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Original Article

Elimination and provocation test in cow's milk hypersensitive children

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Abstract

Background Allergic disease in infancy mostly related to cow's milk allergy. The prevalence of cow's milk hypersenstivity in children has increased steadily in the past years; therefore diagnostic accuracy is important and every symptomatic child with positive specific IgE should be followed by elimination and provocation.

Objective To diagnose cow's milk hypersensitivity on children under three years old using elimination and provocation methods.

Methods This was a clinical diagnosis study, in which children with allergy symptoms were examined for cow's milk sensitivity using prick test or IgE Radioallergosorbent test (RAST). Those with positive results underwent an elimination for minimal of 2 weeks and were challenged aterwards. The study was a qualitative diagnostic test with the gold standard of recurrence of symptoms after challenge test.

Results There were forty subjects included in the challenge process with mean age of 17 months old. Boys and girls were equally distributed. There were 67% subjects with positive results on challenge with positive prick test and 64% positive challenge with history of positive IgE RAST. Sixty-five percents of subjects with positive results on challenge had more than 2 weeks elimination period. There was no statistical significance found in children with positive results on challenge, using neither prick test or IgE RAST.

Conclusions Cow's milk protein allergy can be diagnosed on children less than 3 years old by applying elimination and challenge procedure. IgE sensitivity alone can not determine hypersensitivity **[Paediatr Indones 2008;48:253-6]**.

Keywords: *hypersensitivity, milk, immuglobulin E, child*

Food allergy in infancy usually caused by cow's milk protein. High risk infant exposed to cow's milk protein directly during formula feeding or through breastmilk feeding. The manifestations of allergy are also related to subsequent introduction of food according to age.[1-5] Cow's-milk-based infant formula is the most common formula milk available in the market which contain casein, β-lactoglobulin, and α-lactalbumin that are highly allergenic in high risk population.[1-3] Cow's milk allergy is an immunological reaction with memory capacity, which can be elicited by repeating exposure to cow 's milk protein.[5]

Cow's milk hypersensitivity can be determined by measuring specific IgE or skin prick test. Positive IgE results specific to cow's milk protein could help clinicians to take special precautions and to guide them in taking primary prevention steps. Primary prevention is proven and recommended to high risk infants with atopic mother or allergic siblings with or without positive specific IgE and elevated total of IgE level.[6,7,8] For the high risk group, good methods of prevention available includes exclusive breastfeeding for at least four months, or substitute milk with hypoallergenic infant

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formula. However, Cow's milk sensitisation and allergy may still happen, perhaps later in life. Tolerance to cow's milk protein is usually seen between one and three years old. In children with non-IgE cow's milk allergy, tolerance will be seen at the age of 2 years.[1,8,9]

Cow's milk allergy must be determined accurately, since overdiagnose will lead to malnutrition, eating disorders and psychological problems. Up to this day, the gold standard of diagnosing cow's milk allergy is Double-blind placebo-controlled cow's milk challenge (DBPCCMC) is not routinely applied, instead many centers have delivered open challenge.[10-13]

In this study we conduct an open challenge test to children between zero and three years of age with positive cow's milk IgE, and observe numbers of positive results available.

Methods

This was an interventional study, in which cow's milk open challenge tests were performed to children between zero and three years old. The subjects were children who had been diagnosed suffering from cow's milk allergy by two centres: Allergy Clinic of Cipto Mangunkusumo Hospital, Jakarta, and Allergy Clinic of Zainul Arifin Banda Aceh. All subjects diagnosed between August 2006 and December 2007 were included. The diagnosis of cow's milk allergy was made based on allergic symptoms appeared after receiving any dairy milk product, includes erythema, pruritis, chronic cough, diarrhea, rhinitis. Furthermore, positive allergy history in the family, and positive skin prick test of IgE RAST which showed specific IgE reaction to cow's milk protein are part of subjects inclusion. During this period of time, children were allowed to receive breastfeeding milk, under the condition that the mother also restricted cow's milk intake from her diet. If however, the mothers preferred to provide their children with formula milk, they should choose non cow's milk formula.

Every child in the study then underwent cow's milk elimination for two weeks, and should be omitted from antihistamine treatment for three days prior to the challenge test. Other specific medications such as β2 agonist, Cromolyn, or inhaled steroid must not be taken within six hours prior to challenge test. Finally, patients were on two hours fasting before receiving the first challenge dose.

Cow's milk was given in a portion dose, starting with 5 ml; the dose was doubled every 10 minutes until normal daily servings was reached. The appearance of symptoms led to the procedure termination. Positive criterias included the appearance of symptoms and cummulative challenge dose for at least 80 mililiters. Cow's milk formula applied in this study was the patient's previous formula or standard formula.

Other symptoms which appeared within 24 hours after last dose provocation were also recorded. If no symptoms were noted within that period, then the subjects were declared not allergic to cow's milk formula. Provocation was only conducted once with no repetition test followed. Positive reactions shown were urticaria, exanthema, angioedema, diarrhea, vomitus, abdominal pain and colic, bloating, wheezing, rhinitis and cough.

Results

There were forty subjects who were matched the inclusion criteria. The average age of subjects is 17 months (the range of age is between three to thirty-six months), with the age group of less than one year old showed the highest number of occurance. Sensitization to cow's milk allergen was diagnosed by skin prick test (SPT) or in vitro IgE RAST. With the preference of conducting RAST test in younger babies or in circumstances whenever Skin prick test could not be delivered. Atopic history was identified in father, mother and siblings with distribution as seen in **Table 1**. Clinical manifestation of allergic disease in subjects can be seen in **Table 2**.

Provocation test was performed 2 weeks after the elimination period. Almost all parents brought in their children longer than 2 weeks, for fearing of symptoms recurrence. Fifty percent subjects came after 2 – 8 weeks time, meanwhile the rest returned after eight weeks. During this period of time, we encouraged the parents to attend the second meeting via phone calls. This is reflected in the results of provocation, positivity was seen more on group 2 – 8 weeks (65%), which was unrelated to way of sensitivity diagnosis (SPT versus RAST).

Discussion

Cow's milk usually is the first allergic manifestation in infancy due to cow's milk early exposure.[1,13-15] As other

allergic disease, cow's milk protein allergy is important, with rising prevalence within the last 3 decade.[1,14,16]

In neonate and infancy the TH1 and TH2 immune system is precariously imbalance and fragile. If there were allergic reactions, then the baby is vulnarable to variety of allergens, including early allergen such as cow's milk protein. Persistent sensitization will lead to allergy manifestation in skin, gastrointestinal system and respiratory system by way of type I and IV hypersensitivity reaction.[17,18]

Cow's milk allergy is established through complete history taking, specific signs and symptoms and also laboratory examination.[6,11,19] Sensitization to cow's milk protein can be proven by determining specific IgE and skin test. For those who give positive results, allergy should be proven by elimination and provocation test.[8,9,10,11]

Table 1. Subject characteristics

Characteristics	Number (%)
Age	
< 1 year	16 (40)
1≤ 2 year	14 (35)
2 - 3 year	10 (25)
Gender	
Boy	19 (47.5)
Girl	21 (52.5)
Nutritional status	
Good	16 (40)
Slightly malnourished	24 (60)
Cow's milk specific IgE	
SPT	21 (52.5)
RAST	19 (47.5)
Family history of atopic	
Mother and father	16 (40)
Mother and sibling	8 (20)
Father and sibling	16 (40)

Table 2. Clinical manifestations of allergic disease

Clinical manifestations	Number (%)
Atopic dermatitis (AD)	4 (10)
AD and chronic recurrent cough	25 (62.5)
AD and diarrhea	6 (15)
Chronic recurrent cough and rhinitis	5 (12.5)

Our series consisted of 40 subjects with equal number of boys and girls. Children bellow one year old were observed to be most influenced by parental anxiety, which appeared over symptoms appearance that may caused harm or life threatening to their baby. Older babies arrived with respiratory symptoms which could be related to allergic reaction and were managed inadequately. We observed that 60% of subjects fell behind normal body weight, these could relate to sleep inadequacy or parent's fearsomeness to introduce solid food that may aggravate their children's condition.[8,12-14]

The role of genetics in allergy was observed, almost no subjects without allergic history in the family. Based on these facts we realize how important is the role of early prevention to prevent further sensitization.[5,6,16]

Atopic dermatitis and gastrointestinal symptoms were reported early and when prevention to further sensitization was not applied, then respiratory tract problems such as cough, asthma and rhinitis would appeared.[1,7,17,18]

In this study symptoms in the subjects were atopic dermatitis and chronic cough (62.5%) followed by rhinitis and diarrhea, even in the age above one year old. Deferred of challenge in the subjects were caused by ignorance and lower economic status.[6,19,20]

Specific IgE diagnosis was determined by skin prick test and/or IgE RAST, depend on age of the subjects. All subjects either showed positive prick to Cow's milk allergen or elevated IgE level, then they underwent two weeks elimination procedure were afterwards challenged to cow's milk allergen.[10-12]

In practice, almost all subjects were late presented to provocation test, for fear of symptoms recurrency. This could hamper the result of challenge, because the longer elimination period, the more TH1-TH2 balance to equilibrium that could cause tolerance.[10-12] There were no allergy manifestation on challenge in

Tabel 3. Specific IgE and result of provocation test

Diagnostic result	Challenge procedure					
	Elimination			Provocation		
	2–8 weeks	> 8 weeks	Total	Positive	Negative	Total
Specific IgE						
SPT (++)	10	11	21	14 (9+5)	7	21
RAST (>0,4 µ/dl)	10	9	19	12 (8+4)	7	19
Total	20	20	40	26 (17+9)	14	40

14 (35%) subjects. The rest have recurrency of initial allergy manifestation.

From twenty-six subjects who have symptoms recurrency on challenge were on elimination for > 2 – 8 weeks time. There were no specific differentiation on these subjects, whether sensitivity determined by prick test or IgE RAST, therefore diagnostic of cow's milk sensitivity can be through skin test or IgE RAST.[11,12,20] Children with positive result on challenge test were suggested to use alternative of mik or no milk diet. Some used soy based formula.[19-22]

We conclude that the increased rate of cow's milk allergy prevalence rendered to diagnostic establishment of cow's milk allergy. Diagnosis should be through elimination provocation to established hypersensitivity, but elimination period should be according to protocol, 2 weeks. In these subjects, almost all have elimination period from 2 – 8 weeks. About 65% subjects have positive symptoms recurrence on provocation. Accurate diagnostic by elimination and provocation after sensitivity test can established cow's milk allergy diagnosis and led to accurate management

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