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IgE AND NON-IgE MEDIATED SYMPTOMS ASSOTIATED WITH COW'S MILK PROTEIN ALLERGY

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(Original scientific paper)

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Abstract

Cow's-milk protein is the leading cause of food allergy in infants and young children younger than 3 years.CMPA does seem to peak in the first year of life, with a prevalence of approximately 2% to 3% in the infant population.The clinical spectrum ranges from immediate-type reactions,presenting with urticaria,angioedema,stridor,wheezing to intermediate and late-onset reactions,including atopic dermatitis and symptoms from gastrointestinal tract. A 7-month-old male infant presented with swelling and redness of the lips and cheeks after few minutes of ingestion of cow's milk.He has had atopic dermatitis on the cheeks since he was 3 months old.Family history:infant's first cousin with a proven CMPA.On examination with pale skin and present eczematous changes on the cheeks and on a small area on the lateral sides of both upper legs.Due to suspicion of CMPA,the infant was set on elimination diet without CMP(mother continued breast-feeding while avoiding all milk products from her diet and all infant's complementary feedings were free of CMP). Immunoelectrophoresis showed total IgE =181 IU/ml and specific IgE grade 3 directed to milk, alpha-lacalbumin, beta-lactoglobulin, casein and specific IgE grade 2 directed to white and yolk egg.The infant was fed with extensive hydrolyzate, breastmilk and all infant's complementary feedings were free of CMP.On the last control without eczematous changes on the skin. If acute and objective symptoms of skin occur immediately,or up to 2 hours after a clear history of ingesting dairy products,then CMP should be strictly excluded.Testing for specific IgE against CMP should be performed.A positive test for specific IgE at the time of diagnosis predicts a longer period of intolerance.The child should be given a strict CMP-free diet at least 1 year.Approximately 50% of affected children develop tolerance by the age of 1 year,>75% by the age of 3 years, and>90% are tolerant at 6 years of age.

Key words: *Cow's milk protein allergy, atopic dermatitis, infant, angioedema*

Introduction

Cow's-milk protein (CMP) is the leading cause of food allergy in infants and young children younger than 3 years. CMPA has a peak in the first year of life. Recent data confirm a lower prevalence of CMPA in about 1% of formula-fed infants. The incidence of CMPA in exclusively breastfed infants is almost always reported to be low in the range of 0.4%–0.5% The probability of an IgE-mediated allergic reaction in an infant breastfed by a woman consuming the relevant food can be estimated as ≤1:1000 for CM, egg, peanut and wheat (Schoemaker et al., 2015). But figures as high as 2.1% are reported as well, suggesting an over diagnosis of CMPA in breastfed infants It remains unanswered whether these differences reflect a different genetic background, a difference in selection of patients or both (Turner et al., 2018). History of allergic disease in first degree family members, has been recognized as a risk factor for allergic disease. Having a sibling with allergic disease doubles the risk for food allergy in the child compared with having no family history of allergy, even in the absence of a parental history of allergy. Absence of family history does not exclude the possibility of CMPA. Confounding variables are among others pollution and the administration of medication such as antibiotics (over-use) and proton pump inhibitors early in life(Vallès, Y., & Pilar, F.M. 2018). Living in an industrial versus a rural, farming environment has been known for many years to be a risk factor for allergic disease (Jackson, C.M., Mahmood, M.M., & Järvinen, K.M, 2022). This may be related to a difference in GI microbiome development. The diagnosis of CMPA should

only be suspected on the basis of a complete history and physical examination. CMPA can induce a diverse range of symptoms of variable intensity in infants. It is helpful to differentiate between the ‘‘immediate’’ (early) reactions and ‘‘delayed’’ (late) reactions. Immediate reactions occur from minutes up to 2 hours after allergen ingestion and are more likely to be IgE mediated. Delayed reactions (non-IgE mediated) manifest up to 48 hours or even 1 week following ingestion. Combinations of immediate and delayed reactions (mixed ones) to the same allergen may occur in the same patient. The severity of IgE-mediated allergy may be difficult to categorize as external factors often determine the severity of reaction with anaphylaxis being the most severe presentation. (Venter et al., 2017). Clinical manifestations are predominantly cutaneous (70%–75%), and less frequently gastrointestinal (GI) (13%–34%) and respiratory (1%–8%) (Vandenplas et al., 2024). Up to 1 infant in 4 presents with a combination of symptoms involving more than 1 organ or system (de Boissieu et al., 1997). The existence of a family history of allergy, the involvement of several organ systems (digestive, cutaneous, respiratory) and lack of improvement to usual therapeutic measures increases the likelihood of non-IgE mediated CMPA in these cases. Sensitization to cow’s-milk allergens through breast-feeding manifests primarily as exacerbation of atopic eczema and/or as allergic proctocolitis (Koletzko et al., 2012). Clinical symptoms and signs in the digestive tract may be due to inflammation, dysmotility, or a combination of both (Koletzko et al., 2012). The spectrum of non-IgE-mediated CMPA is broad encompassing symptoms that range in severity from mild rectal bleeding in milk protein induced proctocolitis (FPIAP) to severe vomiting and a sepsis-like presentation that can be seen in food protein-induced enterocolitis syndrome (FPIES). (Vandenplas et al., 2024). FPIAP occurs mostly in breastfed infants, and is in most cases a benign, easily recognized condition that may not need treatment in some breastfed infants, depending on the severity and frequency of blood in the stools. Symptoms of acute FPIES usually appear within 24 hours after food ingestion. FPIES is still underdiagnosed despite being considered a potential medical emergency. Acute FPIES typically presents in infancy with repetitive protracted emesis approximately 1–4 hours after food ingestion. Emesis is often accompanied by lethargy and pallor and can be followed by diarrhoea. Watery diarrhoea (occasionally with blood and mucous) develops in some cases within 5–10 hours of ingestion and can be present for up to 24 hours (Mehr et al., 2019; Hwang et al., 2009 & Katz et al., 2011). Severe cases can progress to hypothermia, methaemoglobinemia, metabolic acidosis and arterial hypotension, mimicking sepsis and potentially making the diagnosis of FPIES difficult. Most children with acute FPIES are well between episodes and show normal growth. FPIES may not develop each time the patient ingests the responsible food, which may be due to its delayed onset and atypical presentation leading to difficult or even misdiagnosis (Nowak-Wegrzyn et al., 2016). Chronic FPIES is almost exclusively reported in infants younger than 4 months of age fed with CM or soy infant formula (Nowak-Wegrzyn et al., 2016). Chronic FPIES develops after repeated ingestion of the triggering food, and presents as chronic/intermittent emesis, watery diarrhoea and faltering growth, potentially leading to dehydration and shock (Nowak-Wegrzyn et al., 2016 & Powell, 1978). Hypoalbuminemia and poor weight gain can hint to the presence of chronic CM-induced FPIES in young infants with persistent GI symptoms (Hwang et al., 2007). With the elimination of the food trigger(s), symptoms resolve, but accidental feeding can induce an acute FPIES reaction within 1 to 4 hours of food ingestion (Nowak-Wegrzyn et al., 2016). The diagnosis of FPIES is based on a clinical history of typical characteristic signs and improvement of symptoms after withdrawal of the suspected trigger food. CPMA is considered a possible factor in the pathogenesis of eosinophilic esophageitis. In patients not responding to conventional therapies for gastroesophageal reflux disease CMPA can be considered, and patients trialled on a time limited elimination diet for 2–4 weeks which should be followed by an OFC.

Case report

A 7-month-old male infant was examinated due to swelling and redness of the lips and cheeks after few minutes of ingestion of cow's milk. He has had atopic dermatitis since he was 3 months old with changes localized to the facial region. Family history:First cousin of the infant has a proven CMPA. The infant was fed with breast milk, egg yolk, fruits and vegetables. On examination afebrile, in general stable condition, pale skin and present eczematous changes on the facial region and on a small area on the lateral sides of both upper legs. Lips with normal coloring without swelling and redness. Due to suspicion of CMPA, the infant was set on an elimination diet without CMP (mother was encouraged to continue breast-feeding while avoiding all milk and milk products from her own diet and all infant’s complementary feedings were free of CMP). CBC - Le= 9,39 x10 /L Er= 4,29x10 /L Hgb = 100g/L HCT = 26,2% PLT= 459x10 /L. Serum iron= 2.1 umol/l. Few days after the first examination with the appearance of liquid stools for three days

and in few of them bloody mucus was observed. The results of immunoelectrophoresis showed increased values of total IgE antibodies=271 IU/ml, specific IgE grade 3 directed to milk (12.6 kU/ml), β-lactoglobulin (11.9 kU/ml), casein (4.78 kU/ml), α-lactalbumin (7.23 Ku/ml) and specific IgE grade 2 diretcted to white (3.12 kU/ml) and yolk egg (1.722 kU/ml). The infant was fed with Extensi ve hydrolised formula, breastmilk (mother avoided all types of milk and milk products from her diet) and all infant's complementary feedings were free of CMP. Iron replacement therapy was introduced. After one month of the elimination diet, the mother introduced a dairy product into her diet, but after 24 hours the infant developed a rash on his back and chest. On the last control without eczematous changes on the skin and with normal stools. Control CBC - Le= 11,91x10 /L Er= 4,69 x10 /L Hgb = 119g/L HCT = 29,69% PLT= 330x10 /L, Serum Iron= 7.5 umol/l.

Discussion

A proper diagnosis of CMPA should always start with an allergy-focused clinical history and a complete physical examination (Venter et al., 2013). Attention should be given to the presenting symptoms and signs that may indicate possible CMPA. Information regarding the infant's feeding history and the personal and familial history of allergic disease should be obtained. For clinical practice, the determination of specific IgE in a blood sample and the skin prick test (SPT) are useful diagnostic tests at any age, but a combination of the 2 tests is not necessary for the diagnostic workup (Boyce et al., 2010). The higher the antibody titer and the larger the diameter of the SPT reaction, the greater is the probability of having a reaction to CMP and allergy persistence (Sampson, 2001 & Verstege et al., 2005). Children with gastrointestinal manifestations of CMPA are more likely to have negative specific IgE test results compared with patients with skin manifestations, but a negative test result does not exclude CMPA (Eggesbo et al., 2001 & Klemola et al., 2002). Positive test for specific IgE at the time of diagnosis predicts a longer period of intolerance as compared with those children who have negative tests (Halken, 2003 & Niggemann et al., 2001). If symptoms are relevant and CMPA is likely, a diagnostic elimination of CMP (in the infant's/child's diet or in the mother's diet in case of breast-feeding) should be initiated for a limited period of time, even in cases with negative specific IgE result. The duration of a diagnostic elimination diet depends on manifestation and should be kept as short as possible, but long enough to judge whether clinical symptoms resolve or not or become stable. This ranges from 3 to 5 days in children with immediate clinical reactions (eg, angioedema, vomiting, exacer bation of eczema within 2 hours) to 1 to 2 weeks in children with delayed clinical reactions (eg, exacerbation of eczema, rectal bleeding). In patients with gastrointestinal reactions (eg, chronic diarrhea, growth faltering), it may take 2 to 4 weeks on a CMP-free diet to judge the response. If there is no improvement in symptoms within these timelines, then CMPA is unlikely; however, exceptions may occur. Infants with significant gastrointestinal symptoms with no improvement using a hydrolyzed or a soy formula may benefit from a further period of observation on an amino acid–based formula (AAF) before CMPA is excluded. This is particularly true in patients with multiple sensitizations (de Boissieu, D., & Dupont, C. 2002). If the clinical symptoms do not improve on a diagnostic elimination diet with AAF, then it is highly unlikely that the symptoms are due to CMP. In non-IgE mediated CMPA, the diagnostic elimination diet typically requires 2–4 weeks before reintroduction, while for IgE mediated allergy the time window may be shorter (1–2 weeks) (Boyce et al., 2010). Improvement will be faster in IgE-mediated than in non-IgE mediated allergy. When CMA is suspected in an exclusively breastfed infant, a diagnostic maternal CM-free diet for 2–4 weeks whilst continuing to breastfeed may be considered. In order to confirm the diagnosis, CM should then be reintroduced in the maternal diet with monitoring of symptoms. (Vandenplas et al., 2024). In formula-fed infants, a CM-derived eHF is the first choice for a diagnostic elimination diet. In patients with CMA and severe diarrhoea and/ or with severe malnutrition, the transient use of a formula without lactose for 2–4 weeks may be preferred. In formula-fed infants, AAF for a diagnostic elimination diet should be reserved for severe cases or patients with severe malnutrition. (Koletzko et al., 2012). Although less studied than CM-based eHFs, HRFs can be considered as an alternative for a diagnostic elimination diet. Soy infant formula should not be used as the first choice for the diagnostic elimination diet but can be considered in some cases for economic, cultural and palatability reasons (Koletzko et al., 2012) An OFC is mandatory in the work-up of infants with CMPA, except for those presenting with life-threatening symptoms such as anaphylaxis and with high levels of sIgE.Icn this situation, the oral challenge test can be omitted. The child should be given a strict CMP-free diet for a period of at least 6 months or up to the moment when the infant reaches 12 months, before an oral food challenge is performed. DBPCFC is recommended for unclear cases and research purposes. (Vandenplas

et al., 2024). A specialist should assess the patient before an oral challenge is performed in a hospital with adequate emergency facilities. In IgE-mediated CMPA, sIgE levels should be measured before the challenge and guide timing of the OFC (Koletzko et al., 2012). The starting dose during an oral milk challenge should be lower than a dose that can induce a reaction. If severe immediate reactions are expected, the OFC should start with a drop on the lips followed by a stepwise increasing dosing of small volumes at 30-minute intervals to end up with 100 mL. (Vandenplas et al., 2024). Patients should be observed for at least 2 hours following the maximum dose. If no reaction occurs during the OFC, CM should be continued at home every day with at least 200 mL/ day for at least 2 weeks. An OFC should preferably be carried out in a hospital setting when: there is a history of immediate allergic reactions; the reaction is unpredictable; and in case of severe atopic eczema with the difficulty in accurately assessing a reaction. (Koletzko et al., 2012). The condition of the skin should be documented and graded according to severity (SCORing Atopic Dermatitis) before and after the challenge and then again 24 and 48 hours later. If the results cannot be clearly interpreted, then a placebo-controlled challenge should be performed as further confirmation, even in infancy. If CMPA manifests clinically with diarrhea, the stool frequency and consistency should be documented (eg, in infants with a stool form scale). If significant diarrhea recurs during the challenge then the diagnosis of CMPA is confirmed and a therapeutic formula can be recommended. If there are no recurrent symptoms, then the child should continue to receive its previous formula (Koletzko et al., 2012).

Conclusion

If acute and objective symptoms of skin (acute urticaria, angioedema), respiratory tract (stridor, wheezing), or systemic reactions (anaphylaxis) occur immediately, or up to 2 hours after a clear history of ingesting dairy products, then CMP should be strictly excluded. Testing for specific IgE against CMP or an SPT with natural cow's-milk or whole-protein formula should be performed. CMPA can be assumed with a high likelihood if testing for specific IgE is positive. In this situation, the oral challenge test can be omitted. The child should be given a strict CMP-free diet for a period of at least 1 year before an oral food challenge is performed. A positive test for specific IgE at the time of diagnosis predicts a longer period of intolerance as compared with those children who have negative tests. The prognosis for CMPA in infancy and young childhood is good. Approximately 50% of affected children develop tolerance by the age of 1 year, >75% by the age of 3 years, and >90% are tolerant at 6 years of age.

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