Managing cow’s milk allergies in children

Cow’s milk allergies affect many toddlers but the prognosis is positive and most achieve tolerance later, writes Emily Stenke and Jonathan Hourihane

Food allergies affect 6% and 8% of children in the UK. Of these, cow’s milk protein allergy (CMPA) is one of the more common allergens and affects 2.5% of children less than one year of age. In Ireland in 2008, this was equivalent to 1,765 babies under one year of age with CMPA. The cause of food allergies, including CMPA, is unknown. However, the incidence is highest in children with a family or personal history of atopy (asthma, eczema, hay fever and food allergies) and a significant proportion of children with food allergy will go on to develop one or more of the three other atopic disorders later in life.

The majority of food hypersensitivities are immunoglobulin E (IgE)-mediated, where exposure to an antigen triggers immediate release of preformed histamine and a reaction occurs within minutes but may be delayed up to two hours. Non-IgE (thought to be cell-mediated) reactions to cow’s milk protein (CMP) are also recognised and these tend to have a more sub-acute presentation. Examples include eczema, food protein induced enterocolitis syndrome (FPIES) and food protein enteropathy (FPE). Finally, there is a group where the reaction is mediated by eosinophils, eg. eosinophilic oesophagitis, which can present as persistent gastro-oesophageal reflux disease, food refusal or failure to thrive.

Clinical presentation

The majority of children with CMPA will present in early infancy if formula-fed or on weaning if breastfed. Less commonly, breastfed babies may react to CMP in the mother’s diet transmitted through breastmilk. Babies with IgE-mediated allergy may present to their GP with a history of vomiting with feeds, a new urticarial rash or worsening of their pre-existing eczema, with swelling of the lips, eyes or all of the face, or with a wheeze. Anaphylaxis is rare at first presentation. An important fact to ascertain in the history is the consistency and timing of the reaction: in a true IgE-mediated allergy the reaction will occur on every exposure, even to very small amounts of the allergen. It will usually occur within minutes of exposure, although it may be delayed by up to two hours.

Babies with cell-mediated hypersensitivity may have eczema, food protein induced enterocolitis syndrome (FPIES) or food protein enteropathy (FPE). The latter two present typically with persistent vomiting, diarrhoea and failure to thrive. In the case of FPIES the vomiting and diarrhoea occur within minutes to hours after exposure to CMP. The diarrhoea may be bloody, microscopy will reveal neutrophils and eosinophils and the patient may be very dehydrated and sick. FPE is more chronic, presenting with vomiting, non-bloody diarrhoea and failure to thrive days to weeks after regular exposure to CMP. Examination may reveal abdominal distension and oedema.

There is a perception among some parents that eczema and/or asthma are caused by intolerance to certain foods and many attempt exclusion diets to improve their child’s condition, to the detriment of their nutrition and quality of life. It is important when taking a history from parents to ask if they have noted an immediate and consistent link between each ingestion of cow’s milk and an eczema flare or wheeze: in the absence of this, IgE-mediated CMPA is highly unlikely and reintroduction of dairy and other foods should be recommended. Eczema can be caused or exacerbated by a non-IgE-mediated reaction to CMP. There is no specific test for this and if it is suspected a trial of exclusion of CMP can confirm or exclude the diagnosis. It must be agreed with parents to reintroduce milk after four to six weeks as any improvement in skin disorders may be due to better topical care or simply the passage of time, rather than the elimination of CMP. This also prevents the onset of sequential unjustified exclusion of other foods when the eczema hasn’t improved on CMP exclusion.

Diagnosis

In the presence of a suggestive history, a provisional exclusion of milk products and referral to an allergy specialist for further investigation is warranted. The cornerstones of investigation for IgE-mediated allergy are skin prick testing (SPT) and specific IgE levels (SpIgE) for CMP. Blanket testing for other allergens is not performed in the absence of a history of possible reaction as false positives occur. SPT is a simple test but is operator-dependent and should not be performed sporadically. Results are read after 20 minutes and a wheal size greater than the control is considered positive.

SpIgE levels are measured in the blood and results are available in a few weeks. The cut-off for a positive result for CMP SpIgE is 3kU (CI of 95%). SpIgE levels are operator-independent and the results are standardised internationally. In a child with a typical history and positive SPT and/or SpIgE, the diagnosis of IgE-mediated CMPA is confirmed. In children with conflicting indicators, eg. an unclear history with low positive results or in those with a clear history but negative investigations, an oral food challenge can be helpful. An oral food challenge is performed in hospital with all rescue medications on hand. It consists of giving the child incremental doses of the suspected allergen until a normal portion size is reached, eg. 100-200ml of milk. At any objective sign of allergic reaction the challenge is stopped and medications given as needed, eg. cetirizine,
salbutamol nebs or, rarely, intramuscular adrenaline. Oral food challenges have been shown to reduce anxiety and improve quality of life in children and their parents regardless of whether they fail or pass. A passed food challenge outrules allergy and allows the food to be reintroduced, while even with a failed food challenge parents are reassured to see how manageable the reaction usually is and can put their nightmare of instant anaphylaxis and death on exposure to tiny amounts of allergen to one side.  

FPIES and FPE can be diagnosed with the help of stool microscopy and small bowel biopsy but more usually by resolution of symptoms on exclusion of milk products.

Management and follow-up

The cornerstone of management of any food allergy, including CMPA, is avoidance. In breastfed babies, avoidance of dairy products by the mother will suffice (in which case she should take calcium supplements) and for bottle-fed babies extensively hydrolysed formulae (eHFs) can be substituted for cow’s milk-based formulas. Amino acid-based formulae are used ab initio for infants with severe symptoms or in those children who do not tolerate eHF. Such infants should be under the care of a paediatrician. Goat’s milk and soya milk-based formulas are not recommended as there is a high incidence of cross-reactivity between cow and goat milk proteins, and soya is not tolerated in up to 50% of children with cow’s milk protein intolerance. Rice milk is not recommended for children under the age of 4.5 years as it is contains relatively high levels of arsenic. In older children, dairy products can be avoided entirely but assessment and review by a dietician is recommended to ensure adequate intake of calcium. Accidental exposure is, however, almost inevitable despite parents’ awareness and indeed usually occurs when the child is temporarily under someone else’s supervision. Carers should be educated and equipped to deal with reactions. In cases of a mild reaction no treatment may be necessary and it resolves by itself over a few hours. In cases of more severe itch or swelling parents can give a non-sedating anti-histamine, eg. cetirizine, to control the symptoms. Anaphylaxis is rare but unpredictable and it is potentially lethal. For this reason the parents of all high risk children with CMPA should be equipped with and instructed in the use of an Anapen (intramuscular adrenaline auto-injector). This includes any child with a history of anaphylaxis to CMP, or history of a generalised allergic reaction with a co-diagnosis of asthma. An Anapen may also be considered if the child has suffered a previous generalised reaction and lives far from emergency medical care.  

The prescription of the Anapen should be reviewed at each clinic appointment to ensure that parents know when to use it, how to use it and that the prescription is appropriate for the child’s weight and age.

Children with CMPA should be regularly followed up and re-evaluated, to monitor their growth, provide support and education to the parents and to assess for emergence of tolerance. Our practice is three-monthly SPT and SpIgE in children under the age of one year, six-monthly up to two to three years of age and yearly thereafter. If SpIgE and/or SPT measurements are decreasing and the child has not had any accidental exposure to CMP in the preceding year, it is reasonable to repeat an oral food challenge to confirm continued sensitivity.

### Summary of CMP allergy

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<tr>
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<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
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<tbody>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Release of pre-formed histamine</td>
<td>Cell-mediated</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Rapid, within minutes of every exposure</td>
<td>Subacute, after repeated exposure</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Urticaria, angio-oedema, wheeze, anaphylaxis</td>
<td>Eczema, FPIES/FPE: vomiting, diarrhoea (+/- bloody), failure to thrive</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>History + skin prick test + SpIgE +/- oral food challenge</td>
<td>History + resolution on elimination, recurrence on reintroduction</td>
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<tr>
<td><strong>Treatment</strong></td>
<td>Avoidance</td>
<td>Avoidance</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Up to 87% tolerance by three years; higher likelihood in non-IgE-mediated form</td>
<td>Better than IgE but rarely conclusively measured</td>
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### Prognosis

Many studies have looked at the natural history of CMPA and the prognosis of children with CMPA is generally positive. Studies of unselected birth cohorts demonstrated a rate of tolerance of 56% at one year, 77% at two years and 87% at three years. In another study, tolerance was shown to develop in 28% by two years, 56% by four years and 78% by six years. The largest study to date, a retrospective study of a highly selected tertiary care cohort of 807 patients followed up to age 16 years, demonstrated tolerance rates of only 19% by four years, 42% by eight years, 64% by 12 years and 79% by 16 years. There is currently no reliable method of predicting which children will develop tolerance. However, there are several indicators. Studies agree that children with IgE-mediated allergies are less likely to develop tolerance than those with non-IgE-mediated. In those with IgE-mediated allergy, low CMP SpIgE levels and small SPT wheal size have been shown to be associated with a higher likelihood of developing tolerance. Studies also show that patients produce IgE against different portions of the CMP molecule and suggest that those who produce IgE against sequential epitopes (unaffected by heating) are less likely to achieve tolerance than those with IgE directed against conformational epitopes (affected by heating). Exposure to heated milk products for the promotion of tolerance to CMP is an emerging treatment strategy but should only be undertaken after expert review. Oral immunotherapy strategies are also emerging but the current consensus is that these remain research activities only.

### Re-evaluation

In summary, CMPA allergy, both IgE and non-IgE-mediated, is common in young children. Diagnosis is primarily based on the history and investigations should not be performed without a strong clinical suspicion. The cornerstone of management remains dietary avoidance with access to rescue medications and frequent re-evaluation to permit early reintroduction of dairy products if tolerance develops.