REVIEW ARTICLE

UNDERSTANDING COW'S MILK PROTEIN ALLERGY

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Abstract

Food allergy is a growing international problem. Milk protein allergy can be found in up to 15% of infants and is among the top five allergy producing foods. Cow's milk protein allergy (CMPA) can occur in completely breast fed infants also. It is of two types: IgE mediated and non–IgE mediated CMPA. The immunologically mediated reactions can vary in severity. IgE mediated CMPA may give rise to immediate symptoms following the ingestion of cow's milk. This is commoner in children than in adults. The non IgE mediated CMPA can produce symptoms an hour to several days later and can be mistaken for lactose intolerance. Elimination of cow's milk in the diet may be associated with improvement of symptoms. The double blind placebo controlled food challenge (DBPCFC) is considered as the gold standard for the diagnosis of CMPA. Partially or extensively hydrolyzed formulas can be used as replacement feeds.

Introduction and incidence

Allergy to various foods is a growing international issue. It is no longer restricted to developed countries, but is also witnessed as a growing problem in several developing countries. Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly following exposure to a given food. (1) Milk protein allergy is a recognized and common entity during infancy, which can affect up to 15% of infants. (2) According to some literature available, CMPA affects 2-3% of children in the developed countries, and is listed amongst the top five food allergens in children from South-East Asia. (3) Some other reports place the prevalence of CMPA between 2-7.5%. (4) It is a viable consideration to suspect CMPA in a formula or bovine milk fed infant. But is a completely breast fed infant safe from developing this entity? Reported literature has shown the presence of CMPA in breast as well as formula fed infants. (2) The incidence of CMPA in a breast fed infant varies from 0.4% to 0.5%, and may reach up to 2.1%. (2)

Classification of CMPA

CMPA develops as a reaction of the body to the casein and whey protein components in the cows' milk. It is an immunological response which may be IgE mediated, which is seen in almost 60% of cases, or non- IgE mediated. (3) The non-IgE mediated CMPA usually present with gastrointestinal symptoms following cow's milk ingestion and is probably caused by a cell mediated reaction. (5)

Composition of cow's milk

Cow's milk protein consists of casein and whey proteins, of which casein constitutes 80% of the protein. Casein is made up of alpha s1, alpha s2, beta and kappa casein which have a poor sequential homology. Caseins play a major role in the transport of calcium phosphate to the newborn. Sensitization to many caseins, notably alpha s1 and kappa casein is common, probably due to cross sensitization that occurs due to shared epitopes. (5) Beta lacto-globulin is the most abundant whey protein in cow's milk which is absent in human milk and is responsible for causing allergy in 13-76% of cases. Bovine serum albumin is an important whey protein that regulates the colloidal osmotic pressure in blood. This fraction causes variable sensitivity ranging from 0-88% of CMPA cases. (5) Immunoglobulins are present in milk, besides other tissues like blood. They are seldom responsible for the symptoms of CMPA.

Caseins are easily and quickly digested as compared to whey proteins. (5) However, studies have not found any co relation between protein digestibility and allergenicity. Processes such as boiling, pasteurization and ultra high temperature processing do not reduce the allergenicity of the proteins and this could possibly be related to the persistence of the allergenic potential of the sequential epitopes.

Mechanism of CMPA

Like any other allergen, cow's milk protein too can stimulate an allergic reaction via any of the basic immunological mechanisms. It may be a Type I or IgE mediated sensitivity, Type II or a cytotoxic reaction, Type III or an Arthus- type reaction and Type IV or a delayed reaction which involves the T cell activation. It is pertinent to understand that the Type I reaction to cow's milk protein signifies the classic IgE mediated immediate hypersensitivity reaction, while all the other three come under the umbrella of non IgE reactions.

The mucosal barrier of the gut, including the gut associated lymphoid tissues is the first barricade that must be crossed by any food antigen. Damage to this barrier may develop due to local hypersensitivity to foods and this has been noted in children with food atopy. Once the milk allergens come in contact with the intestinal mucosa, they interact with the mucosal T and B cells. This interaction may take place with the help of the antigen –presenting cells like macrophages, dendritic cells and M cells. T cell receptors which include the MHC Class I and II cells may also help in the interaction between milk proteins and the intestinal mucosa. These activated T and B lymphocytes present in the lymphoid follicles migrate via the lymphatic system and the circulation to any of the target organs like the GIT, respiratory system, skin and CNS. The response that develops here is based on the balance between the development of tolerance/suppression and sensitization / priming that occurs in the target organ. If there is a deletion of the reactive antigen specific T cells and production of regulatory T cells, then tolerance to the milk proteins develops in the body. However failure or breakdown of this process leads to dysfunctional T regulatory cell function that is associated with the development of milk allergy. This may be antibody mediated or cell mediated or both. In case of IgE mediated CMPA, there is activation of milk –specific T helper cells type2 (TH2), which produces milk specific IgE. In the non IgE mediated

CMPA, there could be a TH1 mediated inflammation associated with the decreased T regulatory cell activity, the formation of immune complexes with resultant complement activation, or due to T cell/mast cell/ neuron interactions, which could induce changes in smooth muscle action and intestinal motility. (5)

Symptom correlation

The IgE mediated CMPA gives rise to immediate symptoms that develop as soon as cow's milk is consumed. The time lag may range from a few minutes to an hour and occurs in a sensitized patient which occurs when the IgE antibodies against milk proteins attach themselves to the mast cells and basophils. Subsequent exposure to milk proteins causes the binding between the cell associated IgE and the allergic epitopes of milk proteins which triggers the release of inflammatory mediators which can cause a rapid anaphylactic response. This type of response can occur during the first exposure of neonates to cow's milk protein. IgE mediated CMPA is commoner in children than adults and resolves in 85% of cases. (5) The non IgE mediated CMPA does not have circulating milk protein-specific IgE. The symptoms develop anywhere between 1 hour to several days later, and hence is referred to as "delayed hypersensitivity". Usually cutaneous or gastrointestinal symptoms are associated like nausea, bloating, diarrhea, intestinal discomfort etc, which may mimic those of lactose intolerance. Anaphylaxis is rare. (5)

Contributory factors

Several factors influence the development of CMPA. While the industrialized nations are observing an increase in the occurrence of allergic disorders, this has been linked to the "hygiene hypothesis" which attributes the lack of early exposure to microbial infections to an increase in the occurrence of allergies. (6) The genetic factors involved in occurrence of CMPA is suggested by the strong family history of food allergy or atopy, wherein a possible four- fold higher incidence of CMPA may be associated with biparental atopy. (7) An early exposure to cow's milk protein in the diet is associated with the higher risk of developing CMPA. (8) Literature has shown that even breast fed infants may have manifestations of CMPA, which is related to the presence of low levels of cow's milk specific IgA in the breast milk that is responsible for sensitization in the infant. (9) Other factors that may influence the occurrence of CMPA and food allergy include the maternal diet during breast feeding, the age of introduction of solid foods and allergenic foods, exposure to pollutants, caesarian section and the maternal age. (8)

Symptoms

An accurate history is an essential frontrunner to pinpointing the symptoms which indicate the likelihood of allergy. (8) This alone could indicate the diagnosis in nearly 30-40% of cases, as has been shown by double –blind placebo controlled trials reported by Sampson. (10) A thorough history would elicit details relating to the amount and form of milk protein ingested and the interval from this till the symptoms developed, as well as the time period until resolution of symptoms. (5)

The symptoms depend on the organ affected- either the skin, GIT or respiratory tract. The symptoms are usually mild, but may occasionally be very severe, resulting in anaphylaxis. There is no pathognomonic symptom of CMPA, but the appearance of symptoms within the first few weeks after introduction of cow's milk could point towards the likely diagnosis. (4) Usually there is involvement of at least two out of the three organ systems, wherein the GIT is involved in 50-60% of cases, the skin in 50-60% and the respiratory tract in 20-30% of cases. (11)

Based on the organs involved, the symptoms of presentation vary (4,5):

GIT symptoms: any of these symptoms could point towards the likelihood of CPMA.

- frequent vomiting, posseting or regurgitation of feeds
- diarrhea, constipation with perianal redness or rash
- persistent and inconsolable cry or colic for ≥ 3hrs/ day at least 3 days /week and over a period of > 3 weeks
- blood in the stool
- persistent iron deficiency anemia

Dermatological symptoms:

- Unexplained urticaria
- Swelling of lips, eyelids etc
- Atopic dermatitis

Respiratory tract symptoms: develop in almost 60% of cases of CMPA. Symptoms include

- chronic cough, nasal pruritus, sneezing
- recurrent or chronic rhinorrhea, otitis media
- wheezing, tightness in the chest, dyspnea

Anaphylaxis

This is the most severe and life threatening form of CMPA. The incidence ranges from 10.9% to 28% of anaphylactic episodes in children. The symptoms can be related to any of the systems like the skin, GIT or respiratory tract. Respiratory anaphylaxis has been observed in almost 79% of the cases, and is associated with high mortality. (5) Symptoms may range from acute laryngeal edema, dyspnea, severe bronchospasm, or stridor. (4,5) Skin rash, severe urticaria including perioral, periorbital and palmo-plantar pruritus can suddenly develop. Nausea and persistent vomiting, severe abdominal pain and diarrhea could indicate severe anaphylaxis. These symptoms usually develop a few minutes after ingestion of cow's milk, and maximally up to 2 hours later. (5) Apart from these systems, there may be cardiovascular involvement which could manifest as hypotension, syncope or incontinence and vascular collapse, which is life threatening. Some confusion, tremors or seizures may also occasionally develop.

Late manifestations of CMPA

These symptoms develop any time after one hour of milk ingestion, maybe upto several days later. (5) These symptoms are not IgE mediated and may be non-specific, hence the diagnosis can be easily missed.

Cutaneous symptoms: usually moderate to severe atopic dermatitis which is found in almost 1/3 of the children. This can occur in extremely low birth weight babies also. Some reports have shown only umbilical and periumblical erythema, called as the "red umbilicus" to signify a localized form of atopic dermatitis due to CMPA. (12)

GIT symptoms: can be more extensive and varied. The spectrum could range from non specific symptoms like vomiting and long standing diarrhea to malabsorption and failure to thrive. (4,5) Gastroesophageal reflux disease related to CMPA is noted in 40-56% of cases and may be associated with delayed gastric emptying and gastric dysrhythmia which in turn may induce vomiting. (4,13)

CMPA can masquerade as symptoms of pyloric stenosis with an obstructive lesion. (5) It may also present with symptoms suggestive of crico-pharyngeal spasm and allergic esophagitis with post prandial vomiting, diarrhea and blood loss. It may also give rise to the food protein-induced enterocolitis syndrome (FPIES) which is generally noted when cow's milk is first introduced into the diet. The patient has repeated projectile vomiting, hypotonia and pallor which may or may not be associated with late diarrhea. Cow's milk protein induced enteropathy that is associated with failure to thrive and variable diarrhea, anemia and hypoproteinemia can lead to metabolic acidosis in young children. (5) CMPA must be considered in the differential when examining children who present with these varied GI symptoms. Mild to moderate anemia due to the vomiting and protein losing enteropathy usually has increased alpha -1-antitrypsin in the stools. Constipation is another manifestation of CMPA. (4,5,8) Cow's milk protein induced proctocolitis syndrome is observed especially in breast fed children, and is a benign disorder. (5) Low grade rectal bleeding is observed with flecks of blood noticed in the stools. This responds to elimination of cow's milk from the mother's diet. Heiner's syndrome is a rare condition that is caused by pulmonary hemosiderosis which develops secondary to CMPA. Recurrent pulmonary infiltrates are noted, which is associated with chronic cough, wheezing, tachypnea, recurrent fever and failure to thrive. (5)

Diagnosis

A strong suspicion along with a good clinical history would point towards the likelihood of CMPA as the diagnosis. The age of onset generally coincides with the addition of cow's milk in the diet. However, this may not also occur, as CMPA has been found to occur in completely breast fed babies. In suspected cases, an elimination diet followed by provocation and re-elimination is considered the standard procedure to diagnose CMPA, especially in young children. (5) The elimination of the offending antigen, in this case the cow's milk protein, for a few weeks is usually followed by the remission of symptoms. (5,8) Once there is improvement of the symptoms, a challenge of cow's milk is given under supervision and clinical observation. (4,5) Recurrence of the symptoms would point to the CMP as the causative agent. However, this method of diagnosis is unreliable and may result in false positive tests. (4,5,8) Double blind, placebo-controlled food challenge (DBPCFC) has been considered to give almost 70% positive results and may be the gold standard for diagnosis. (2,5) However, the risk of substantial allergy during the food challenge could limit the efficacy of this test. The food challenge tests must be carried out under direct medical supervision with the child hospitalized, so that any untoward reactions can be immediately identified and attended to. The test must be performed at least 2-3 hours after the last meal. The open challenge can be performed as the first step towards diagnosis of CMPA. In the first year, the challenge should be performed using an infant formula based on cow's milk. Above 1 year of age, fresh pasteurized cow's milk can be used. The starting dose should be below a dose that can give rise to a reaction. Where delayed reactions are anticipated, it is good to have a small amount starting at 1 ml with stepwise increments every 30 minutes until 100 ml volume is reached. In case severe reactions are anticipated, it is good to start with 0.1 ml volumes and increase in a step wise manner. If no reactions occur, the patient should be given milk feeds of 200 ml /day for at least 2 weeks, and the parents must be contacted at home for documentation of any late reactions. (1,5) If the child is able to ingest the milk without any reaction, the challenge is considered as negative for immediate reaction.

In cases of IgE mediated CMPA, the ideal method of diagnosis would include skin prick test and measurement of serum IgE levels. (2,4,5,8) Serum IgE levels are not useful as screening tools, as they only detect the presence of antibody, but do not indicate that ingestion of that particular food will cause symptoms. In those with suspected CMPA, the skin testing will aid in detection of circulating specific IgE antibodies, and is invaluable in those with IgE mediated CMPA. (8) False negative results do not occur but false positive tests may be problematic. The skin prick test is useful only when the suspicion of IgE mediated CMPA is suspected, as it is 95% sensitive, but only 50% specific. (8) Studies have shown that the combination of strongly positive skin tests along with allergen specific IgE assays, produce a 95% positive predictive value in those with IgE mediated CMPA. (8) In cases of non IgE mediated CMPA, these skin prick test and IgE estimation does not have a role, but patch testing may be useful in these cases. (2)

The radio allergosorbent assay (RAST) is a semi quantitative test that helps to detect IgE mediated food allergy. (8) A quantitative assay of the food specific IgE, referred to as the CAP- system fluorescent enzyme immunoassay has been shown to be much more effective in diagnosing CMPA, resulting in the virtual elimination of food allergen challenge tests by nearly

50%. (10) A wider utilization of this method of testing will go a long way in decreasing the false positives and reducing the false negative tests.

Newer advances in molecular technology have resulted in the mapping of the IgE binding regions of milk proteins and other food allergens. This makes it possible to accurately locate the binding region of the patient's IgE. In those with antibodies that react to the sequential isotopes, there is an allergic reaction to minute amounts of milk protein and this tends to be persistent. In those who have antibodies to conformational epitopes, it is possible to accept small quantities of processed milk protein which is extensively heated or partially hydrolyzed, as the epitopes are. significantly modified or even destroyed due to the processing. (10,14)

In case of non IgE mediated CMPA, there are no confirmatory laboratory investigations. Supportive tests may be indicative of the diagnosis in clinically suspected cases. These supportive tests are:

- Decreased serum albumin could be suggestive of enteropathy, while increase in acute phase reactants, increased platelet count and elevated fecal leukocytes are non specific indicators of inflammation 2.
- Eosinophilic leukocytosis may be found in both IgE mediated as well as non –IgE CMPA.
- Colonic biopsies may show mucosal eosinophilic infiltration, which is usually focal in distribution. (8) These can be missed during the procedure and result in false negative results.
- Wireless capsule endoscopy is a newer advance which allows visualization of the entire small intestine. Areas of focal villous edema or atrophy are suggestive of CMPA.

According to the European Academy of Allergy and Immunology (EAACI GA2LEN), skin prick tests and serum IgE estimations are only indicated in cases of persistent moderate to severe food allergy. Diagnostic elimination diet for 4-6weeks, followed by an oral challenge after a period of stabilization is the preferred method of diagnosis recommended by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and also recommended by the EAACI-GA2LEN. (5)

Mixed IgE and non IgE mediated reactions to cow's milk protein can also occur and this is suspected in cases which involve the GI tract and are not very closely associated with the ingestion of cow's milk. (15) This manifests with non-specific symptoms like reflux, abdominal pain, dysphagia and food impaction. Eosinophilic esophagitis is noted on intestinal study and biopsy, which is detected by the presence of over 15-20 eosinophils per high power field. Sometimes, it could also manifest as a contact urticaria.

Management of CMPA

Elimination diet

In suspected cases of CMPA, the avoidance and elimination of dairy products serves as a diagnostic test as well as a therapy. It is essential to completely eliminate all dairy products, so that there is no accidental ingestion of cow's milk, no likelihood of inhalation of cow's milk vapors and no skin contact with it. The cross reacting animal milks like buffalo, goat or sheep milk must also be avoided. In cases of suspected CMPA in breast fed babies, the mothers must be advised to have a milk free diet with adequate calcium supplements. (1,2) For non-breast fed infants and toddlers, a hypoallergenic formula must be prescribed, while in those over the age of 2 years, no formula is generally required. It has been opined that in the absence of any definitive diagnostic test, the clearing of symptoms that are noted upon elimination of the milk protein is sufficient to make a diagnosis. (15) The duration of the elimination diet should be at least 2 weeks but can extend upto several weeks in case of delayed reactions. The ESPGHAN recommends an elimination diet of at least 6months or until the age of 9-12months and those with severe reactions upto 12-18 months, before undertaking an open challenge test. (1) Once there is improvement of the symptoms, further diagnostic steps may be undertaken, or the challenge test could be performed to look for recurrence of symptoms or development of tolerance to cow's milk.

Replacement feeds

In non-breast milk fed infants, it is essential to provide a hypoallergenic formula (HF) that will provide all the nutritional requirements for growth. Extensively hydrolyzed milk (eHF) formulas are those that contain only peptides with a molecular weight < 3000 Da derived from casein or whey proteins. (1,2,5,8) These preparations have an efficacy of almost 90% in the treatment of CMPA. However, these products do have potentially allergenic substances, and hence may produce symptoms similar to an allergic reaction. A rice based eHF is available that is useful but not commercially available. (2) Hence, in cases of severe allergy, or resistance to e-HF formulas, it may be necessary to recommend amino acid based formulas (AAF). (5,8) Formulas containing amino acids as the only nitrogen source could be considered as the best option for the group which reacts to eHF formulas. This may be approximately 10% of all cases of CMPA, but the prevalence may be higher in those with severe enteropathy or multiple food intolerance. (1,5,8) AAF is well tolerated by at least 90% of infants of CMPA infants. (5) AAF is the first choice in cases of anaphylaxis, eosinophilic esophagitis as well as in cases of delayed GI reactions in infants older than 6 months. The ESPGHAN and Australian Consensus Panel recognize the AAF as non-allergenic and recommend it as the choice of formula for highly sensitive patients. (5) It may also be used in cases of Heiner's syndrome as recommended by the Australian Consensus panel.

A partially hydrolyzed formula (pHF) has been developed to provide better palatability and more cost effectiveness as compared to the eHF. (8) Although this formula was aimed at developing natural tolerance to milk proteins, without causing sensitization with better organoleptic properties, these preparations do retain some antigenicity and hence are not indicated for use in established cases of CMPA, but may be of use in

preventing CMPA in infants at risk. (8)

Soy based formulas may be used in infants with IgE associated symptoms of CMPA, especially above the age of 6 months. (5) These formulas are cheaper and often better tolerated than eHF or AAF. However, the protein present in soy may stimulate the development of allergic symptoms. Concomitant CMPA and soy protein allergy in CMPA infants ranges from 0-60% according to various studies. (8) Also, the presence of a high concentration of phytate, aluminum and isoflavones in the soy can produce undesirable side effects. (5) A recent study including 170 infants with documented CMPA were randomized to receive either soy protein formula or cow's milk based eHF. The results showed that almost 10% reacted to the soy protein formula versus only 2.2% in the eHF group. (16) The usage of soy based formulas is recommended only in soy naïve IgE positive CMPA. (8) The ESPGHAN and AAP recommend the use of soy protein formulas only in infants over 6 months of age who do not tolerate e-HF or if the cost of these formulas are inhibitory factors. (1)

Other animal milk has been tried as alternates to using formulas in cases of CMPA. Goat's milk is less allergenic as it contains lower levels of alpha casein. However, cross reactivity between goat's milk and cow's milk exists, hence almost 95% of children with CMPA do react to goat's milk also. (5) Camel's milk is used in some geographical regions of the world, and may be useful as a substitute to cow's milk as it has lesser amounts of beta lactoglobulin that could induce allergy in those with CMPA. (17)

Other treatment modalities:

- Immunomodulation using various products has been attempted as a method of inducing desensitization in cases of CMPA. Some studies have shown the value of using probiotics to skew the immune response in children over the age of 2 years, but definite evidence is lacking. (1,5)
- Polyunsaturated fatty acids (PUFA) especially gamma linoleic acid and n3-long chain PUFA have been investigated in children with eczema. These are precursors of prostaglandins, especially PGE1, which is lacking in children with allergy. The PGE1 is in competition with PGE2, the inflammatory mediator, which gives rise to alterations in T cell mediated immune responses. (5) PUFA's may be useful in some cases of CMPA.
- Complementary and alternative medicine: Herbal medications have been tried in cases of food allergy and asthma. Chinese herbal medications have been useful in treating vomiting and diarrhea. (5) These medications provide symptomatic relief, and there are as yet no studies to document their preventive effects in CMPA.
- Role of heating and pasteurization of cow's milk: The process of pasteurization is done mainly to sterilize the cow's milk. However, this also has some actions on the proteins that are present in the milk. Pasteurization induces the aggregation of the whey proteins like α-lactalbumin and β-lactoglobulin, but has no effect on casein. (18) These aggregates are pushed towards the Peyer's patches and produce higher levels of IgE and Th2 cytokine responses which are associated with sensitization to them. Heating the milk is not associated with aggregation of the milk proteins. Some studies have shown that heating the milk at 100 degree C for 30 minutes was associated with no alteration of the α lactalbumin and β lactoglobulin. (19) Rytkonen et al opined that the allergenicity was maintained despite severe heat treatments. (20) Roth –Walter et al however felt that cooking and heating was associated with diminished antigenicity of α lactalbumin and β lactoglobulin and hence this was better tolerated by patients. (18)

Prognosis of CMPA

Long term outcome: The natural course of CMPA usually involves the resolution of the allergy and development of tolerance to cow's milk later in life. The time course for this varies and may extend upto teenage years. A possible prognostic factor is the initial level of IgE at diagnosis especially in the first 2 years of life, which is indirectly proportional to the rate of resolution of symptoms. (15) A drop in IgE levels over time, in children could be indicative of the development of tolerance. Some recent studies have shown that by age 4, approximately 5% of children developed tolerance, while 21% were tolerant by age 8 years. The absence of other allergic conditions like allergic rhinitis and childhood asthma are associated with better outcomes. Those with less reactive skin prick tests and lesser specific IgE levels developed milk tolerance earlier. (2) Cow's milk protein must be slowly and gradually reintroduced in a trial manner, above the age of 1 year. As the natural history of CMPA shows that many of these children outgrow their allergy, periodic re-evaluation of tolerance through diagnostic challenges will help to prevent the continuance of elimination diets. (5)

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