointestinal, which have been encountered in 50–75% of patients with CMA (Ghosh et al., 1989). Respiratory and the skin symptoms are also commonly involved in CMA. These symptoms were recorded in 10–30 and 50% of patients with CMA, respectively (Ghosh et al., 1989). Rhinitis is the most common respiratory manifestation of CMA in some infants. Anaphylactic shock is a particularly serious symptom of CMA. In some cases, death can result. Anaphylaxis was noted in 12% of patients with CMA, but it was less commonly observed than most other symptoms (Lebenthal, 1975; Host, 1994).

5. Milk protein allergy diagnosis

The clinical diagnosis of milk allergy differs widely due to the multiplicity of symptoms. Diagnosis can be achieved by skin or blood tests. The positive blood or skin test is accomplished only with the immediate milk allergy reactions, that develop after a few minutes because these detect IgE that are involved in the immediate type reaction. In the young child about 60% of milk allergy reactions are not of the immediate type but are the delayed type “intolerant”, consequently unlikely to give positive results with blood and skin tests. Different

reliable diagnostic tests (Dean et al., 1993; Heine et al., 2002; Hidvegi et al., 2002) are:

- skin prick test (SPT),
- radioallergo-sorbent test (RAST),
- enzyme linked immuno-sorbent assay (ELISA), in addition to
- elimination-challenge test.

5.1. Skin prick test

SPT is especially accurate in the young child (Majamaa et al., 1999). The test is based on immunoglobulin E (IgE) being produced in patients when subjected to cow milk proteins, that reside on the surface of mast cells present in the skin. Therefore, small drops of the suspected milk are placed on the forearm of patients to expose the mast cells present in the skin to the specific allergens (milk proteins). After 15 min a wheal and flare reaction may appear revealing the patient is allergic to milk (Ghosh et al., 1989). Generally, the use of SPT for the diagnosis of milk allergy cannot be considered reliable unless a strong reaction is noted (Majamaa et al., 1999). If it is desired to know to which particular protein the allergic individual is sensitive, then purified proteins must be used. Meanwhile, a "patch" test may be more sensitive than SPT or RAST to detect CMA (Majamaa et al., 1999; Vanto et al., 1999; Heine et al., 2002). There is no minimum age for SPT, which can be performed in babies and older children with useful results.

5.2. Blood tests

Two different tests, RAST and ELISA can be used to diagnose CMA. Both of them measure the levels of IgE in blood serum of the patient (Norgaard et al., 1995; Garcia-Ara et al., 2004). In RAST, the milk allergen is attached to a solid phase such as a cellulose disc and then incubated with the patient's serum. The disc is raised and incubated with radiolabelled anti-IgE. Finally the activity associated with anti-IgE bound to specific IgE is measured and used to determine the amount of IgE in serum. In ELISA an enzyme rather than the radioisotope is attached to anti-IgE and the activity of the bound enzyme is proportional to the amount of anti-IgE bound to antigen specific IgE (Ghosh et al., 1989). Both RAST and ELISA assays are used frequently to give more reliable results.

5.3. Elimination-challenge test

In this test milk allergy is confirmed, if elimination of cow milk and products containing cow milk from the diet results in symptomatic improvement and re-introduction of cow milk causes recurrence of symptoms. Recently, a combination of assays was used for CMA diagnosis, such as proliferative assay of peripheral blood mononuclear cells to cow milk, the quantitation of TNF α (one of the mediators involved in adverse reactions to cow milk proteins), and serum specific IgE (Motrich et al., 2003). These assays are useful to identify CMA among patients with immediate and non-immediate adverse reactions, and they reduce the need for allergen challenges in young children.

6. Cow milk allergens

Cow milk contains more than 20 proteins (allergens) that can cause allergic reactions (Gjesing et al., 1986; Cavagni et al., 1994; Docena et al., 1996). The main proteins are casein and whey protein. Casein is fractionated into α-, β-, and κ-casein. Whey proteins include: α-lactalbumin (α-la), β-lactoglobulin (β-lg), bovine serum albumin (BSA) and immunoglobulin (Igs). In addition to those, several minor proteins are also present in cow milk. Most studies revealed, that casein and β-lg are the main allergens in cow milk (Goldman et al., 1963; Docena et al., 1996; Bernard et al., 1998; Busse et al., 2002; Cocco et al., 2003). Jarvinen et al. (2002) found, that five IgE-binding epitopes (2 on α-s1-casein, 1 on α-s2-casein, and 2 on κ-casein) were recognized in patients with persistent allergy. The IgE antibodies were against at least one of three epitopes. Amino acid (AA) 123–132 on α-s1-casein; AA 171–180 on α-s2-casein, and AA 155–164 on κ-casein. Allergic reactions to BSA, IgG heavy chain and α-la were also noted (Jarvinen et al., 2001; Natale et al., 2004). The structure of sequential epitopes recognized by IgE antibodies to α-la and β-lg was found in CMA patients. Four IgE-binding regions were identified on α-la and seven IgE-binding epitopes were detected on β-lg (Jarvinen et al., 2001). It was found that genetic polymorphisms of milk proteins play an important role in CMA development. Goat milk with the α-s2-casein genotype caused less intestinal and systemic sensitization than goat milk with the α-s1-casein genotype in guinea pigs (Bevilacqua et al., 2001). This is very interesting and may have great potentials in selecting goat breeds for different casein genotypes, especially for α-s2-casein, which is not found in cow milk, and against α-s1-casein, which is dominant in cow milk.

Allergic responses to lactoferrin and some cow milk enzymes have been detected in some patients with CMA (Taylor, 1986; Sharma et al., 2001), but none to mammalian lysozyme (Aalberse and Stapel, 2001). It was

also found that a balance between casein and whey proteins in cow milk may determine its allergenicity (Lara-Villoslada et al., 2005). Allergenicity, even anaphylactoid reaction to goat and sheep milk caseins and cheese has been reported from some patients using SPT and specific IgE test (Umpierrez et al., 1999; Orlando and Breton-Bouveyron, 2000).

7. Alteration of CMA

Different attempts have been made to reduce the allergenicity of cow milk proteins, and various technological processes have been applied in order to have better use of cow milk in infant formulae.

7.1. Heat treatment

Attempts to modify the protein components of cow milk in an effort to reduce their allergenic potential have included the application of prolonged heat (Crawford, 1960; Hanson and Mansson, 1961; Luz and Todd, 1964). It was found, that milk proteins differ markedly in their resistance to heat treatment, since α-casein is the most heat stable, whereas BSA is the most labile, and β-lg is relatively heat stable (Bahna and Gandhi, 1983b). Heating milk at 120 °C for 15 min did not affect the antigenicity of bovine casein (Hanson and Mansson, 1961), buffalo or goat casein (El-Agamy, 2006a,b). BSA and Igs lose their antigenicity at 70–80 or 100 °C (Hanson and Mansson, 1961; Fiocchi et al., 1998). It was found that heating bovine whey protein at 100 or 115 °C for 30 min resulted in no sensitization of guinea pigs or anaphylaxis (Heppell et al., 1984). On the contrary, heating of goat milk at 100 °C for 30 min resulted in alteration of serum albumin and IgG, whereas the antigenicity of α-la and β-lg was not affected by heat treatment (El-Agamy, 2006a). Allergenicity of bovine β-lg is affected by heat treatment, since rats immunized with native β-lg had higher levels of total serum IgE than those immunized with heat-denatured β-lg. Rytkonen et al. (2002) found, that bovine milk retained its allergenicity even when subjected to severe heat treatments.

Generally, it should be taken into account that in spite of the alteration of allergenicity of some milk proteins by severe heat treatment, significant loss of the nutritional quality of the product has to be expected.

7.2. Enzymatic treatment

Another attempt to reduce allergenicity of milk proteins was by enzymatic treatment with a variety of enzymes (Haddad et al., 1979; Alting et al., 1998). However, it was found that products resulting from enzymatic treatment have not had acceptable taste due to the development of bitterness and off-flavors, which are attributed to the liberation of peptides and amino acids from proteolysis. Meanwhile, the proteolytic digestion might itself generate new antigenic substances. It was reported that partial digestion of bovine milk with pepsin or pepsin and trypsin resulted in peptides belonging to β-lg, that bound to IgE from patient's sera with CMA (Haddad et al., 1979). Jost et al. (1987) found that the antigenicity of bovine β-lg and α-la decreased by treatment with soybean trypsin inhibitor for 1 h, while BSA and Igs were more stable. In another study (Selo et al., 1999), it was noted that bovine β-lg treated with trypsin retained its own antigenicity, because the derived peptides were capable of a specificity to bind human IgE. Schmidt et al. (1995) determined the degree of hydrolysis of bovine α-la, β-lg, BSA, and IgG by pepsin in the pH range 2–4 as well as the antigenic properties of the resulting hydrolysates. No differences were found in the antigenic properties of the hydrolysates at pH 2 or 3, however, at pH 4 a decrease in pepsin hydrolysis resulted in enhancement of antigenicity of all proteins except β-lg. In another study (Duchateau et al., 1998), 222 sera from CMA patients were tested for the degree of binding between IgG antibodies to its β-lg (native or pepsin treated). The results revealed that the binding capacity was higher with native β-lg than when it was pepsin treated. El-Agamy (2006a) found, that the effect of peptic or tryptic treatment on the allergenicity of goat milk proteins was different. Goat casein lost its own antigenicity by pepsin or trypsin treatment for 3 h, whereas goat α-la lost its whole antigenicity by pepsin but not by trypsin treatment. On the other hand, goat β-lg antigenicity was not altered by either pepsin or trypsin treatment for 3 h.

7.3. Infant formula

An alternative cow milk substitute is an infant milk formula in which the protein is a hydrolysed cow milk protein (Cavagni et al., 1994; Terracciano et al., 2002) or goat milk protein (Dean et al., 1993). Casein and whey or soy protein is hydrolysed by proteolytic enzymes to develop a number of casein, whey or soy protein hydrolysates. The products have been classified according to the degree of protein hydrolysis as extensively or partially hydrolysed protein products. Casein hydrolysates have been used for almost 50 years, whereas whey hydrolysates are a more recent alternative. Both casein and whey hydrolysates appear to have

a similar clinical tolerance (Martin-Esteban et al., 1998). Generally, infant formulae can classified into three categories.

7.3.1. Extensively hydrolysed formula (EHF)

This is a cow milk-based formula, that has been treated with proteolytic enzymes. This formula often has a poor flavor and the taste may be bitter; however, it is recommended as a first alternative in children with CMA before using other formulae (Terracciano et al., 2002). EHF is different from the partially hydrolysed formula, since the latter is not indicated as a supplement for cow milk allergic children. In Italy, formulae made from goat milk are used and recommended by some physicians for feeding babies with CMA (Bellioni-Businco et al., 1999).

7.3.2. Amino acid-based formula (AABF)

This is another cow milk-based formula. AABF is necessary in around 10% of CMA children, who are allergic to EHF (Kelly et al., 1995; de Boissieu et al., 1997).

7.3.3. Soy formula

Soy formulae offer equivalent nutritional benefits to EHF but are more palatable. Soy formulae are not recommended for all cases of CMA infants, since 17–47% of milk allergic infants can have adverse reactions to soy. However, around 53–83% of CMA children can tolerate soy-based formula (Hill et al., 1999).

8. Cow milk cross-reactivity

Human milk composition is different from that of other mammalian milk in both ratios and structure of milk constituents. The protein content in human milk is lower than in milk of ruminant dairy animals: cows, buffalo, yak, camel, goat, sheep, reindeer, but is closer to that of donkey and mare milk (El-Agamy et al., 1997). The ratio of casein within total protein is lower in human milk, because whey proteins (soluble proteins) are higher than in cow, buffalo, and sheep milk, whereas they are at similar level in donkey and mare's milk (El-Agamy et al., 1997). This condition gives human milk the special property of forming a soft curd during digestion in the infants' gut, although goat milk is also known for this uniquely different property. The softness of the curd is due to the lower ratio of soluble calcium. This condition may explain, why in many parts of the world mare and donkey milk as well as goat and camel milk are used as human milk substitutes for bottle fed infants (El-Agamy, 1983; Zhao, 1994; El-Agamy et al., 1997). On the contrary, both cow and buffalo milk give a hard curd, which of course is preferred in cheese making. Dilution of bovine milk with water before using it in baby feeding must be practiced for safe nutrition, especially for very young babies.

On the other hand, human milk proteins are different in their composition and structure from those of the milk of other species. It is known, that the major whey proteins of bovine milk are β-lg with 55% of total whey proteins, α-la with 20%, and BSA with 7% (Taylor, 1986). These proteins differ in their types and ratios between goat, sheep, cow, camel, human, buffalo, mare and donkey milks (El-Agamy et al., 1997). Human milk is free of β-lg (Kappeler, 1998), one of the major allergens in cow milk, similar to camel milk, which also has no β-lg (El-Agamy and Nawar, 2000). On the contrary, β-lg is a major whey protein in cow, buffalo, sheep, goat, mare and donkey milk (El-Agamy et al., 1997). Caseins in the milk of these species differ in fraction number and their electrophoretic behavior on polyacrylamide gel, amino acid composition and their peptide mappings (El-Agamy et al., 1997). β-Casein is the major casein fraction in goat milk, while α-s is the minor one. Their ratio is 70 and 30% for β-casein and α-s-casein, respectively, which is more like that of human casein and different from cow casein (El-Agamy, 2006a). This similar property of both goat and human casein composition may explain the higher digestibility of goat and human caseins by pepsin than cow casein. β-Casein was more sensitive in goat and human casein to the action of pepsin than α-s-casein (El-Agamy, 2006a). The peptide mappings of goat α-la and β-lg are completely different from those of cow milk (El-Agamy, 2006a).

9. Cow milk alternatives

Several studies have evaluated the clinical use of plant proteins or milk from different animals such as goat (Cant et al., 1985; Park, 1994; Alvarez and Lombardero, 2002; Muraro et al., 2002; Restani et al., 2002; El-Agamy, 2006a), camel (El-Agamy, 2006c), sheep (Dean et al., 1993; Restani et al., 2002), mare and donkey (El-Agamy et al., 1997; Carroccio et al., 2000; Muraro et al., 2002), and buffalo (El-Agamy, 2006b). The available data in the literature show contradictory results concerning the use of animal milk as alternatives to human milk. Some studies revealed that goat (Cant et al., 1985; Coveney and Darnton-Hill, 1985; Razafindrakoto et al., 1994; Bevilacqua et al., 2001), mare and donkey (El-Agamy et al., 1997; Carroccio et al., 2000) and camel milk (El-Agamy, 2006c) can be considered as proper

alternatives to human milk due to hypoallergenic properties of their proteins.

On the other side, other studies showed that milk of goat (Jelert, 1984; Cant et al., 1985; Wuthrich and Johansson, 1995; Spuergin et al., 1997; Orlando and Breton-Bouveyron, 2000; Alvarez and Lombardero, 2002; Muraro et al., 2002; Restani et al., 2002; Haenlein, 2004; Pessler and Nejeat, 2004), sheep (Wuthrich and Johansson, 1995; Spuergin et al., 1997; Alvarez and Lombardero, 2002; Restani et al., 2002), and buffalo (Restani et al., 2002; El-Agamy, 2006b) cannot be useful in all cases as alternatives to human milk, because they can be as allergic as cow milk, which also has been documented for soy milk in some cases. The study of Infante et al. (2003) with goat milk revealed that only 25% of 12 patients with CMA benefited and showed adequate immediate and late oral tolerance and negative results in immunological tests with RAST, specific IgE, SPT and challenge tests, but other studies have found higher cure rates (Haenlein, 2004).

10. Milk protein cross-reactivity

Cross-reactivity between milk allergens from different mammalian species and humans occurs, when they share part of their amino acid sequence or when they have a similar capacity to bind specific antibodies due to their molecular structures. The cross-reactivity between milk proteins from different animal species has been studied (Prieels et al., 1975; El-Agamy, 2006a,b,c; El-Agamy et al., 1997; Carroccio et al., 1999; Restani et al., 2002). Restani et al. (1999) showed that IgEs from sera of children allergic to cow milk are capable of recognizing most parts of milk proteins from European mammals: sheep, goat and buffalo. Weak cross-reactivity was observed with milk proteins from mares and donkeys, but none with camel milk. IgEs from a child allergic to sheep milk did not recognize any proteins of camel milk. Immunological relationships between human milk proteins and their counterparts in goat, sheep, cow, buffalo, camel, donkey, and mare milk were studied by El-Agamy et al. (1997). Human milk caseins had relationships with donkey and mare milk proteins, while relations were weak with goat and camel milk, and had no relations to cow, buffalo and sheep milk proteins.

Antiserum to human milk whey proteins was applied to immunodiffusion test and strong immunological relationship was found between human and donkey whey proteins, while relations were weak with whey proteins of other species. Cross-reactivity between α-casein from goat, sheep and cow milk and their allergic potential was studied by Spuergin et al. (1997). In the three types of milk, α-casein was sharing more than 85% identical amino acids. When sera of allergic children to cow milk proteins were tested, significantly higher IgE and IgG binding to goat and sheep α-casein was recorded, supporting a conclusion, that goat and sheep α-caseins have an allergic potential and are not always suitable for the nutrition of cow milk allergic patients (Umpierrez et al., 1999). Another study (El-Agamy, 2006a) showed cross-reactivity between goat and human caseins, when antigoat casein was used in immunoblotting technique. Prieels et al. (1975) found that no cross-reaction between human α-la and antibodies against bovine α-la was detected, when immunodiffusion test was applied. However, Aalberse and Stapel (2001) noted that human α-la is highly homologous to bovine α-la with 66% identity. Baroglio et al. (1998) stated that purified polyclonal antibovine β-lg showed 10% cross-reactivity with α-la, both in native and denatured form. However, there was no cross-reactivity with BSA, when either antiserum to bovine β-lg or α-la was used. Four amino acids common to α-la and β-lg might be responsible for the cross-reactivity. Cross-reactivity between β-lg and casein from cow and goat milk was detected by immunoblotting technique (Sabbah et al., 1996). Bevilacqua et al. (2001) reported, that guinea pigs fed cow milk proteins and goat milk proteins with high α-s1-casein content developed high titres of anti-β-lg, IgG1, with an important cross-reactivity between goat and cow β-lg.

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