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MILK INTOLERANCE: A BIG TROUBLE FOR LITTLE PATIENTS

INTOLLERANZA AL LATTE: UN GRANDE PROBLEMA PER PICCOLI PAZIENTI

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Abstract
Our aim was to develop a diagnostic algorithm for milk intolerance. We distinguish adverse reaction to milk assumption in lactose intolerance and in cow milk protein intolerance. Anamnesis, clinical examination, laboratory investigations and double blind challenge procedures are discussed and argued in this paper, with the above mentioned aim to help paediatricians in diagnosis and management of milk intolerance. When is it necessary that patients refer to a specialist paediatrician gastroenterologist? How long time elimination diet must be followed? All these and other questions will have an answer in this paper.

KEYWORDS: Cow Milk Protein Intolerance, Lactase Deficiency, Double Blind Challenge Test.

Riassunto
Il nostro obiettivo è quello di proporre un algoritmo diagnostico per l'intolleranza al latte. Distinguiamo la reazione avversa all'assunzione del latte in intolleranza al lattosio ed intolleranza alle proteine del latte vaccino. L'anamnesi, l'esame obiettivo, le indagini di laboratorio ed il test di scatenamento in doppio cieco sono discusse ed argomentate in questo articolo, con il proposito sopra menzionato di aiutare i pediatri nella diagnosi e nella gestione dell'intolleranza al latte. Quando è necessario inviare questi pazienti allo specialista in gastroenterologia pediatrica? Per quanto tempo va seguita la dieta di eliminazione? Queste ed altre domande troveranno risposta in questo articolo.

PAROLE CHIAVE: Intolleranza alle proteine del latte vaccino, carenza di lattasi, procedura di scatenamento in doppio cieco.

Introduction

Food intolerance or food sensitivity is a reproducible adverse reaction to aliments, that could be related, or not, to the immune system. It can be caused by the absence of specific enzymes needed to digest a substance, or to the body's response to certain food constituents either natural or artificial (1,2).
Milk intolerance is an interesting topic for all pediatricians. In fact milk would be the exclusive food for all younger babies. Both breast fed and formula fed infants use milk nutrients to grow up in their first months of life until weaning is started.
Amongst milk intolerances we can distinguish Cow's Milk Protein Intolerance (CMPI) from lactose intolerance and galactosaemia.

Biochemical and immunological pathogenesis

Cow's milk protein intolerance is a complex disorder involving an abnormal immunological response towards one or more of milk's proteins or towards some of their fractions (mediated by one or more of four Gell and Coombs immunological mechanisms) (2). Most major cow's milk proteins, both casein and whey (e.g., beta-lactoglobulin, alfa-lactalbumin), have been implicated in allergic response. Immunological

mechanisms underlying cow's milk proteins intolerance include IgE-mediated allergy (CMPA) with immediate hypersensitivity, which is rather common, and non-IgE-mediated allergy due to delayed hypersensitivity or to class two or three by Gell and Coombs. The last two forms have respectively rare and unusual gastroenterological clinical features. The reasons why some individuals develop cow's milk allergy are not well understood, probably a complex interaction between genetic and environmental factors are involved. A family history of atopy and early exposure to cow's milk are risk factors for cow's milk allergy. Immunological pathogenesis differentiate CMPI from others adverse reactions, like lactose intolerance and galactosaemia: both of these are characterized by an enzymatic deficit in milk digestion. Galactosaemia is a congenital metabolic disease, indeed it is classified like inborn error of metabolism; enzymatic deficit in lactose intolerance is more complex because there are two components of small bowel's lactase. One is variably genetically expressed, encoded by a gene sited on chromosome 2 q21, the other is induced. Intestinal lactase is a dysaccharidase, *id est* an enzyme that hydrolizes lactose in its two constituents: one molecule of glucose and one molecule of galactose.

Epidemiology and Clinical Features

Primitive lactase deficiency is very rare and is caused by genetical mistakes or post-transcriptional abnormalities. The inducible amount of lactase gains the top level during breast feeding, then physiologically decreases after the first year of life. It could become insufficient to lactose loads in the second childhood or in adulthood. Secondary deficits are more common and they can be caused by a transient reduced bowel absorption, like in gastroenteritis, celiac disease and Crohn's disease. The reduced expression of the inducible amount of lactase is the most common reason of lactose maldigestion in adults (3-5).

Breath test with labelled H_2 demonstrates the lactose deficiency also in asymptomatic individuals (lactose "maldigesters"). The presence of gastrointestinal complaints (abdominal bloating and acid diarrhoea) characterizes the true lactose "intolerants" who experience adverse clinical features (6,7).

Cow's milk proteins intolerance is the most common food allergy in young children: about 5-15% of children's as having manifestations of adverse reactions to cow's milk protein while the real prevalence is minor (2-7.5%). The reason is that there are many different diagnostic criteria and study design, so it would be important to have a common method for diagnosis of CMPA.

We can differentiate early symptoms, like urticaria, angiooedema, lip swelling, probably characterized by IgE mediated reaction; infants with early reaction were more likely to have a positive skin test or test positive for specific IgE. Infants with non IgE-associated mechanisms may have atopic dermatitis and gastrointestinal symptoms as an expression of a later reaction.

There are many signs and symptoms that may be useful for diagnosis. Most of them are listed below in table 1.

In most cases, at least two organ systems are involved; the difference between severe and mild-moderate CMPI depends on the presence of alarm symptoms and findings, like anaphylaxis, acute laryngoedema or bronchial obstruction with difficult breathing, essudative atopic dermatitis with hypoalbuminaemia, macroscopic blood loss. The possibility of becoming tolerant to CMP represents the prognosis of these infants and depends on the patient's age and titre of specific IgE at the time of diagnosis. Furthermore, atopic diseases like asthma, atopic dermatitis and rhinoconjunctivitis are more frequent in children with IgE mediated

Tab. 1: Most frequent and alarm symptoms of CMPI

Organ involvement	Most frequent symptoms	Alarm symptoms
Gastrointestinal tract	Vomiting, gastro-oesophageal reflux, Sandifer syndrome, diarrhoea, constipation (with or without perianal rash), blood in stool, iron deficiency anaemia, abdominal pain and/or bloating	Macroscopic blood loss
Skin	Atopic dermatitis, angioedema (swellling of lips or eye lids), urticaria	Essudative atopic dermatitis with hypoalbuminaemia
Respiratory tract	Runny nose (otitis media), chronic cough, wheezing, asthma	Acute laryngoedema, bronchial obstruction with difficulty breathing
General	Impaired growth, hypotension, tachycardia	Anaphylaxis, shock

history of CMPA.

Diagnosis and Management

A reliable marker of CMPI does not exist; sometimes gastro-oesophageal reflux disease, atopic dermatitis and adverse reaction to other foods (egg, soy) can be associated; for these reasons, differential diagnosis can be difficult and include several diseases, including metabolic disorders, malignancy and infections.

About 0.5% of exclusively breast-fed infants show mild-moderate symptoms of CMPI, especially dermatological and gastrointestinal manifestations: in fact in breast milk the level of CMP is 100000 times lower than in cow's milk. The different prevalence of CMPI in breast-fed infants compared to formula-fed infants depends on differences in antigenic load, in the gut flora composition and in immunomodulators present in breast milk. Breast fed infants, rarely, show severe manifestations of CMPI, like severe atopic dermatitis with protein losses and failure to thrive or anaemia due to colitis with rectal bleeding and protein-losing enteropathy.

Breast feeding is considered as the primary prevention of allergy, but in breast-fed infants with CMPI it's necessary a treatment with allergen avoidance that can result in elimination diet for the mother.

In breast-fed infants with mild-moderate symptoms of CMPI, breastfeeding must be continued. Elimination diet is necessary in mother, up to four weeks. Calcium supplementation is mandatory (1000 mg/die divided into several doses). Lactant mother should avoid dairy products and eggs too. Indeed breast fed baby may sensitize also to egg proteins (8).

If there is an improvement it's possible to reintroduce CMP in the mother's diet:

- If symptoms re-appear, it's necessary to maintain an elimination diet in mother, as long as she is breast feeding; after breast feeding, the child should receive an extensively hydrolysed formula (eHF) with demonstrated clinical efficacy
- If symptoms improve or disappear during elimination diet, one food per week can be reintroduced into the mother's diet, in order to find early symptoms of relapse.

Cases with alarm symptoms should be referred to a paediatric specialist for further diagnostic work-up and management at the same time.

On the other hand, in formula-fed infants with suspected CMPA, the first step is clinical assessment with a correct history taking, including establishing if there is a family history of atopic disease. If there aren't alarm symptoms, it's possible to initiate a diagnostic challenge procedure followed by elimination diet without hen's egg, soy protein and peanut, and with eHFs (extensively hydrolysed formula) or AAF (amino acid-based formula), that are therapeutic formulas tolerated by 90% of CMPI infants (8). Patients with alarm symptoms and life-threatening, in particular respiratory symptoms and anaphylaxis, should be treated with an elimination diet, for a minimal 2-4 weeks and these cases should be referred to paediatric specialist or to an emergency department experienced in the treatment of this condition, according to the severity of adverse reactions. After 6 months also these patients may undergo challenge procedure (8).

A diagnostic test for CMPI does not exist, for this reason elimination diets and challenge procedures are the gold standards for the diagnosis.

Unfortunately we cannot predict the severity of adverse reactions during the challenge: previous mild reactions may be followed by severe reactions like anaphylaxis during the challenge.

In a case of previous anaphylaxis a challenge is not recommendable unless skin prick tests (SPTs) and/or specific IgE measurement show an improvement. In fact children with severe IgE mediated reactions in their medical history (like breathing problems) can be monitored for a period with SPTs or specific IgE measurements. In these cases a strict exclusion diet should be maintained until there is an improvement of the allergy tests.

If during the challenge or up to one week after symptoms of CMPI re-appear, the diagnosis is confirmed, while children who don't show any symptom can resume their normal diet, although they should be observed for any adverse reaction.

Lactose intolerance and CMPI may have a similar clinical presentation, for this reason we propose two double-blind challenges to some of our patients; this pathway is composed by two different challenges. Usually this method is performed in hospital, because of its risks; it's

Tab. 2: The two challenges executed to demonstrate adverse reactions to lactose or to cow's milk proteins.

Biberon A	Biberon B
T0: 10 ml	T0: 10 ml
T30: 20 ml	T30: 20 ml
T60: 30 ml	T60: 30 ml
T90: 40 ml	T90: 40 ml
T120: 50 ml	T120: 50 ml

important doing a correct history taking, accurate clinical examination and laboratory test investigations:

- Total blood cell count: it's possible to observe an hypereosinophilia and/or anaemia.
- Transaminase, to differentiate CMPI from other metabolic disorders.
- IgG,IgA, IgM, for a correct evaluation of immunological system.
- Total IgE levels.
- RAST for specific IgE titre.
- Beta-lattotest to observe immunological reactions non-IgE associated.
- Prick tests (beta-lactoglobulin, alfa-lactalbumin, casein), to predict prognosis and the gap of time until the next challenge.
- Prick by prick (milk, apple, banana), because fresh foods are more reactive.
- Chemical and physical examination of the stools, to evaluate faecal fat and reducing substances that can be index of malabsorption.
- Faecal eosinophilia, index of intestinal immunological activation.
- Clinitest, to detect all faecal reducing substances.
- Breath test, to evaluate increment of C and H in the expired air in lactose intolerant subjects due to increased availability of lactose for colonic microbial flora.

The concordance between a positive skin prick test and positive challenge is about 58.8% using commercial extract and 91.7% using fresh foods, that is the reason why fresh cow milk is preferred.

Prick-test and RAST can be helpful in predicting the prognosis and the gap time until the next challenge.

If infants have a positive Prick-test with a diameter >7mm or very high titres in the RAST-test, food challenge will be positive in over 90% of cases; in these children the challenge can be postponed until they show a reduced reaction at these tests. Patch test method still needs to be standardised; it could be useful to the diagnosis of non-IgE associated reactions.

For our challenges, we use these kind of formulas:

The first challenge: to diagnose Lactase Deficiency.

- First formula is a lactose containing soya milk (lactose +; CMP -): Soyamil Unico by MilteTM.
- Vs Placebo extensive hydrolysed formula (lactose-; CMP-) Alfarè by NestlèTM.

The second challenge: to diagnose Cow Milk Protein Intolerance.

- First formula is milk derived lactose free formula (lactose -; CMP+): AL 110 by Nestlè;
- Vs Placebo extensive hydrolysed formula (lactose-; CMP-) Alfarè by NestlèTM.

The two challenges are executed in two different moments and they must be distant at least one week, each one from the other, at the aim to demonstrate adverse reactions to lactose or to cow's milk proteins. During the challenge we monitor early adverse reactions. The parents of the patient check for any possible later reaction at home, fulfilling an appropriate form.

In the first challenge, we use a formula with lactose and without CMP, in comparison with a placebo; in the second, the formula admits CMP with or without lactose, in comparison with a placebo too. In every challenge we divide 300 cc of milk in ten administrations in the way proposed in table 2. In adult patients (> 7-8 years old), we redouble the single doses of milk in order to better mimic the physiological intake.

In patients with suspected lactose intolerance we prefer to administrate 500 ml of whole cow's milk (containing 25 gr of lactose) more than 25 gr of water melted pure lactose. Because of noteworthy difference between adverse reactions afterwards assumption of milk sugar (8%) more than afterwards assumption of pure lactose (33%) (4). It's necessary that biberon A and biberon B assumption are distant at least 3 hours, to respect gastric emptying and the immunological times.

If any severe, IgE mediated adverse reaction appears, we promptly administrate the following drugs in this sequence:

1. Adrenalin i.v (diluition 1:10000)
2. Hydrocortisone 500 and/or 1000 mg i.v.
3. Chlorpheniramine maleate (Trimeton) 5 and/or 10 mg i.m. and/or i.v.

If the symptoms of CMPI re-appear during the challenge or within 48-72 hours, the diagnosis of CMPI is confirmed and the infants must use eHF or AAF for at least 6 months, then the challenge could be repeated. Infants who don't develop symptoms during challenge and after a week far from it can resume a normal diet.

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