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SUPPORTING THE APPROPRIATE DIAGNOSIS OF COW'S MILK ALLERGY:
LEARN FROM AN EXPERT

Webinar summary booklet

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WEBINAR SPEAKERS



DR NICK MAKWANA (leading the session)

Consultant Paediatrician, Sandwell and West Birmingham NHS Trust Group Director (Women and Child Health), Sandwell and West Birmingham NHS Trust Accredited Paediatric Allergist (EAACI) MBChB Paediatric Curriculum Lead, University of Birmingham



DR GEORGINA BENNETT

General Practitioner, Birmingham

INTRODUCTION

This booklet is a summary of a webinar entitled "Supporting the Appropriate diagnosis of Cow's Milk Allergy". Rather than the traditional webinar format, this was a discussion between a leading allergy expert Dr Nick Makwana from Birmingham in the UK, in conversation with Dr Georgina Bennett a recently qualified General Practitioner keen to understand more about recognising and managing cow's milk allergy (CMA) in her patients.

The discussion between the colleagues will cover the challenges General Practitioners face, the allergy guidelines, the role of testing and also the first line management of cow's milk allergy.

WEBINAR SUMMARY

BRIEF INTRODUCTION TO CMA



Dr Makwana first set the scene by describing cow's milk allergy (CMA). CMA is a reproducible reaction to one or more milk proteins, mediated by several immune mechanisms. The EuroPrevall Birth Cohort Study showed us that the incidence of CMA across Europe is around 1%, with individual variation between countries.[1]

Dr Makwana explained that the onset of CMA usually occurs after exposure to cow's milk or a cow's milk containing product. The development of symptoms can be within a day or two of first exposure or it can take weeks for symptoms to develop; a child may have been consuming cow's milk products for some weeks before showing a reaction.

Dr Makwana shared that most infants with CMA will present by six months old. However, the average age of presentation is around three months old, coinciding with the introduction of additional milk into the diet. CMA is one of the most common reasons for General Practitioners (GP) to make a referral from primary to secondary care, particularly given that CMA symptoms overlap with dermatological and gastroenterological issues.

THE CHALLENGES OF RECOGNISING CMA



Dr Bennett asked Dr Makwana to share some of the challenges GP might face when recognising CMA. Dr Makwana explained that recognising CMA is particularly challenging with non-IgE-mediated allergy. IgE-mediated food allergy can be recognised quickly with obvious and definitive symptoms (e.g. hives, eye, and lip swelling) which occur shortly after eating a trigger food. Non-IgE-mediated allergy, however, can mimic symptoms of common childhood conditions seen in primary care (e.g. reflux, eczema, constipation, and colic).

Dr Bennett asked if there are any key indicators for these symptoms that could suggest CMA. Some such indicators include:

- Reflux with back arching (Sandifer's Syndrome) and not responding to standard treatments such as thickening of milk, proton pump inhibitors, reducing the amount of feed and feeding more frequently
- Eczema persisting beyond optimised treatment
- Constipation with straining but normal stools (dysmotility)
- Colic which unsettles a child for a full day rather than just in the evening

There is often a long route to diagnosis of CMA due to this symptom overlap. Dr Makwana recommended that CMA should be considered for patients with repeated visits for whom treatments are not working.

THE CHALLENGES OF RECOGNISING CMA continued



Dr Bennett expressed that there is often a concern about mis- or overdiagnosis of CMA in primary care. There is the potential for misdiagnosis of CMA, for example when mistaking symptoms for non-immune conditions such as lactose intolerance. Overdiagnosis of CMA may also occur due to the described symptom overlap with common conditions. Dr Makwana explained that overdiagnosis can be reduced by addressing these symptoms first. If response to treatment is poor, or if there is a combination of symptoms triggering "alarm bells" (e.g. severe eczema and faltering growth); Dr Makwana recommended considering CMA. Parents also may present with their own diagnoses or expectations of a CMA; it is important to work through parents' concerns if they suspect CMA.

Our panel discussed how current issues limiting access (e.g. COVID) have made it difficult for the diagnosis of CMA. Timely access for parents has been a problem and the move to virtual consultations has made it more difficult for GPs to assess patients for CMA (e.g. reviewing severity of eczema, measuring faltering growth).

ALLERGY GUIDELINES



Dr Bennett asked if there are any guidelines for health professionals to follow when diagnosing and managing CMA. Dr Makwana shared the key guidelines for the diagnosis and management of CMA in primary care that can be put into place with ease. These include:

- The National Institute for Health and Care Excellence (NICE) Food Allergy Guidelines[2] – These include an overview of prevalence, diagnosis, management and when to refer to secondary care
- iMAP (Milk Allergy in Primary Care) Guideline[3] – CMA specific, these are interactive with decision algorithms that can be used online
- British Society of Allergy and Clinical Immunology (BSACI) Guidelines[4] – These cover both primary and secondary care, including an overview of testing, exclusion diets and reintroduction ladders

Dr Makwana also shared international guidelines. They include:

- European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce
- World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines (updated 2022)[5]

He noted that most guidelines are similar in terms of diagnostic processes, but can differ slightly in terms of management and in their recommendations around infant formula feeding. CMA diagnosis is based on an allergy focussed history (for example, as seen in the NICE guidelines) with diagnosis placed in one of four groups; mild to moderate non-IgE-delayed onset, severe non-IgE-delayed onset, mild to moderate IgE-mediated immediate onset or severe IgE immediate onset (anaphylaxis).

ALLERGY GUIDELINES continued

Most infants with suspected CMA will present with mild to moderate non-IgE symptoms. These infants should be diagnosed and managed in primary care providing secondary care referral is not indicated. Remaining children with suspected severe non-IgE or IgE CMA should be referred onward to secondary care.

All guidelines also recommend that for all infants presenting with suspected CMA, breastfeeding should be continued and should only be stopped at an age and time as chosen by the mother. If an initial hypoallergenic formula does need to be prescribed, then the correct one must be chosen (an extensively hydrolysed formula should be considered as a first line option).

UNDERSTANDING THE DIFFERENT TYPES OF CMA

Dr Bennett asked Dr Makwana to expand on how the different types of food allergy can make diagnosis more complex. Dr Makwana explained that in non-IgE-mediated allergy, the mechanism is unknown, therefore no distinctive test is available. Additionally, symptoms are delayed, making it difficult to connect food triggers. Presentation history, and the use of food diaries is key for making these connections.

Dr Makwana emphasised the impact of timely diagnoses on quality of life (QoL) of the child and family. IgE-mediated allergy is recognised and referred quickly to secondary care; with less impact on QoL. Non-IgE-mediated allergy, however, has a delayed diagnosis and therefore is more often associated with a significant impact on QoL for the child and family.

Dr Makwana summarised the different presentations of CMA, below (table one).

Table One: Cow's Milk Allergy Presentations: IgE-mediated vs non-IgE-mediated

IgE-mediated	Non-IgE-mediated
Skin Pruritis, erythema Acute urticaria - localised or generalised Acute angioedema - most commonly of lips, face and around eyes **Gastrointestinal system** Angioedema of lips, tongue and palate Oral pruritis; nausea, vomiting, diarrhoea Colicky abdominal pain **Respiratory system (usually with above)** URT symptoms (nasal itch, sneeze, rhinorrhoea or congestion) LRT symptoms (wheeze, cough, DIB) **Anaphylaxis**	**Skin** Pruritis, eczema, atopic eczema* **Gastrointestinal system** Gastro-oesophageal reflux disease* Loose or frequent stools Blood and/or mucus in stools* Abdominal pain; infantile colic Food refusal or aversion Constipation Perianal redness Pallor and tiredness Faltering growth with at least one or more of GI symptoms (± eczema)

*Do not respond adequately to treatment

PRACTICAL STEPS TO CMA DIAGNOSIS



Dr Makwana outlined practical steps in the diagnosis of CMA. He suggested that alongside symptom-based questions, the allergy focused history is key and recommended that the following should be considered:

- Frequency of reaction to a food
- Speed of the reaction
- The amount of food causing the reaction
- What action has been taken because of symptoms (e.g. have foods been eliminated or substituted)

Family history of atopy and any associated symptoms (e.g. faltering growth) should be considered alongside weaning practices, immunisation history and use of medications.

"Red Flags" to recognise when taking an allergy history were discussed. Dr Makwana explained that "red flags" to watch for include IgE-mediated symptoms (such as anaphylaxis). For non-IgE-mediated allergy, factors such as faltering growth or parental anxiety should be assessed. Unusual presentations of CMA include food protein induced enterocolitis syndrome (FPIES), eosinophilic oesophagitis (EoE), and proctocolitis.

THE ROLE OF TESTS IN DIAGNOSIS OF CMA



Acknowledging the importance of the allergy history, Dr Bennett asked if there are any tests that should then be considered for the diagnosis of CMA. Dr Makwana explained that for IgE-mediated allergy, there are two types of tests that can be used: skin testing and specific IgE tests. He pointed out that for these tests, results such as the specific IgE number or the size of the skin test indicate the probability of a true allergy rather than severity.

Dr Makwana emphasised the importance of the allergy history and determining a "pre-test probability" of food allergy when interpreting skin test results. He explained that care must be taken in the interpretation of such tests; and only specific foods/suspected allergens should be tested for. Specific IgE panels investigating multiple foods should be avoided.

Unfortunately, for non-specific IgE allergy, there is no test. In this case, an exclusion/elimination diet can be put into place for at least four weeks whilst monitoring for improvements in symptoms. On improvement, this can be followed by a reintroduction of the suspected allergen whilst monitoring for deterioration. Improvement followed by deterioration confirms a non-IgE-mediated allergy. It was discussed parents may be reluctant to reintroduce the allergen to confirm diagnosis following improvements in symptoms. Dr Makwana suggested working with the parents to agree an acceptable plan for reintroduction.

Dr Bennett also asked about the later reintroduction of milk back into the diet, how best to approach this phase and if the process is the same for IgE and non-IgE allergy. Dr Makwana explained that for non-IgE-mediated allergy, trial reintroduction using milk ladders should be undertaken every three months. iMAP guidelines for reintroduction can be followed in primary care, ideally with the support of a dietitian. Patients with IgE-mediated allergy should be referred to secondary care (as detailed in the NICE guidelines) to determine tolerance before any reintroduction of allergens.

MANAGEMENT OPTIONS



Dr Makwana explained the steps to take following a diagnosis of CMA. He explained that as most children with CMA are diagnosed before six months old, maternal feeding choices will determine management options. Breastfeeding should be recommended. Despite recent controversy about the presence of B-lactoglobulin in breastmilk, Dr Makwana suggested that most breastfeeding mothers should be able to continue to consume dairy unless showing any temporal relationship to symptoms in the infant. Calcium and vitamin D supplementation should be recommended in the few cases where dietary restriction is required.

Hypoallergenic formula is available in cases where the mother is unable or chooses not to breastfeed. These include extensively hydrolysed (EHF) and amino acid formulas (AAF). Guidelines recommend EHF as a first choice of hypoallergenic formula, tolerated by 90% of infants. AAF is recommended for infants unable to tolerate EHF, with faltering growth, with multiple allergies or for highly sensitive infants for whom breastfeeding causes symptoms. Hydrolysed rice milk formulas are also becoming available for use in some markets. Dr Bennett asked whether a child not tolerating EHF meant that the diagnosis of CMA could be incorrect. In 10% of cases, children may not tolerate EHF, in which situation AAF should be trialled. If AAF is then not tolerated, Dr Makwana suggested that the diagnosis of CMA may need to be reconsidered.

Unsuitable infant formulas include standard formula, lactose free formula, and partially hydrolysed formula. For children over six months of age, soya formula may be recommended. However, Dr Makwana pointed out that care must be taken as some children with CMA may also have problems with soya. In many countries, soya formula is not recommended for infants under six months of age.

Dr Makwana noted that management of CMA can be supported by a multidisciplinary team (e.g. dietitians, health visitors), local guidelines and local specialist allergy services.



SUMMARY POINTS

Dr Makwana summarised our online seminar in a few key points:

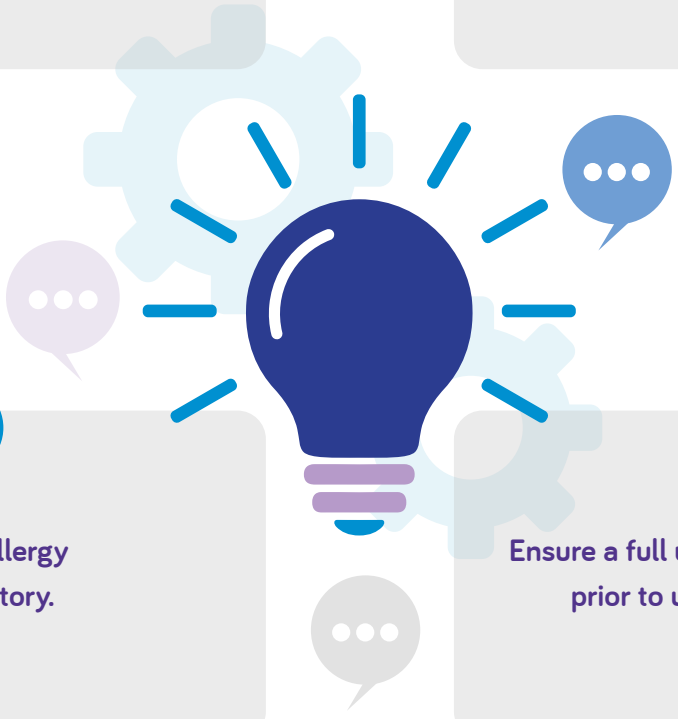
- The diagnosis of CMA should only be made after a carefully focused allergy history.
- Careful consideration needs to be given before contemplating a diagnosis of CMA when reviewing common symptoms that present in the infant period.
- Do not use serum specific IgE testing to diagnose delayed food allergy. Suspected non-IgE-mediated allergy can be diagnosed using an appropriate exclusion and reintroduction of cow's milk, and then managed in primary care (using iMAP) if confirmed.
- All children who are excluding foods should be referred to a paediatric dietitian, where available. Breastfeeding should be continued and encouraged in all mothers and should only be stopped at a time chosen by the mother.
- For most infants, where a mother chooses not to or is unable to breastfeed, EHF (or appropriate alternative formula) would be the first line alternative.
- Ensure you are aware of the local criteria to refer for secondary care assessment for infants with suspected CMA.

TAKEAWAY TIPS

Dr Bennett asked Dr Makwana for some final "top tips" for GP when diagnosing CMA. His top five tips are:

1. Always consider CMA in infants with symptoms which are recurrent or don't respond to usual treatment.

2. Consider a face-to-face consultation with a visual assessment, including growth parameters; these are important for making a diagnosis.



3. Conduct an allergy focussed history.

4. Ensure a full understanding of test results prior to undertaking any testing.

5. In CMA management, breastfeeding is recommended. In cases where breastfeeding is not adopted, ensure an appropriate hypoallergenic formula is recommended.

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New guideline recently published Managing food allergy: GA2LEN guideline 2022 Muraro A, et al.; GA2LEN Food Allergy Guideline Group; GALEN Food Allergy Guideline Group. Managing food allergy: GA2LEN guideline 2022. World Allergy Organ J. 2022 Sep7;15(9):100687. doi: 10.1016/j.waojou.2022.100687. PMID: 36119657; PMCID: PMC9467869.

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