Approach to milk protein allergy in infants

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ABSTRACT

OBJECTIVE To provide a practical, evidence-based approach to the diagnosis and management of milk protein allergy in infants.

SOURCES OF INFORMATION MEDLINE was searched from 1950 to March 2008 using the MeSH heading *milk-hypersensitivity.* Additional sources were derived from reviews found with the initial search strategy. Evidence was levels I, II, and III.

MAIN MESSAGE Milk protein allergy is a recognized problem in the first year of life; cow's milk protein allergy is the most common such allergy. Diagnosis is suspected on history alone, with laboratory evaluations playing a supporting role. Confirmation requires elimination and reintroduction of the suspected allergen. Management includes diet modification for nursing mothers and hydrolyzed formulas for formula-fed infants. Assessing the underlying immunopathology can aid in determining prognosis.

CONCLUSION The therapeutic model presented allows rapid assessment of the presence of allergy, timely management, and surveillance for recurrence of symptoms. Breastfeeding can be continued with attentive diet modification by motivated mothers.

RÉSUMÉ

OBJECTIF Proposer une méthode pratique fondée sur des données probantes pour diagnostiquer et traiter l'allergie aux protéines du lait chez le nourrisson.

SOURCE DE L'INFORMATION On a consulté MEDLINE entre 1950 et 2008 à l'aide de la rubrique MeSH *milk-hypersensitivity*. D'autres sources d'information ont été tirées des revues repérées par la stratégie initiale. Les preuves obtenues étaient de niveaux I, II et III.

PRINCIPAL MESSAGE L'allergie aux protéines du lait est un problème connu chez l'enfant de moins d'un an; l'allergie aux protéines du lait de vache est la forme la plus fréquente. L'historique est suffisant pour suggérer ce diagnostic, les tests de laboratoire jouant un rôle de support. La confirmation exige le retrait et la réintroduction de l'allergène présumé. Le traitement comprend une modification du régime pour la mère allaitant et des préparations hydrolysées pour les bébés au biberon. L'évaluation de l'immunopathologie sous-jacente peut aider à établir le pronostic.

CONCLUSION Le modèle thérapeutique proposé permet la détection rapide de l'allergie, un traitement opportun et la surveillance d'une réapparition des symptômes. Les mères motivées peuvent continuer d'allaiter si elles modifient correctement leur alimentation.

This article has been peer reviewed.
Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2008;54:1258-64

Milk protein allergy (MPA) is a recognized problem in infancy and might affect up to 15% of infants.[1] Most cases of MPA can be managed successfully in the outpatient setting. This article summarizes the current evidence for diagnosis and management of MPA.

Case description

Baby M. is a full-term, 4-kg infant girl delivered vaginally of a 22-year-old primiparous mother after an uneventful pregnancy. At the 2-week follow-up visit, Baby M. has regained her birth weight. Her mother reports frequent episodes of regurgitation after breastfeeding, which do not distress her. Family history is significant for environmental allergies in both parents and a paternal uncle with eczema and severe asthma. At the 4-week follow-up visit, the mother reports ongoing regurgitation followed occasionally by crying. Stools have become more frequent and appear watery. The baby's weight is 4150 g, a gain of 10 g/d since the last visit.

Sources of information

A MEDLINE search was conducted using the MeSH heading *milk-hypersensitivity.* English-language articles studying subjects younger than 1 year of age were selected. Additional articles were derived from review articles found with the initial search strategy, yielding a total of 36 publications. Evidence was levels I, II, and III.

Epidemiology

Cow's milk protein allergy (CMPA) appears to be the most common MPA, with controlled challenge trials demonstrating an incidence of 2% to 5% among formula-fed infants (level I evidence).[1] The incidence in breastfed infants is 0.4% to 0.5% according to 2 trials (level I evidence),[2,3] but might be as high as 2.1% (level II evidence).[4] Determining the incidence of allergy to milk proteins from other sources is complicated by the widespread use of bovine milk. A population-based cohort study found the incidence of soy allergy to be 0.25% (level II evidence).[5] Among high-risk infants, CMPA appears to outweigh soy milk protein allergy (SMPA) by a factor of 6 to 1 (level I evidence).[6] A study by Klemola et al found the incidence of SMPA to be 10% among children with CMPA.[7] Interestingly, qualitative observation alone suggested a cross-reactivity as high as 30%, but only a 10% rate was observed using rigorous quantitative measures. This underscores the importance of appropriately testing diagnostic suspicions. Cross-reactivity between milk protein from ewe, goat, or buffalo and bovine milk protein has been demonstrated in vitro.[8] Unfortunately, Canadian data are lacking.

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Pathophysiology

Milk protein allergy can manifest via IgE-mediated and non–IgE-mediated pathways.[9] An IgE-mediated allergy (also known as *type I hypersensitivity reaction*) occurs when antigens bind to IgE antibodies bound to mast cells. Cross-linking of 2 IgE antibodies by an antigen causes the mast cell to release histamine, a potent inflammatory mediator, resulting in an immediate allergic reaction. Non–IgE-mediated MPA is likely multifactorial and includes immune complexes of IgA or IgG antibodies bound to milk antigens (*type III hypersensitivity reaction*) and direct stimulation of T cells by milk protein antigens (*type IV hypersensitivity reaction*). The interactions result in cytokine release and increased production of antibodies that recognize the offending milk proteins, contributing to an inflammatory cascade. These more complex immune interactions result in delayed onset of clinical symptoms. While there is overlap of clinical symptoms in the 2 groups of immune reactions,[9] a non–IgE-mediated allergy is certain with isolated blood-streaked stools (level III evidence). With the other symptoms, while a distinction might be suspected it cannot be confirmed by clinical history alone (**Table 1**[10-12]). Making the distinction is important, as IgE-mediated MPA is associated with a higher risk of multiple food allergies and atopic conditions such as asthma later in life (level I and II evidence).[10,13]

Cross-sensitization between protein sources is well established. Among infants with CMPA, 13% to 20% have allergies to beef (level II evidence).[14] Restani et al demonstrated that antibodies harvested from children with CMPA recognize milk proteins from ewe, goat, and buffalo species, but not from camels (level II evidence).[8] Completely different organisms produce soy and bovine proteins. Rozenfeld et al demonstrated that a monoclonal antibody specific to casein (a bovine milk protein) displayed affinity to a component of glycinin, an ingredient in soy-based formulas.[15]

Clinical presentation

Infants with MPA usually present with symptoms similar to allergic reactions in older individuals. These include cutaneous symptoms such as urticaria, rash,

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

Table 1. Symptoms of milk protein allergy and their differential diagnoses

REACTION TYPE	PRESENTATION	DIFFERENTIAL DIAGNOSES TO CONSIDER
IgE mediated		
Respiratory	Rhinoconjunctivitis Asthma (wheeze, cough) Laryngeal edema Otitis media with effusion	Primary respiratory problem
Cutaneous	Atopic dermatitis Urticaria Angioedema	Food allergy Environmental allergy Primary atopy
Gastrointestinal	Oral allergy syndrome Nausea and vomiting Colic Diarrhea	Food or environmental allergy Infection, delayed gastric emptying, malrotation, celiac disease (younger than 6 mo), cystic fibrosis
Non–IgE mediated		
Respiratory	Pulmonary hemosiderosis (Heiner syndrome)	None
Cutaneous	Contact rash Atopic dermatitis	Food or environmental allergy Primary atopy
Gastrointestinal	Gastroesophageal reflux Transient enteropathy Protein-losing enteropathy Enterocolitis syndrome Colitis Constipation Failure to thrive	Physiologic reflux, delayed gastric emptying, celiac disease (younger than 6 mo), cystic fibrosis Anal fissure Hypercalcemia, Hirschsprung disease, hypothyroidism, functional gastrointestinal disorders
Other		
Unclassified (rare)	Anemia (without colitis) Arthritis Henoch-Schönlein purpura Migraine	Broad

Data from Høst,[10] Heine et al,[11] and Salvatore and Vandenplas.[12]

and pruritus, as well as respiratory symptoms such as wheeze and cough (level I evidence).[11] These symptoms are usually indicative of IgE-mediated MPA.[9]

Milk protein allergy can also present with gastrointestinal and nutritional manifestations. These include gastroesophageal reflux, esophagitis, gastritis, delayed gastric emptying, enteropathy, colitis, constipation, and failure to thrive (level I to II evidence).[12] These symptoms might be the cause of behaviour such as crying inconsolably and refusing feeding. The symptoms are the same among breastfed and formula-fed infants. Gastrointestinal symptoms are particularly challenging owing to their nonspecificity and wide differential diagnosis, but MPA should always be suspected. One study administered a cow's milk–free diet to 10 infants with refractory gastroesophageal reflux that had not improved with pharmacologic therapy and reported that 2 of the infants' symptoms improved (level II evidence).[16] Jakobsson et al administered hydrolyzed formula to 15 infants with severe colic and demonstrated a 60% to 70% reduction in daily crying time (level II evidence),[17] but caution should be used in generalizing these results to all infants with colic.

Diagnosis

Confirming the diagnosis of MPA is important owing to the discrepancy between parental description of symptoms and scientific confirmation.[7,9] Double-blind, placebo-controlled food challenge has long been regarded as the criterion standard (level I evidence),[18] however, owing to the risk of substantial allergy during food challenge, an alternative test with equal efficacy is preferred. Other investigational options include skin-prick testing (SPT), serum measurement of IgE antibodies to the specific allergen, and patch testing. A recent study suggests that a combination SPT and measuring IgE antibodies results in a positive predictive value of 95% for diagnosing IgE-mediated CMPA, obviating the need for the food challenge if an IgE-mediated CMPA is suspected (level I evidence).[19] A similar study, however, failed to reproduce these results (level II evidence).[20] Skin-prick testing and specific IgE levels are not useful for the diagnosis of non–IgE-mediated MPA,[9] but patch testing shows promise.[21]

Laboratory investigations are not diagnostic but can support a diagnosis made on clinical grounds. A decreased albumin level is suggestive of enteropathy (level III evidence). Increased platelets, erythrocyte sedimentation rate, C-reactive protein, and fecal leukocytes are all evidence of inflammation but are nonspecific; normal values do not rule out MPA (level III evidence). Eosinophilic leukocytosis might be present in both types of MPA.[20]

Management

The main principle in management of MPA is to avoid allergens while maintaining a balanced, nutritious diet for infants and mothers. Although it is difficult, breastfeeding can be continued if allergens are avoided. For CMPA, a breastfeeding mother must sequentially eliminate all cow's milk protein, then all bovine protein (milk and meat), and occasionally other protein sources such as soy (level II evidence).[22,23] A similar broad restriction is recommended for other MPAs given their low incidence and association with CMPA (level III evidence). Consultation with a dietitian is essential for a mother who continues

breastfeeding; particular attention must be paid to adequate calcium intake. A list of foods containing cow's milk and soy proteins is found in **Table 2**.[24,25]

Table 2. Sources of cow's milk protein and soy protein

SOURCES OF COW'S MILK PROTEIN	SOURCES OF SOY PROTEIN
Foods that contain cow's milk protein	**Foods that contain soy protein**
Milk, skim milk, buttermilk	Soya, soybean, soy protein
Cream, evaporated or condensed milk	Miso, edamame, okara, bean sprouts
Butter, margarine, milk solids, curds	Tofu, tempeh, yuba
Whey	Textured vegetable protein
Lactose, caseinate, casein, lactalbumin	Monodiglyceride, lecithin
Cheese, yogurt, sour cream	
Foods that MIGHT contain cow's milk protein	**Foods that MIGHT contain soy protein**
Commercially prepared meats	Baked goods
Scalloped or creamed vegetables	Cereals
Canned or dehydrated soups	Breaded foods, bread crumbs
Candies	Chewing gum, desserts
Gravies	Processed meats
Breads, hamburger and hot dog buns	Sauces, gravies, marinades, dressings
Beverages	Simulated fish and meat products
Cakes, cookies, other desserts	Snack foods
Salad dressings	Soups
Foods sautéed or fried with butter or margarine	Thickening agents

Data from McMaster Pediatric GI Clinic[24] and the Government of Canada.[25]

For formula-fed infants, current options include specific allergen avoidance, extensively hydrolyzed protein formulas (EHFs), and amino acid–based formulas (AAFs) (**Table 3**). Extensively hydrolyzed protein formulas incorporate hydrolysates of casein or whey derived from cow's milk. Their efficacy among those with CMPA is approximately 90% (level I to II evidence),[23,26-29] though their efficacy among those with other forms of MPA is less well demonstrated. These formulas do have potentially allergenic material,[30] and allergic reactions have been reported.[31,32] A rice-based EHF shows promise in young children,[33] but is not commercially available. Amino acid–based formulas are created from constituent amino acids and have demonstrated efficacy of approximately 99% (level I evidence)[28,34]; they can be considered as an immediate or secondary alternative to EHFs. However, even AAFs contain potentially allergenic material, such as soy lecithin, so their use must be monitored. The taste of the formula might be an issue for compliance; as a rule of thumb, the more hydrolyzed a formula, the worse the taste.

Specific allergen avoidance, such as substituting soy-based formulas for milk-based in CMPA, is not recommended. The concomitant presence of multiple MPAs reduces the likelihood of success of milk protein substitution.[7,8] Additionally, cross-sensitization of milk proteins correlates with increased intestinal permeability (level II evidence).[35] Thus, allergy-induced enteropathy might increase the risk of cross-sensitization if specific allergen avoidance is pursued during the acute phase (level III evidence). If the expense of EHFs or AAFs is a concern, in order to avoid the risk of cross-sensitization, have patients avoid alternate protein sources for at least 1 month to give the intestinal mucosa time to heal, then challenge with a protein alternative (level III evidence).

Table 3. Hydrolyzed formulas available in Canada

AGE	TYPE OF FORMULA	BRAND	COST PER 6 OZ BOTTLE, $*
Infant (younger than 12 mo)	Partially hydrolyzed	Good Start	0.72
	Extensively hydrolyzed	Nutramigen	1.48
		Alimentum†	1.99
		Pregestimil	1.25
	Amino acid based	Neocate	2.94
Toddler (1-5 y)	Extensively hydrolyzed	Nutren Junior†	2.01
		Peptamen Junior†	7.99
	Amino acid based	Neocate Junior	4.14
		Vivonex Pediatric	6.31

*Retail costs from McMaster Outpatient Pharmacy, April 2008.
†Only available in liquid.

Introduction of solid food can occur at the usual age barring complications such as feeding aversion. Education regarding diet restriction is essential and is best achieved with the help of a dietitian (level III evidence).[36] The importance of a dietitian referral is underscored by a study demonstrating a high rate of parental error in avoiding milk protein–laced foods at the grocery store (level II evidence).[37] Parents might also worry about lactose intolerance, and they should be reassured of the extreme rarity of lactase deficiency in infants younger than 1 year of age.[38]

Prognosis

The timing of reintroducing milk protein is of great concern to parents. Traditionally, it was thought that MPA resolved by 1 to 2 years of age (level III evidence).[9,39] Two recent studies, however, suggest a more complex answer. Carroccio et al[40] found the proportions of Italian infants with CMPA who had milk tolerance at 1, 2, and 3 years after initiation of milk-free diets were 30%, 54%, and 70%, respectively. Vanto et al[41] demonstrated a difference in tolerance when considering the type of CMPA among Finnish infants (level II evidence). At 2, 3, and 4

years of age, children with non–IgE-mediated CMPA had milk tolerance at rates of 64%, 92%, and 96%, respectively, while children with IgE-mediated allergy were milk tolerant at rates of 31%, 53%, and 63% (level II evidence). Furthermore, children with less reactive SPT results and fewer specific IgE antibodies were milk tolerant sooner than children with more dramatic findings. Taken together, these results suggest that cow's milk protein can be reintroduced in trial fashion at 1 year of age in children deemed to have non–IgE-mediated allergy, while children suspected of IgE-mediated allergy should not be exposed to cow's milk for longer time periods, with the length of time guided by allergy testing. Data regarding resolution of other types of MPA are lacking, though children with multiple food allergies are more likely to remain allergic.

When to refer

There are no published guidelines on when to refer infants with MPA to specialist care. A list of potential situations in which it is prudent to refer infants for specialized care can be found in **Table 4**[10] (level III evidence).

Table 4. When and to whom to refer infants with milk protein allergy

CONSULTANT	WHEN TO REFER
Dietitian	Counseling for lactating mothers at the time of diagnosis Counseling for introduction of solid foods
Allergist	Suspected anaphylactic allergy Allergy testing before reintroducing milk (if IgE-mediated allergy is suspected) Suspected multiple food allergies (not just milk proteins)
Pediatrician or pediatric gastroenterologist	Significant weight loss (> 20% of birth weight or > 10% current weight if birth weight surpassed) Failure to thrive refractory to initial management Symptoms refractory to amino acid–based formula Feeding aversion

Data from Høst.[10]

Summary of a practical approach

A diagnostic and treatment algorithm is provided in **Figure 1**.

- Weight should be followed closely (**Table 5**[42]).
- The timing of clinical response to protein elimination depends on the symptoms observed and the manner of infant feeding.
  - In formula-fed infants, esophagitis and behavioural symptoms should respond within 72 hours.
  - Other non–IgE-mediated symptoms should start to improve within 7 days.
  - Colitis can take up to 3 weeks to heal; ongoing bloody stools can persist even when patients are improving generally.
  - Advise breastfeeding mothers that a 7-day washout of milk proteins is required when instituting a restricted diet, delaying the expected clinical response.

Table 5. Appropriate weight gain in infancy

AGE (MO)	APPROPRIATE WEIGHT GAIN (G/D)
0-3	30
3-6	15-20
6-12	10-15
12-24	8-10

Data from Overby.[42]

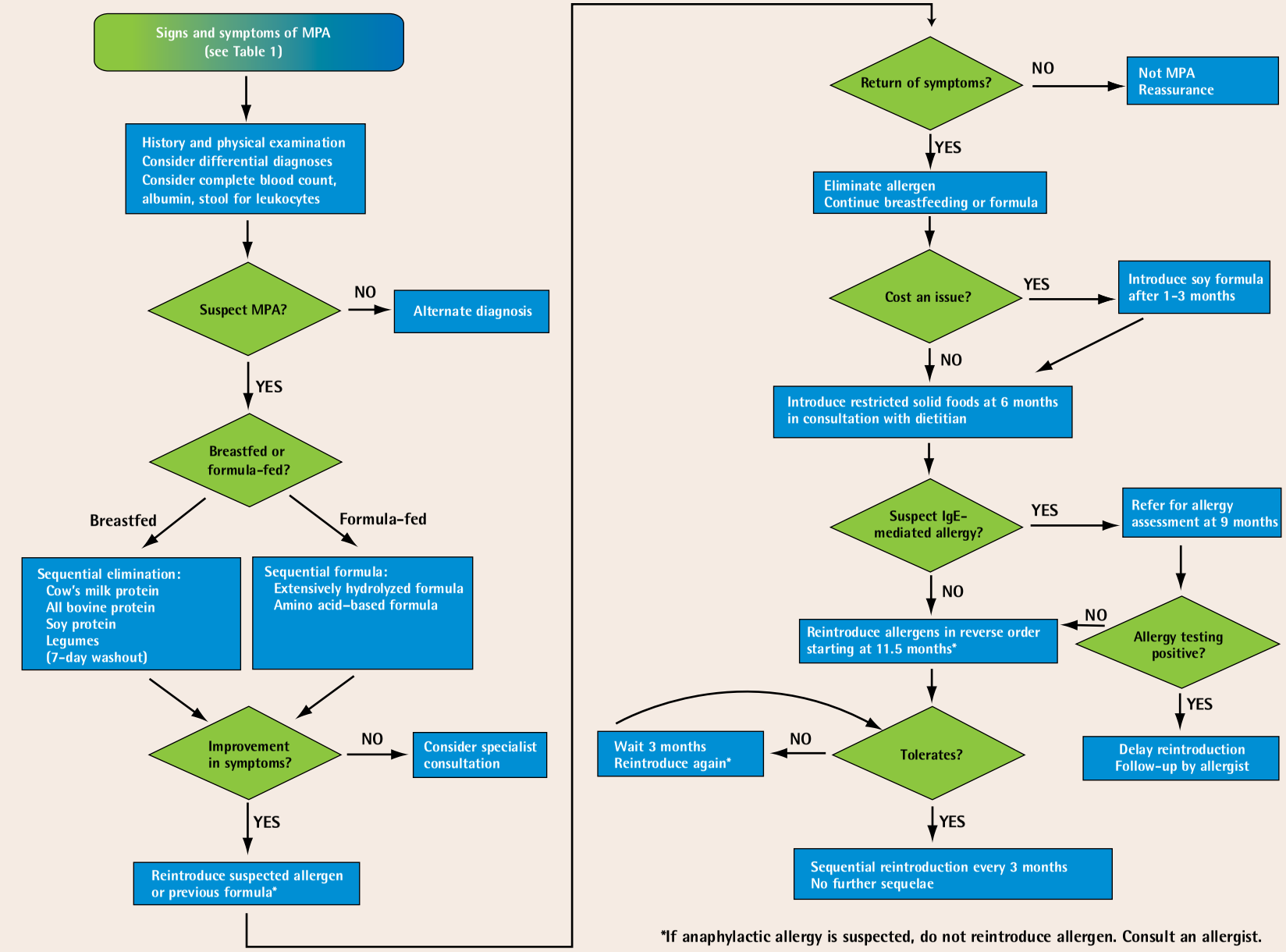
EDITOR'S KEY POINTS

- Milk protein allergy can occur in both formula-fed and breastfed infants, usually in the first year of life. The presentation can be cutaneous (eg, rashes, pruritus), but can also include respiratory, gastrointestinal, and nutritional manifestations. Some might present with behaviours such as crying inconsolably and refusing feeding.
- Milk protein allergy is suspected based on history. Investigational options include food challenge, skin-prick testing, serum measurement of specific IgE antibodies, and patch testing.
- The main principle in management is to avoid allergens while maintaining a balanced, nutritious diet for infants and mothers; breastfeeding can be continued if allergens are avoided by the mother. Infants' weight should be followed closely.
- Milk protein allergy can be successfully managed in primary care with the support of a dietitian; consultation with other specialists should be reserved for severe allergies, failure to respond to standard management, and specific allergy testing if indicated.

POINTS DE REPÈRE DU RÉDACTEUR

- L'allergie aux protéines du lait peur survenir durant l'allaitement au biberon ou durant l'allaitement maternel, habituellement avant l'âge d'un an. Les manifestations initiales peuvent être cutanées (p.ex. rash, prurit), mais elles peuvent aussi être d'ordre respiratoire, digestif ou nutritionnel. Certains nourrissons présentent d'abord des pleurs irréductibles et refusent toute nourriture.
- L'historique permet de soupçonner une allergie aux protéines du lait. Les investigations possibles incluent la provocation alimentaire, le prick-test, la mesure du taux sérique des anticorps IgE spécifiques et l'épidermoréaction.
- Le traitement cherchera principalement à éviter l'allergène tout en maintenant un régime nourrissant et équilibré, pour le nourrisson comme pour la mère; l'allaitement au sein peut être poursuivi si la mère évite les allergènes. Le poids du bébé doit être étroitement surveillé.
- L'allergie aux protéines du lait peut être traitée avec succès en soins primaires avec le soutien d'une diététicienne; les autres spécialistes ne devraient être consultés qu'en cas d'allergie sévère ou d'échec du traitement standard et quand des tests d'allergie spécifiques sont indiqués.

Figure 1. Algorithm for diagnosis and treatment of milk protein allergy (MPA)



- Milk protein allergy can be successfully managed in primary care with the support of a dietitian; consultation with other specialists should be reserved for severe allergies, failure to respond to standard management, and specific allergy testing if indicated.

Case resolution

Baby M.'s bloodwork results revealed the following: platelet count 474×10^9/mL; albumin 34 g/L; and no eosinophilic leukocytosis. Stool microscopy results revealed many fecal leukocytes per high-powered field. The mother was advised to remove all bovine milk products from her diet. She returned for a follow-up visit 2 weeks later and reported normalization of stools and resolution of crying with regurgitation. She was advised to resume consumption of cow's milk products. She called the office 3 days later and reported a recurrence of the looser, more frequent stools. Upon removing cow's milk from the diet, the stool pattern improved. A diagnosis of CMPA was made. A dietitian saw mother and infant when Baby M. was 5 months of age and provided advice regarding introduction of solid foods. Cow's milk was reintroduced at 11.5 months of age without a relapse of symptoms, and Baby M. ate cake at her first birthday party.

Acknowledgment

I thank **Dr Deanna Telner** *for her assistance with this manuscript.*

Competing interests

None declared

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