# COW'S MILK PROTEIN ALLERGY

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Cow's milk protein allergy (CMPA) is one of the most common food allergies in children. It affects between 2%-3% of children in developed countries and is amongst the top five food allergens in children in South-East Asia (Bahna, 2002). In Singapore, CMPA ranks as the second most frequent cause of food allergy in children.

CMPA is due to an adverse immunological reaction to cow's milk protein (most commonly casein or whey). It needs to be distinguished from lactose intolerance, which is due to a relative (or absolute) lactase deficiency and is a non-allergic reaction to cow's milk (Barnetson and Rogers, 2002).

Intolerance to food may be caused by enzyme deficiency, such as lactose intolerance, or toxic effects, as is seen in the case of bacterial contamination, or specific pharmacological properties of the food itself, such as histamine release. This is distinct from an allergic reaction, which is an immunological reaction.

**Classification of CMPA**

The immunological reaction to cow's milk protein may be IgE-mediated or non-IgE mediated (Barnetson and Rogers, 2002). IgE-mediated reactions are often immediate, and include urticaria, angioedema, anaphylaxis, bronchospasm, atopic dermatitis, and acute vomiting and diarrhea. Intermediate reactions are predominantly gut related. An example would be an entity known as eosinophilic gastroenteritis. Delayed reactions are mainly gastrointestinal (GI) in nature and include symptoms of gastrointestinal reflux, proctitis, enterocolitis, and protein-losing enteropathy. Pulmonary hemosiderosis is an example of a pulmonary manifestation of a delayed reaction. Children with CMPA may also have allergies to other foods; most commonly soy protein and egg. Many of them also have a personal history of atopy, or family history of atopy.

Sixty percent of CMPA is IgE mediated, with the remainder non-IgE mediated. In addition, half of patients with CMPA will also have atopic dermatitis, particularly those less than 1 year of age. It is also common that children with CMPA (~35%) may also have allergies to other foods.

**Clinical presentation**

CMPA typically presents within the first few months of life. In most instances, a good history and physical examination are sufficient to make a diagnosis. In children with moderate to severe eczema, 35% may have food allergy as a contributing factor (Eigenmann *et al*, 1998). However, in children with mild eczema, less than 10% would have food as the trigger (Høst, 2002). Coughing or wheezing as the sole manifestation of food allergy is very rare. Children with CMPA usually develop symptoms in at least 2 sites; GI, skin or respiratory (Hill *et al*, 1997).

The manifestations of IgE-mediated

food allergy are easily recognized with the rapid onset (usually within 30 minutes) of GI anaphylaxis, periorbital edema, and the oral allergy syndrome. Non-IgE mediated reactions, however, are more challenging to recognize, mainly because these manifestations are delayed (hours to days), with no clear temporal association with the offending food.

A commonly encountered scenario is a young infant, perhaps 3 weeks old, exclusively breastfed who presents with recurrent episodes of vomiting, irritability, and fussing. Possible differential diagnoses include GER, CMPA, or infantile colic. It is sometimes difficult to distinguish between GER and CMPA, as both share common features: similar symptoms, similar age of onset (first year of life), and similar natural history (resolution within the second year of life). In addition, 20%-30% of infants with GER could also have CMPA. However, it may be possible to distinguish these two diseases with a careful history. Children with GER in whom CMPA is also present, will have additional features. These include nasal congestion, eczema, blood in the stool, and/or a strong family history of atopy.

Investigations are usually unnecessary if (uncomplicated) GER is suspected. It would be important to reassure parents, as well as give simple feeding advice, such as positioning the infant during/after feeds, and the use of milk thickeners. In children with GERD and complications, further investigations, and/or referral to a specialist should be considered (Iacovou *et al*, 2012).

Reassuringly, 90%-95% of infants with infantile colic do not have an underlying organic cause. A detailed history and physical examination are important to establish this. Pathological causes of infantile colic can be considered broadly in three categories: GI causes, infections, or trauma. GI causes include CMPA, lactose intolerance, GERD, intussusceptions, or strangulated inguinal hernias. Infections can be of the central nervous system, middle ear, or urinary tract. Trauma from subdural hematomas, fractures or foreign bodies in the eyes may also be (rare) causes of symptoms that mimic infantile colic.

Red flags that would alert one to possible organic causes of infantile colic include symptoms suggestive of GERD (vomiting, arching, choking, gagging, coughing), food allergy (atopic child or family history of atopy), or signs such as blood in the stool (CMPA), failure to thrive or an abnormal physical examination (Iacovou *et al*, 2012).

The issue whether CMPA or other food allergies contribute towards the development of infantile colic has been studied. A recent systematic review looked at the dietary management of infants aged 6 months or less with infantile colic (Vandenplas *et al,* 2013). Mothers in the study were aged between 18-45 years and otherwise healthy. A variety of studies with different study designs were included: randomized controlled trials, cohort studies, case-control studies, and cross sectional studies. The review interestingly found that a reduction in infantile colic was seen in mothers who eliminated common food allergens from their diet; these included dairy, soy, eggs, peanuts, wheat, and fish. Use of an extensively hydrolyzed formula also showed a reduction in crying time from 4.9 to 2.7 hours/day.

Another commonly encountered scenario would be an exclusively breast-fed

infant with blood in the stool. This infant typically develops blood streaks in his stool when cow's milk formula is introduced. The infant is otherwise clinically well and thriving. This is a typical example of food protein-induced proctocolitis of infancy. Fresh bleeding is often noted *per rectum*. It is rarely severe. The child is healthy, with no signs of vomiting, diarrhea, anemia, or failure to thrive. A family history of allergy, such as eczema, can be seen in up to 25%, and the commonest precipitants are CMP or soy protein. Histology performed to confirm the diagnosis typically reveals eosinophils and crypt abscesses on biopsy. In most cases, invasive procedures for investigation are unnecessary. Most times, in patients with a suggestive typical history, a 2-week trial of elimination of the offending food (CMP) and watching for resolution of symptoms is sufficient to reach the diagnosis.

Another typical presentation would be that of an older child, for example, 13 months of age, presenting with increasing pallor, anorexia, and irritability. On examination, the child may have clinical features of hypoalbuminemia (such as periorbital edema, or pitting edema of the lower limbs). Laboratory testing reveals iron deficiency anemia and hypoalbuminemia but no proteinuria. This describes a picture typical of food-induced enteropathy with malabsorption, failure to thrive, hypoproteinemia, with or without diarrhea and vomiting. The prototype for this condition is Celiac Disease, which is uncommon in Asian populations. Histology is necessary if this diagnosis is suspected, and this typically finds patchy villous atrophy with cellular infiltrates and eosinophils. Treatment is with the complete exclusion of cow's milk, and if needed, the use of an extensively hydrolyzed formula.

**Diagnosis**

Most of the time, a careful history is all that is required to make the diagnosis of CMPA (Vandenplas *et al*, 2007). The number of children needing confirmatory investigations is actually very few. If IgE-mediated reactions are suspected, skin prick tests (SPTs) and specific serum IgE testing may be performed. IgE-mediated testing has a good negative predictive value (>95%) but is less robust in its positive predictive value. SPTs are also not as reliable in infancy.

Although the diagnosis of non-IgE-mediated CMPA requires histology, most times this is not done, because a presumptive diagnosis can be made based on a therapeutic response to CMP exclusion. However, infants in whom there is no response to CMP exclusion, or there is suspicion of multiple food protein allergies, or the presence of other complications, then endoscopy and biopsy should be performed.

Food challenges to diagnose food allergy may be indicated where the diagnosis is in doubt. While the gold standard is a double-blind placebo controlled challenge, open label studies are logistically more practical to organize. In-hospital food challenges should be performed for children in whom severe IgE-mediated reactions are anticipated.

**Management**

The key to management of CMPA is total avoidance of cow's milk (Vandenplas *et al*, 2007). It is also important to inform parents that children with CMPA should also not take other mammalian milk, such as goat or sheep milk. For breastfed

infants, mothers should be advised to completely exclude cow's milk from their own diet. It is also important to educate mothers on alternative sources of calcium, how to maintain a balanced nutritious diet, and teach them how to read food labels to avoid foods with traces of CMP.

In formula-fed infants with IgE mediated CMPA, soymilk may potentially be used. However, 10%-15% of them may also be allergic to soy. For infants with non-IgE mediated CMPA, up to 50% will also be allergic to soy. In these instances, an extensively hydrolyzed formulas (EHF) or amino acid based formulas (AAF) is indicated.

Fortunately, prognosis in CMPA is excellent. Resolution of CMPA at 2, 3, and 4 years is ~30%, 53%, 63%, respectively in IgE-mediation allergies, and 64%, 92%, 96%, respectively for non-IgE-mediated allergies (Hill *et al*, 1997). Clinicians can plan to re-challenge children at 1 year of age, and if the child fails this, they may be re-challenged at 6-monthly intervals. For children who have IgE-mediated reactions, clinicians may choose to wait until a skin prick test is negative before attempting to re-challenge them.

In summary, it is important in CMPA to make an accurate diagnosis, distinguishing allergy from intolerance. The history is an extremely key element in making the correct diagnosis. Treatment is to avoid exposure to the allergen in formula-fed child and to the mother in a breastfed infant. Children in whom referral should be considered are when alarm symptoms and signs are present; failure to thrive, feed refusal, feed aversion, iron deficiency anemia from GI blood loss, hypoalbuminemia, and symptoms refractory to amino acid formula. These children should be referred to a pediatric gastroenterologist for further assessment. If anaphylaxis or multiple food allergies are suspected, referral to an allergist may be helpful. Any child with chronic ENT and respiratory symptoms can be referred to a chest physician or ENT surgeon for assistance in further management.

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