Cow's milk protein allergy

Cow's milk protein allergy (ABKM) is the most common food allergy in children under 3 years of age.

⚠**You can often come across an imprecise term** Milk allergy (see article), which the lay public can use to refer to both lactose intolerance and allergy to cow's milk protein - **it is important to find out** which of these disorders the patient suffers from.

The disease affects about **1-3% of infants**. In 90% of cases, it manifests itself already *in the first 3 months of life*, it rarely occurs after the 1st year of life. The clinical manifestations mainly include *blood and mucus in the stool* (allergic proctocolitis), or mild diarrheal disease without alteration of the general condition, days to weeks after ingestion of cow's milk protein (CMP). It is less often manifested by hives and eczema, rarely by respiratory problems (wheezing, cough or dyspnoea hours after ingestion) and exceptionally by anaphylaxis (swelling of the lips, laryngospasm, hives, vomiting, diarrhea, shortness of breath minutes after ingestion of BKM). The elimination-exposure test *is used for diagnosis, when cow's milk protein is excluded from the diet for 2-4 weeks and is gradually reintroduced after the symptoms disappear. The treatment of proven ABKM is the elimination of allergens, i.e. for fully breastfed babies, it is recommended that the mother exclude dairy products from the diet (necessary calcium supplementation of 1 g per day) and babies on artificial nutrition are switched to formulas with highly hydrolyzed protein, or on the amino acid formula. ABKM has a* ***good prognosis*** *– it disappears in 50% of children in the 1st year and in 90% in 6 years.*[1]

The term ABKM is understood as an "immunologically conditioned reaction" to one of the proteins in cow's milk. Since the narrower concept of allergy is understood in the sense of a reaction mediated only by IgE, the term **cow's milk protein hypersensitivity** is sometimes used instead of ABKM to express all possible types of allergic reaction to cow's milk protein, especially when there is no laboratory proof of allergy. Special algorithms are recommended for breast-fed and formula-fed infants. The recommendations emphasize the importance of a detailed history and a careful physical examination. Patients with severe symptoms should be referred to a specialist. Elimination of cow's milk proteins from the child's or mother's diet and exposure is the gold standard for diagnosis.[2]

> Note: Due to the fact that new findings have emerged in the field of diagnosis, therapy and prevention of cow's milk protein allergy (CMP) - motility disorders as a manifestation of CMP, the concept of so-called severe CMP, a new attitude towards the introduction of complementary nutrition in the sense of ABKM prevention - the recommended procedure published in 2001 by the Czech Medical Society of Jan Evangelista Purkyně, reg. number: o/035/073 (www.cls.cz/dokumenty2/postupy/r073.rtf (http://www.cls.cz/dokumenty2/postupy/r073.rtf)).[2]

Epidemiology

According to prospective studies with a re-exposure test, the incidence of ABKM is 2.2-2.8% in children under three years of age. ABKM in fully breastfed children has an incidence of 0.5%.

According to a prospective study conducted in Prague in 2004–2006, ABKM was diagnosed in 2.2% of infants ([3]).

Pathophysiology

Pathophysiologically, in addition to IgE-mediated reactions, other types of allergic reactions are also used. It is reported that 50% of infants and older children with clinically proven allergy have no evidence of an IgE-mediated reaction. A risk factor for the development of ABKM is a family allergy load, while if there is an anamnestic load of allergies in both parents or in one parent and ABKM is manifested in a sibling, this is considered a reason for preventive dietary intervention. The anamnestic information about the so-called first bottle (sensitizing), i.e. administration of artificial infant milk before the development of lactation is serious.

Clinical picture

Clinical symptoms of ABKM are listed in Table No. 1.

Table no. 1: Clinical symptomsy ([4], [5])	
affected system:	**clinical manifestations:**
anaphylactic reaction	drop in blood pressure, shock
skin	oral allergic syndrome, rash, urticaria, angioedema, eczema
gastrointestinal tract	vomiting, diarrhea, malabsorption, GER, enterorrhagia, constipation
respiratory tract	runny nose, expiratory dyspnoea, cough
behavior disorders	irritability, abdominal colic

The relationship between the development time of ABKM and the amount of milk drunk and the usual clinical manifestations is shown in table no. 2.

Table no. 2: Relationship between the development time of ABKM and the amount of milk drunk and usual clinical manifestations				
reaction:	**skin:**	**respiration:**	**GIT:**	**amount of milk required to cause a reaction**
minutes	+++, urticaria, angio-edema, exanthema	+, within anaphylactic r.	-/+, vomiting	small amount of milk
hours	-	-	++, vomiting and/or diarrhea	moderate amount of milk (60-200 ml)
days	+, eczema	++, cough, runny nose	+++, diarrhea	normal milk volumes

ABKM usually manifests itself in infancy, and it is reported that 60% of affected have gastrointestinal symptoms, 50-60% of patients have skin manifestations, and about one-third of infants with ABKM have respiratory symptoms, and the symptoms are often combined. It is estimated that about 10% of infants with abdominal colic can be successfully controlled by eliminating cow's milk (KM). Recently, works have been published that draw attention to the connection of ABKM with motility disorders.

The characteristic features of these manifestations are:

- beginning in the first weeks of life,
- failure of usual therapy,
- improvement after elimination of KM,
- relapse after introduction of KM,

- coexistence of multiple problems: GER + colic + constipation.

Anaphylactic reaction (symptoms with a decrease in blood pressure is reported in the literature in 9% of children with ABKM). Anaphylactic shock as a manifestation of ABKM can be expected in about 2%. 50% of ABKM manifests within one week after contact with KM, but it is reported that the first reaction can manifest itself up to 2 months. ABKM is unlikely if the child tolerates full portions of KM for more than 3 months.

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Diagnosis

Diagnostically, there is no unequivocal laboratory test that could affect the entire ABKM complex. The examination of different antibodies against KM may therefore not yield a clear answer, and their positivity is only an auxiliary diagnostic factor and can be false positive - **the examination of IgA and IgG antibodies is completely unnecessary *and misleading, which leads to false diagnoses and completely unnecessary dieting*** Positive antibodies in the IgE class are not evidence of allergy to KM**. Only 20–30% of children with IgE antibodies to CM have a positive exposure test (4). Better is the negative predictive value of the test -** negative antibodies in the IgE class exclude an anaphylactic reaction*. The decision to change the diet must still be made before the evaluation of the antibody test. Currently, prick tests are the most valued, but even their sensitivity and specificity are not 100%. Patch tests are generally not recommended (time consuming, subjectivity, limited information benefit).*

The diagnostic gold standard therefore remains the evaluation of KM elimination from the diet and subsequent re-exposure to confirm the allergic nature of the reaction. KM is reintroduced into the diet usually after 1-4 weeks of previous elimination. According to various sources, when the diagnosis is carried out in this way, the original hypothesis about ABKM is confirmed in only 30-60% of the original suspicions of ABKM. The essence of the re-exposure test is the administration of an increasing amount of KM under medical supervision in the first hours of administration, when the most serious reactions requiring acutely, in addition to the interruption of KM administration, should be detected. medication in case of an anaphylactic reaction (adrenaline 0.01 mg/kg/dose s.c., possibly also corticoids). The methodology for administration of KM during re-exposure is shown in Table No. 3. It is advisable to use milk with a reduced lactose content or without it, in order to exclude the simultaneous assessment of protein and lactose tolerance.

Table no. 3: Exposure test methodology	
day 1 beginning in a medical facility, if there is no reaction, the child goes home after 4-6 hours	8.00 1 ml on the edge of the lip 8.30 5 ml KM p.o. 9.30 10 ml KM p.o. 10.00 50 ml KM p.o. 10.30 100 ml KM p.o. and further increase
day 2-6	full doses of KM
day 7.	control

Methodologically, the most correct elimination test is with an amino acid preparation (AAF), forso that a certain number of infants with ABKM (up to 10%) do not even tolerate extensive hydrolyzate (eHF). Failure to subside after eHF can be interpreted as a failure of elimination and therefore the diagnosis of ABKM – as the cause of clinical complaints – is questioned. Elimination in the case of eosinophilic and non-IgE reactions must last at least 2 weeks, in the case of atopic dermatitis and allergic colitis 4 weeks. In the event that it is an assessment of some reactions that are difficult to interpret correctly (irritability of the infant, colic, eczema and its changes), it is advisable to perform the test as a double-blind study, i.e. the parents do not know whether the child will receive the real test food or a placebo, i.e. .the protein hydrolyzate that the child received as a therapeutic. Only after the evaluation of the record sheet (table no. 4) after carrying out the load with KM and placebo is the re-exposure test definitively evaluated (the preparation of the placebo and the test food is shown in table no. 5, the weighed powder is issued to the parents in an unmarked can).

Table no. 4: Record sheet for the child's parents during the exposure test							
name and year number:							
day:	1.	2.	3.	4.	5.	6.	7.
date:							
dose ml							
skin							
itching							
rash							
blushing							
digestion:							
vomiting							
number of chairs							
normal							
volumetric							
diarrhea							
another observation:							
restlessness							
whistling							
cold							
weight							

Table no. 5: Test dishes	
test dish:	10 g of amino acid preparation + 20 g of cow's milk formula, preferably with low or no lactose 180 ml boiled and cooled water
placebo food:	30 g of amino acid preparation + 180 ml boiled and cooled water

Differential diagnosis

As a differential diagnosis, one must take into account lactose intolerance *(rare primary manifests itself after childbirth, more frequent secondary usually after gastrointestinal infections, celiac disease), gastroesophageal reflux can have similar symptomatology , immunodefects or milk intolerance due to metabolic defects'*. In some cases, differential diagnosis also requires an enterobiopsy.

Therapy

The therapeutic measure is the complete elimination of preparations with cow's milk from the child's diet. For ABKM, it is *not appropriate to use goat and sheep milk as a substitute* because there is a similar antigenicity and allergenicity to that of cow's milk. It should also be emphasized that within the framework of the existence of multiprotein allergies, an allergy to soy products is reported in 17-47% of infants with ABKM and therefore the use of soy products in the treatment of ABKM is inappropriate. Although heat treatment of milk (pasteurization, drying, condensation) reduces the antigenicity of milk, it is not considered a sufficient treatment of milk for ABKM (the therapeutic preparation should be tolerated by 90% of those affected with ABKM). From the above, it follows that

for a small group of infants with ABKM, even extensive protein hydrolysis of protein is an insufficient measure, and it is necessary to administer a preparation whose protein component consists only of a mixture of amino acids. The basic technological process in the production of protein hydrolyzates is protein hydrolysis (whey, casein, bovine collagen, soy protein). From the point of view of the depth of intervention in the protein structure, we then divide the preparations into hypoallergenic – extensively hydrolysed, i.e. therapeutic and hypoantigenic – partially hydrolysed, i.e. preventive. For proven ABKM, so-called hypoantigenic formulas (marked by HA manufacturers) are also unsuitable. Breast milk can be considered hypoallergenic in terms of ABKM.

The concept of so-called severe ABKM was defined, when the administration of amino acid preparations is primarily indicated (table no. 6).

Table no. 6: Heavy ABKM	
gastrointestinal manifestations	▪ failure: chronic diarrhea and/or refusal to eat and/or vomiting ▪ anemia from occult or macroscopic losses ▪ hypalbuminemia ▪ endoscopically and/or histologically proven enteropathy or colitis
dermatological manifestations	▪ exudative or severe atopic dermatitis with hypalbuminenia or failure to thrive, or anemia
respiratory manifestations	▪ acute edema of the larynx ▪ bronchial obstruction with dyspnoea
overall reaction	▪ anaphylactic reaction

The diagnostic algorithm - scheme 1 and 2 - is based on this division and method of nutrition (breastfeeding, artificial nutrition).

Therapy

Table no. 7: Preparations for the treatment and prevention of ABKM and their indications			
Preparations:	-	1.Amino acid mixtures (AAF)	▪ severe ABKM, ▪ intolerance of extensive hydrolysates in the treatment of ABKM, ▪ conducting an elimination test in case of suspicion of ABKM
2a.Extensively hydrolyzed formulas (hypoallergenic – eHF)	▪ ABKM		
2b.Extensively hydrolyzed formula (hypoallergenic – eHF) with part of the fat in the form of MCT	▪ ABKM with manifestations of malabsorption		
3. Partially hydrolyzed formulas (hypoantigenic – HA)	▪ prevention of ABKM in infants with an increased risk of development		

Medicinal therapy is less important than diet therapy and therapeutic effect in relation to ABKM event. multiprotein allergies has been demonstrated in some controlled clinical studies only with cromoglycate, with other antiallergic drugs there are no controlled clinical studies in children.

Prognosis

Prognostically, only about half of patients with ABKM tolerate KM at the age of two years. The number of children who tolerate KM is gradually increasing, so that at school age tolerance can be expected in about 80% of the original patients with ABKM. The development of other allergic manifestations is more common in the group of children with ABKM than in the rest of the population, not only in the sense of multiprotein food reactions (most often eggs, soy, peanuts and others), but also respiratory allergies.

Breastfeeding up to 4 months - in children with a higher risk of allergies - reduces the risk of atopic dermatitis. Breastfeeding also reduces the risk of wheezing in infants and toddlers. It does not appear to be relevant in relation to the development of asthma. It is also not clear whether breastfeeding reduces the incidence of food allergies.

Dietary precautions for nursing mothers are considered questionable. Dietary measures in pregnant women to prevent or delay the early development of atopic eczema are ineffective (table no. 8).

Table No. 8: Preventive measures to reduce the risk of ABKM ([6], [7])		
methods:		**execution:**
identification of at-risk infants		family history (at least one parent or already born sibling allergic)
reducing exposure to food antigens	- during pregnancy	not recommended
	- while breastfeeding	not recommended
	-in the infant diet	▪ breastfeeding at least until 4-6 months ▪ feed with hypoantigenic (HA) preparations ▪ solid foods at the end of the 4th month at the earliest, there is no evidence that delaying the introduction of any food after the 4th - 6th month reduces the incidence of allergic diseases
non-dietary measures		▪ non-smoking environment ▪ reduction of aeroallergens ▪ minimization of viral infections (breastfeeding, individual care, not collective facilities)

The use of hydrolyzed formulas in non-breastfed children with a higher risk of developing allergies has a protective effect and reduces the risk of atopic dermatitis. Dietary measures in the nursing mother to prevent or delay the early development of atopic eczema are considered ineffective.

There is no evidence that delaying the introduction of any foods after 4–6 months reduced the incidence of allergic diseases.

The prescription of therapeutic preparations - they are partially covered by health insurance companies - is directed at eHF to a general practitioner for children and adolescents, a pediatrician, an allergist and a pediatric gastroenterologist. Amino acid preparations can be prescribed in the ABKM indication by a pediatrician, a pediatric gastroenterologist and an allergist.

This recommended procedure was discussed and approved by the Working Group for Pediatric Gastroenterology and Nutrition of the Czech Pediatric Society, the final review was carried out by Prof. MUDr. Jiří Nevoral, CSc. The work is supported by MZO VFN 2005.

Links

Source

- FRÜHAUF, Pavel. *Revised guideline for the diagnosis, treatment, and prevention of cow's milk protein allergy* [online]. [feeling. 2012-03-10]. < https://el.lf1.cuni.cz/p74547423/ >.

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