

An overview of cow's milk allergy in children

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Summary

Food allergies have increased over the past decade and are an important problem in daily clinical practice. They affect 6% of children and 3 to 4% of adults. Furthermore, around 20% of the population falsely believe that they are allergic to some foods and follow unnecessarily restrictive diets. For infants, the problem is even more acute as they need appropriate feeding in order to achieve normal growth and avoid bone and metabolic problems.

Although any food can cause a reaction, few foods are responsible for the large majority of the symptoms: i.e., milk, eggs, wheat, peanuts, nuts, fish, shellfish. Of these, cow's milk allergy is fre-

quently suspected in small children. It can be responsible of a variety of symptoms and can be caused by IgE-mediated or non-IgE-mediated reactions. The diagnosis relies on a detailed history, skin tests, laboratory tests, an elimination diet and food challenges. The overall natural evolution of the disease is favourable with most patients achieving tolerance to milk by the age of five years, but some patients will remain allergic for life.

Key words: cow's milk; milk; food allergy; eosinophilic oesophagitis; food protein-induced enterocolitis; children

Introduction

Adverse reactions to foods or "food hypersensitivity" are defined by reactions triggered by ingestion of food proteins. They can be divided into allergic reactions and food intolerance [1]. Intolerance to foods can be caused by a specific component of the food, such as pharmacological agents like monosodium glutamate or histamine found in scombroid fish, non-specific mast cell activation by irritating foods such as strawberries or additives, or may be due to host factors, like in lactase deficiency [2, 3].

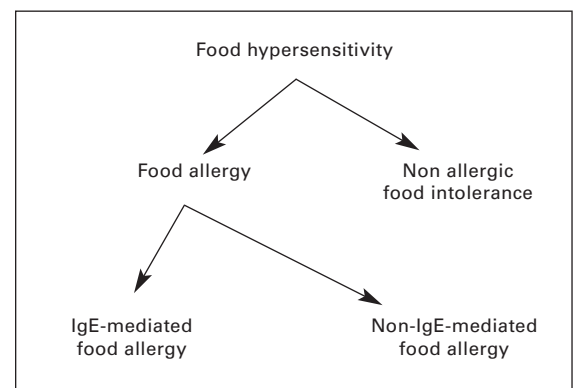
The term food allergy refers to an immune reaction to the proteins in foods and can be further split into IgE and non-IgE (mostly cellular)-mediated reactions (fig. 1). While IgE-mediated reactions are well recognised with validated diagnostic tests, the non IgE-mediated immune reactions that can arise in the gastro-intestinal tract are not so well defined and more difficult to recognise. Some of the reactions can also involve both types of mechanism or evolve secondarily towards an IgE mediated allergy. Table 1 summarises the different forms of food allergy.

Cow's milk proteins are among the major allergens involved into both types of allergy and precise diagnosis is crucial for proper management. Children are the age group most frequently affected by this disease and should be followed carefully as severe complications of a restrictive

diet have been described such as severe growth retardation, kwashiorkor, hypocalcaemia and rickets [4]. The term "bovine proteins intolerance" is frequently used in cases of non specific symptoms attributed to milk, but should not be used in case of milk allergy, whether they are IgE or non-IgE-mediated, these pathologies being caused by an immune reaction to milk proteins. Symptoms suggestive of cow's milk allergy may be encountered in about 5–15% of infants but when strict diagnosis criteria are used, the incidence of milk allergy seems to be about 2–5% [5, 6]. Most patients develop symptoms before twelve months of age,

Figure 1

Classification of food hypersensitivity. Adapted from Johansson SG [52].



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often within one week after introduction of cow's milk based formula but cases of development of a milk allergy at any age have been described.

Concerning meat, only around 10% of IgE-mediated milk allergic patients are also sensitised

to bovine serum albumin [7]. This protein is degraded by heat and well cooked beef or veal meats are usually perfectly tolerated.

Table 1

Food Allergies.
Adapted from
Sampson HA [11].

	IgE-mediated	Mixed IgE and cell mediated	Cell mediated
Gastrointestinal	Oral allergy syndrome	Eosinophilic oesophagitis	Food protein-induced enterocolitis
	Gastrointestinal anaphylaxis	Eosinophilic gastroenteritis	Food protein-induced proctocolitis Food protein-induced enteropathy
Cutaneous	Angio-oedema, urticaria	Atopic dermatitis	Contact dermatitis
	Morbiliform rashes		Dermatitis herpetiformis
	Flushing		
Respiratory	Acute rhinoconjunctivitis		Food induced pulmonary haemosiderosis (Heiner syndrome)
	Acute bronchospasm		
Generalized	Anaphylaxis		

IgE-mediated milk allergy

Pathophysiology

IgE-mediated allergy presents when the organism fails to achieve normal tolerance to food allergens. The major food allergens involved in children's allergies are heat, acid, and protease stable, water-soluble glycoproteins 10 to 70 kd in size. They include e.g., proteins in milk (caseins), peanut (vicillins), and egg (ovomucoid) and non-specific lipid transfer proteins found in apple (Mal d 3). Heating or the method of cooking of foods might reduce (egg) or enhance (roasted peanut) allergenicity by modifying conformational epitopes [8].

When food antigens are ingested, they are processed in the gut where the gastrointestinal mucosal barrier displays complex physical (mucus, epithelial cell tight junctions, acid, and enzymes) and immunological protective mechanisms. Abrogation of the barrier through stomach pH neutralisation might promote food allergy [9]. Similarly, developmental immaturity of components of the gut barrier (enzymatic activity and IgA production) might account for the increased prevalence of food allergy in infancy.

Antigen-presenting cells, especially intestinal epithelial cells and dendritic cells, and regulatory T cells play a central role in oral tolerance through expression of IL-10 and IL-4. Commensal gut flora might also influence the mucosal immune response. Tolerance is largely established in the first 24 hours after birth and produces immunomodulatory molecules that have a beneficial influence on the development of certain immune responses. Recent studies have shown that imbalances in the composition of the bacterial microbiota might be a major factor in allergy, asthma or inflammatory bowel disease [10].

IgE-mediated allergy begins with sensitisation. The allergens are ingested, internalised and expressed at the surface of antigen presenting cells (APC). The APC interact with T-lymphocytes and promote the transformation of B-lymphocytes to antibody secretors cells. Once formed and released into the circulation, IgE binds, through their Fc portion, to high affinity receptors on mast cells, leaving their allergen specific receptor site available for future interaction with allergen.

The process by which a non-IgE-mediated allergy develops is less well understood but the initial antigen recognition phase is probably similar, and drives an inflammatory reaction primarily mediated through T cells and eosinophils, involving activation by different cytokines such as IL-5.

For an allergic reaction to occur, re-exposure is needed with, in case of IgE-mediated allergy, binding of the allergen to allergen-specific IgE antibodies. Cross-linking of a sufficient number of mast cell/basophil-bound IgE antibodies by allergen initiates a process of intra-cellular signalling; this leads to degranulation of cells, with the release of histamine and other mediators of inflammation.

Clinical syndromes

The most severe manifestation of IgE mediated milk allergy is anaphylaxis. After mast cell degranulation, released inflammatory mediators affect multiple organs systems. Symptoms include pruritus, urticaria, angio-oedema, vomiting, diarrhoea, abdominal cramps, respiratory difficulty, wheezing, hypotension, syncope, and shock. Cutaneous symptoms are the most common, however, up to 20% of anaphylaxis can present with-

out involvement of the skin, particularly in children. The onset of symptoms from food-induced anaphylaxis is variable but the majority of reactions manifest themselves within seconds to the first hour after exposure.

Among symptoms attributed to food allergy, atopic dermatitis is often cited. Indeed, it has been well established that approximately 30% of children suffering from moderate to severe atopic dermatitis present an associated food allergy that worsens eczema. The most frequently involved food is cow's milk and milk-specific IgE can be found in most patients. However some of them suffer from non-IgE-mediated allergy and additional tests such as epicutaneous tests or oral provocation test can be essential to confirm the diagnosis.

Diagnosis tests

Skin Prick Tests (SPTs)

SPT is a rapid and inexpensive means of detecting sensitization in IgE-mediated disorders and can be done in infants as well [11]. The negative predictive value is excellent (>95%) and can confirm the absence of IgE-mediated allergic reactivity. However, a positive test response does not necessarily prove that the food is causal (poor specificity), and only establishes sensitivity to the food (atopy, in absence of symptoms of allergy).

Serum IgE antibody dosage

The quantitative measurement of food-specific IgE antibodies is often the next step. The allergen of interest is bound to a solid matrix and exposed to the patient's serum. IgE antibodies specific for the allergen bind to the protein-matrix and are detected by use of a secondarily labelled antibody specific for the Fc portion of human IgE. Similar to skin tests, sensitisation can exist without clinical reactions and the tests cannot be used to diagnose food allergy without consideration of the clinical history. However, increasingly high concentrations of food-specific IgE correlate with an increasing likelihood of a clinical reaction. Different predictive values are being generated from emerging studies, which might represent nuances of diet, age, disease, and challenge protocols [12].

Despite an excellent sensitivity, a small subset of patients can still occasionally suffer from clinical reaction while serum food-specific IgE is undetectable. Consequently, if there is a strong suspicion of allergic reactivity, even with negative IgE tests, an oral food challenge is necessary to confirm the absence of clinical allergy.

Oral food challenge (open or double blind)

When the diagnosis remains uncertain, the oral food challenge is the gold standard. A well described protocol was published by SA Bock in 1988 [13] and a standardised protocol has been proposed by the European Academy of Allergy and Clinical Immunology in 2004 [14]. The pa-

tient ingests, over two hours, progressively increasing quantities of the suspected food. The procedure is interrupted when clinical symptoms appear (positive test) or after a substantial quantity has been ingested without reaction (negative test). Because of the risk of anaphylactic reaction, this test must be performed under close medical supervision, with a trained team and an adequate setting for resuscitation. This protocol is lengthy, costly and can cause anxiety and/or unpleasant clinical reactions, but is undoubtedly indicated in patients with an unclear diagnosis [15].

Treatment

Elimination diet

The cornerstone of food allergy treatment is the elimination diet. Patients and their families must be taught to read food labelling, which is especially crucial for milk and eggs, both contained in many different preparations under various names (for example butter, casein, cream, lactalbumin, lactoglobulin or lactose for milk).

Booklets and educational materials are available online in French [16] (<http://allergoped.hugge.ch>) or in English [17] (<http://www.foodallergy.org>).

For small children, elimination diets must be considered with the greatest caution and require regular medical follow up, as they can seriously impair the quality of life and involve potentially severe side effects. When a cow's milk allergy is diagnosed in an infant, the practitioner must recommend to the parents the use of a substitution preparation based on extensively hydrolysed cow's milk and must follow the patient to decide the best timing for the potential reintroduction.

Most parents wish to substitute cow's milk for another mammalian's milk or a soy-based preparation. However, virtually all cow's milk allergic patients suffer from a cross-reactivity to ewe and goat's milk and in addition, these milk varieties have an inadequate nutritional composition to suit the infant's needs and might cause for example megaloblastic anaemia through folic acid deficiency [18]. Some studies suggest that camel and donkey's milk might be immunologically better tolerated but their composition is very different from human milk and may not be used [19].

Soy preparations, although historically the first prescribed, are not perfectly suited to the nutritional needs of children. Furthermore, despite the absence of protein homology and cross-allergy, around 10% of IgE-mediated and 60% of non IgE-mediated allergic children are also allergic to soy [20, 21].

Extensively hydrolysed formulas are composed of a mixture of peptides and amino acids produced from predigested bovine casein or whey and are tolerated by 95% of milk allergic children. In case of persistent symptoms, an amino-acids based formula can be used, especially in children with multiple food allergies or growth impairment. In Switzerland, 3 extensively hydro-

lysed formulas (Althéra, Damira or Pregomin Pepti) and 2 amino acids formulas (Pregomin AS and Neocate) [22] are available.

Therefore, the use of soy preparation should be discouraged and reserved, after an extended allergy work-up, to infants suffering from galactosaemia and to children older than six months whose parents refuse hydrolysed milk for financial or ethical (vegan) reasons [23].

Thus, an extensively hydrolysed formula is the recommended substitute in cases of milk allergy of infants and small children.

Emergency treatment

The physician must prescribe and explain the use of an emergency treatment in case of accidental exposure. This treatment includes oral antihistamine for mild cutaneous or digestive reactions and self-injectable adrenaline (Epipen® or Anapen®) for systemic or respiratory reactions. A self-injectable adrenaline prescription is indicated for patients at risk of a severe reaction, as shown in table 2. Steroids can also be prescribed to prevent rebound and late phase symptoms but the patient must be clearly informed of their delayed effect and that their use should not delay adrenaline therapy.

Promising treatments

Treatments directed at curing food allergy are currently under development. Several studies have shown that oral immunotherapy is a promising approach, especially in patients with severe

and persistent food allergy and recent studies have described successful trials with hen's egg and cow's milk [24]. Immunomodulatory approaches such as anti IgE or anti IL-5 have also shown interesting results in recent clinical studies but need to be validated in larger trials.

Food allergy prevention

Maternal diet modulation such as dietary antigen avoidance during pregnancy or lactation have failed to show efficacy in atopic diseases prevention (atopic dermatitis, food sensitisation or asthma) [25, 26].

For infants, actual European and American recommendations rely on exclusive breast feeding for 4–6 months, followed by the delayed introduction of solid foods in children with atopic risk (atopic parents or siblings, or children with atopic dermatitis) [26]. However, recent studies suggest that infants who are exposed to food allergens early in life through the oral route are less likely to have food allergies than infants without such exposure. Such prevention strategies may evolve in the next few years [27]. Conversely, it has been demonstrated that a precocious cutaneous exposure to food allergens could promote sensitisation and development of food allergy, at least for peanuts [28, 29].

Currently, there is no evidence for a beneficial effect of early introduction of specific foods to prevent food allergy.

Supplementation with pre and probiotics has shown contradictory results and further studies are therefore necessary to determine their possible utility in allergy prevention[30].

Evolution

IgE-mediated milk allergy in children has been shown to resolve in most patients before the age of three years. Therefore, infants should be regularly evaluated by a specialist (paediatric allergologist or gastro-enterologist), who will decide the best timing for milk reintroduction.

However, around 20% of patients will remain allergic for a longer time period. Prognostic factors for oral tolerance development depend on milk-specific IgE levels and their decrease over time. Even adult milk allergic patients can develop tolerance at a later time and regular follow-up should be proposed.

Table 2

Indications for prescribing self-injectable epinephrine. Adapted from Muraro A [14].

Absolute indications:
– Previous cardiovascular or respiratory reaction to a food, insect sting or latex
– Exercise induced anaphylaxis
– Idiopathic anaphylaxis
– Child with IgE-mediated food allergy and co-existent persistent asthma
Relative indications:
– Any reaction to small amounts of a food (e.g., airborne food allergen or contact only via skin)
– History of only a previous mild reaction to peanut or a tree nut
– Remoteness of home from medical facilities
– Food allergic reaction in a teenager

Gastrointestinal cow's milk allergy

Pathophysiology

The basic mechanism leading to a breach of tolerance leading to allergy is yet not well established. Various factors, related to the patient (genetic factors, gut flora) and unrelated (timing, dosage, frequency of allergen exposure) interact in the pathogenesis of this disease. In gastrointesti-

nal allergies, most patients suffer probably from a type IV reaction with an abnormal responsiveness of TH2 lymphocytes. These produce increased quantities of inflammatory mediators, such as IL-4 and IL-5, as well as chemokines, leading to eosinophil activation and recruitment. In some patient, a mixed IgE and non IgE-mediated al-

lergy can develop and diagnostic tests should address both mechanisms [31].

Clinical syndromes

Patients with gastrointestinal milk allergies may present with various clinical symptoms, according to localisation of the inflammation (table 3). Heiner's syndrome is another expression of non IgE-mediated milk allergy in which patient present with chronic respiratory symptoms, pulmonary infiltrates, pulmonary haemosiderosis and serum precipitating antibodies to multiple cows' milk protein fractions. This rare disease has been well described in a recent article by Moissidis and colleagues [32].

Eosinophilic gastroenteropathies

These are defined by infiltration of the intestinal wall by eosinophils. Historically and anatomically, three clinical entities have been described: milk-induced colitis, eosinophilic oesophagitis and food protein-induced enterocolitis.

Those pathologies have an increasing clinical importance, as their recognition is relatively recent, and their prevalence seems to be markedly increasing. The differential diagnosis of digestive eosinophilia is broad and must include inflammatory bowel disease, parasitic infections, and hypereosinophilic syndrome or drug hypersensitivity. No diagnostic test is pathognomonic and the diagnosis of gastrointestinal eosinophilic allergy must rely on the clinical presentation, cutaneous/epicutaneous tests, biopsy and/or oral food challenges.

Food and cow's milk colitis

Rectal bleeding is an alarming symptom but is generally benign and self-limiting but can be attributed to milk allergy in about 20% of the cases [33]. Affected infants may present with isolated rectal bleeding with mucus emission from the first hours of life, probably through *in utero* sensitisation, or before the first 3 to 6 months of life but usually remain in excellent general condition. Rectal biopsy demonstrates a typical eosinophilic inflammation with occasionally erosion of the epithelium, microabscess or fibrosis. Symptoms are induced by cow's milk proteins contained in formula milk or breast milk, half of the patients being diagnosed while exclusively breast-fed. Most of those infants are only allergic to milk but approximately 20% can also react to eggs and less frequently to other food proteins. Clinical evolution is usually excellent with resolution of symptoms within five days after a cow's milk free diet for the mother or the change to a hydrolysed preparation for the baby. In case of failure of maternal diet, an additional removal of eggs from the diet may be considered. Occasionally, the affection is more severe and a fully hydrolysed or amino-acid diet is required. This allergy usually resolves in a few months, allowing milk reintroduction between 6 and 12 months of age.

Eosinophilic oesophagitis

This disease has only been identified as a proper entity in the last 15 years and studies show a rising prevalence. It affects mainly men in their second or third decade of life, but it is increasingly reported in the paediatric literature [34]. It is defined by an infiltration of the oesophagus by eosinophils, and associated with symptoms of reflux resistant to proton pump inhibitor therapy.

Table 3

Non-IgE-mediated food allergies.

Digestive allergies	Symptoms	Complications	Diagnosis Tests	Evolution	Treatment
Non IgE-mediated or mixed					
Food and milk colitis	Rectal bleeding with mucus emission on an infant	Anaemia (seldom)	Elimination diet for the mother or extensively hydrolysed milk (non breast fed infant or maternal diet failure), colonic biopsy if resistant to treatment stool culture	Resolution in 6–12 months	Elimination diet followed 6 month later by a reintroduction test
Eosinophilic oesophagitis	Regurgitations, reflux, anorexia, dysphagia or food refusal, vomiting, gastric pain	Failure to thrive, weight loss, oesophageal stricture	Endoscopy, biopsy, cutaneous and epicutaneous tests, amino-acid diet and oral provocation tests	Long lasting	Elimination diet, topical (swallowed) or systemic steroids
Food Protein-Induced Enterocolitis Syndrome (FPIES)	Intractable vomiting and/or diarrhoea 2–4 h after the ingestion	Leucocytosis, hypovolemic shock, metabolic acidosis, hypotension	Suggestive history, possibly epicutaneous and/or oral provocation test	Children: resolution in 2–5 years Adults: resolution or persistent	Elimination diet followed by reintroduction test
Food protein-induced enteropathy	Insidious symptoms, abdominal discomfort, dysphagia, weight loss, vomiting, diarrhoea	Hypereosinophilia, haematemesis/rectal bleeding, iron deficiency anaemia, hypoalbuminemia, failure to thrive	Endoscopy, biopsy, skin prick and epicutaneous tests, oral provocation tests	Milk: resolution in 1–2 years Solid foods: slow resolution or persistent	Elimination diet and double blind placebo controlled provocation tests

Patients usually complain of ill-defined symptoms of discomfort, dysphagia and tend to avoid eating fibrous or dry foods. Children present aspecific symptoms such as abdominal pain, vomiting or regurgitation and anorexia, or isolated growth failure. Endoscopy can show various features from normal to patchy white or red areas with occasionally oesophageal strictures, with a typical tracheiform aspect. Biopsies reveal dense infiltration of the wall by eosinophils (>15–20/field). This oesophagitis can be complicated by oesophageal stenosis and food impaction [34, 35]. Eosinophilic oesophagitis is usually caused by a food allergy with a mixed IgE and non IgE-mediated mechanism, in particular in children and teenagers. In adult patients, the prevalence of atopy is also very high, but in addition to foods, sufferers may also react to inhaled allergens. Non-allergic immune reactions also seem to co-exist.

Allergen identification must be coordinated by a specialist as it can be very troublesome as various antigens might be involved. An adapted elimination diet with elemental (amino acids) or semi-elemental formulas can lead to symptom resolution in 30–70% of affected patients [36, 37]. Nevertheless, the use of topical or systemic steroids is frequently required, especially if the causal food can not be clearly identified or if the inflammation lasts for a long time.

Food protein-induced enterocolitis

This allergy can present with spectacular symptoms of intractable vomiting and/or bloody-mucous diarrhoea that can lead to lethargy and hypovolaemic shock. The symptoms appear after a free interval, mostly two hours after ingestion of the allergen. Children presenting with these symptoms are frequently worked-up for suspicion of sepsis. The blood count during the acute episode exhibits a marked leukocyte reaction with high levels of immature forms (non-segmented neutrophils). The mechanism is non-IgE-mediated and food specific IgE remains undetectable. Colonic biopsies reveal cryptic abscess with diffuse inflammatory infiltration. This allergy can also be caused by food proteins other than milk, as reactions to soy, fish, rice, potato and chicken have been described [38].

The natural history of milk-induced enterocolitis is usually good after a 2–3 year elimination diet whereas the evolution might be more prolonged in patients with solid food protein-induced enterocolitis. Patients with unclear clinical pictures should have a thorough diagnostic work-up with endoscopy and biopsies in order to exclude an eosinophilic disease.

Food protein-induced enteropathy

This insidious form of allergy is slowly evolving within several days or weeks. Patients suffer from chronic diarrhoea, bloating, vomiting and weight loss or failure to thrive in children, similar

to that appearing in coeliac disease. The diagnosis is most often made on the basis of clinical experience and elimination/challenge tests. However, depending on the clinical presentation, gastrointestinal biopsies are helpful to adequately identify the disorder at the tissue level and exclude other disorders. On small bowel biopsy, a picture similar to coeliac disease, though usually less pronounced, such as patchy partial villous atrophy and crypt hyperplasia may be found with increased numbers of intraepithelial lymphocytes.

Intestinal protein and blood loss leading to the hypoalbuminaemia and anaemia are frequently observed in this syndrome. It usually affects infants in the first months of life and responds to cow's milk elimination. In older children, soy must also be considered and a case report of reactions to eggs has also been published [39].

Diagnosis

Skin Prick Tests (SPT)

They are much less useful in food-sensitive digestive allergy than in IgE-mediated allergies. In non-IgE-mediated allergies, such as food-protein induced enterocolitis or milk colitis, the test is negative. However, the SPTs can be useful to rule out an IgE-mediated allergy or in pathologies involving combined mechanisms, especially in eosinophilic oesophagitis where they can help the identification of the causal allergen [40].

Atopy patch test

In this test, the food is applied for 48 hours against the skin in a sealed patch. The test is positive if erythema, induration and/or vesiculous lesions appear 24 to 48 hours later at the site of the patch. It reproduces theoretically a T-cell mechanism similar to the possible mechanism of an enteropathy. However, T-cells from different sites express different homing markers, such as CLA (Cutaneous Lymphocyte Antigen) for the skin and $\alpha 4\beta 7$ -integrin for the gut, which may alter the sensitivity and specificity of the test [41]. This test has been better studied in severe atopic dermatitis where its sensitivity is around 65%. It has been shown to be helpful in identifying the causal food in eosinophilic oesophagitis in children [40] but is frequently negative in adult patients.

Elimination diet and oral food challenges

The cornerstone of diagnosis of food-induced gastrointestinal allergy is a response to an elimination diet, with recurrence of the symptoms upon challenge. As allergic reactions are usually delayed, the elimination diet must be performed for at least one month before the food challenge. In obvious cases where a single food is implicated and the patient improves dramatically during the elimination period, the food challenge may be omitted. However, the identification of the causal food(s) is often strenuous and the specialist might sometimes have to prescribe an extremely restrictive "oligo-antigenic" diet. When symptoms are

well controlled, the diet is then progressively diversified to determine the patient's tolerance. This type of investigation should be reserved for particularly complicated cases [42, 43]

In some allergic syndromes such as food protein-induced enterocolitis, the challenge can cause a very serious clinical reaction leading to hypovolaemic shock. Therefore, it is mandatory to insert an intravenous line and have medical supervision with resuscitation facilities and appropriate treatment available. For late reactions, the cumulative intake must also be sufficient as some patients can tolerate a small quantity of the allergenic proteins without demonstrating overt symptoms. The food challenge is used as a diagnosis test but should also be envisaged for the follow up when it is reasonably likely that tolerance has been regained [44].

In vitro tests

In vitro tests such as ECP (Eosinophilic Cationic Protein), basophil activation tests or lymphocyte proliferation tests have not demonstrated an acceptable sensitivity and/or specificity in the diagnosis of food allergies [45, 46].

Endoscopic examination and biopsies

Endoscopic examination demonstrates and characterises inflammation of the gut mucosa and enables verification of the absence of other aetiologies such as inflammatory bowel disease, neo-

plasia or infectious disease. Histological characteristics may vary according to the clinical syndromes and are detailed earlier.

Treatment

Elimination diet

Similarly to IgE-mediated allergies, elimination is the only effective measure. After diagnosis, patients must be reassessed regularly to decide on the best timing of reintroduction, especially in young children in whom a diet must be as limited as possible to avoid possible deficiency and whom allergies tend to spontaneous rapid resolution.

Steroids and other medical treatments

In cases of multiple food allergy or when the causative antigen cannot be clearly identified, in particular for long lasting eosinophilic oesophagitis, steroids might be necessary to achieve disease control. Initially, steroids were used systemically, mostly orally, but recent studies have demonstrated good results with swallowed fluticasone, administered via an inhaler without spacer [47].

Anecdotal reports of successful use of cromoglycate [48, 49] or montelukast [50] have been published. Novel therapies, such as humanised anti-IL-5 (mepolizumab) may be a useful adjunct in the treatment of severe refractory eosinophilic gastroenteropathies and other hypereosinophilic disorders [51].

Conclusion

Cow's milk allergies are frequently suspected by patients and the general population incriminating milk in many symptoms, often without any medical justification. The various clinical syndromes related to milk are indeed quite diverse but are nevertheless well defined. Furthermore, elimination diets are cumbersome, impair quality of life, and can lead to serious detrimental effects, especially in children and should only be prescribed after a proper allergy workup. An elimination diet must be clearly explained to the patient, with the help of a dietician if needed, and the patient should be adequately substituted, especially

with calcium, in order to avoid any nutritional deficiency. Regular medical evaluation usually allows milk to be reintroduced after a few months or years.

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