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The Effect of Growth Disorder in Children with Cow's Milk Protein Allergy

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Abstract— Cow's milk protein allergy is an important issue in children because it can lead to growth disorder. This study aims to analyze effect of growth disorder in clinical manifestation of children with cow's milk protein allergy.A cross sectional study was performed in children with cow's milk protein allergy between March to April 2018 in Pediatric ward, Dr. Soetomo Hospital, Surabaya, Indonesia. Age, body weight, height, and clinical manifestation of gastrointestinal tract or respiratory tract were recorded from medical record. Data analysis was performed using chi square and odds ratio to determine effect of growth disorder in clinical manifestation of children with cow's milk protein allergy.Clinical manifestations of gastrointestinal tract were more often had underweight, stunted, and wasted (60%, $p < 0,05$; 52,9%, $p > 0,05$; 65,7%, $p < 0,05$, respectively) compared to clinical manifestation of respiratory tract. The effect of clinical manifestations in children with cow's milk protein allergy to have underweight and wasted was higher in clinical manifestation of gastrointestinal tract compared to clinical manifestation of respiratory tract (OR 2.455 for underweight and OR 6.024 for wasted).The effect clinical manifestations in children with cow's milk protein allergy of underweight was 2.455 times higher and wasted was 6.024 times higher in clinical manifestation of gastrointestinal tract.

Keywords— cow's milk protein allergy, malnutrition, anthropometry measurement

1. Introduction

The prevalence of allergy to cow's milk protein in the world ranges from 2-3%, which is a higher incidence in children than in adults [1].The prevalence of cow's milk allergy in children in Indonesia is 2-7.5% and allergic reactions to cow's milk are still possible in 0.5% of infants who are exclusively breastfed [2]. Most allergic reactions to cow's milk are mediated by IgE with an incidence of 1.5% [3].

Children with manifestations of cow's milk protein allergy often get growth disorders [4] which are caused by digestive tract manifestations such as vomiting, regurgitation, chronic diarrhea. This results in reduced calorie intake, inadequate calorie absorption, and normal calorie intake with an increase in metabolic requirements, causing growth disorders in children [5,6]. Precautions and proper management are needed to prevent a prolonged allergy to cow's milk protein, so as to prevent growth disorders [1].

The reaction caused to an allergy to cow's milk protein can disrupt all organs of the body and impair growth. In the first year of life, a child's immune system is relatively immature and very vulnerable. The phenomenon in children who are allergic to cow's milk protein has a lot of growth problems seen from anthropometrics such as underweight, stunted, and wasted.This study aims to see what manifestations of cow's milk protein allergy are the most and associated with the incidence of abnormal anthropometry in children allergic to cow's milk protein at Dr. Soetomo Hospital, Surabaya.

2. Method

A cross sectional study was performed using medical records of children with cow's milk allergy in Dr. Soetomo Hospital, Surabaya, Indonesia during March to April 2018.

2.1 Participants

Children with cow's milk allergy were grouped based on age, sex, clinical manifestation (gastrointestinal and respiratory tract), and anthropometric measurement. The inclusion criteria in this study included age <5

years and suffering from cow's milk protein allergy. The exclusion criteria in this study included incomplete medical document data, congenital abnormalities and chronic diseases. The number of samples obtained by calculating the formula:

$$n = \frac{Z\alpha^2 \times P \times Q}{d^2} + \text{correction factor } 10\%$$

n = number of samples; α = 0.05; Zα = 1.96; P = proportion of events (growth disorders, respiratory tract manifestations, and digestion), Q = 1-P; d = deviation of the magnitude of the intersection, namely 10% [7]

Gastrointestinal manifestations in this study include acute diarrhea (defecating in infants or children more than 3 times per day, accompanied by changes in the consistency of watery stools with or without mucus and blood less than one week)[8]; vomiting (explosively excreting the contents of the stomach through the mouth due to contraction of the abdominal muscles)[8], bloody diarrhea (passing stool more than 3 times a day, accompanied by a change in the consistency of the stool to become runny with or without mucus and the presence of blood[9,10], and chronic diarrhea (increased passage of stool with a consistency that is softer or more watery than usual, and occurs at least 3 times in 24 hours)[8].

Respiratory manifestations in this study include under-five asthma (a chronic inflammatory airway disease characterized by coughing, wheezing, difficulty breathing, more than 10 days, more than 3 episodes/year, or severe episodes and/or worsening at night. Between episodes. the child may cough, wheezing or have difficulty breathing with a family history of allergies)[11], and recurrent pneumonia (two or more episodes of pneumonia in 1 year or 3 episodes where a chest X-ray shows improvement between the 3 episodes)[12].

Anthropometric measurements were carried out to measure children's growth using the WHO growth chart, with the results being underweight (weight per age <-2SD), stunted (height per age <-2SD), wasted (weight based on height <-2SD).

2.4 Data Analysis

Descriptive analysis was performed using statistical measures (mean, and frequency distribution tables) to assess the profile of most clinical manifestations in cow's milk protein allergy and to obtain growth disturbance data assessed by anthropometry. Chi square test with a significance value of $p < 0.05$ was carried out to analyze the comparison of the effect of clinical manifestations of cow's milk protein allergy. Analysis of the effect of gastrointestinal and respiratory manifestations on the occurrence of growth disorders assessed by anthropometry was performed using odds ratios (ORs) with 95% confidence intervals (CI). Data analysis was performed using SPSS for windows version 22.00.

2.5 Ethical Statement

Informed consent of participants were obtained from their parents or legal guardians. Ethical approval was provided by Health Research Ethic Committee of Dr. Soetomo Hospital, Surabaya, East Java Province, Indonesia (0186/KEPK/IV/2018).

3. Result

Forty-point-four percent of children in this study were in age group >12-60 month (40 of 99), and 70.7% of children had clinical manifestation in gastrointestinal tract (70 of 99). The anthropometric status from 99 children with cow's milk protein allergy showed that 53 children were underweight (53.5%), 54 children were stunted (54.5%), and 53 children were wasted (53.5%). The basic characteristics of the subject are shown in table 1.

Table 1. Characteristic of Subject

Variable	n = 99
Age (month)	
• 1-6	29 (29,3)
• > 6-12	30 (30,3)
• > 12-60	40 (40,4)

Gender (n/%) • Male • Female	 62 (62,6) 37 (37,4)
Clinical Manifestation (n%) • Gastrointestinal tract • **Respiratory tract**	 70 (70,7) 29 (29,3)
Anthropometry Measurement (n/%) • *Underweight* • *Stunted* • *Wasted*	 53 (53,5) 54 (54,5) 53 (53,5)

Clinical manifestations of gastrointestinal tract were found more frequent compared to clinical manifestation of respiratory tract in each age group. Age group >12-60 month have the most frequent clinical manifestations of gastrointestinal tract compared to other age group (87.5%), p value <0.05. Children with clinical manifestation of gastrointestinal tract were more often had underweight and wasted (60%; 65,7%, p < 0,05, respectively) compared to children with clinical manifestation of respiratory tract (37,9%; 24,1%, p < 0,05, respectively) (Table 2).

Table 2. Comparison of the manifestations of the gastrointestinal and respiratory tract

Variable	**Gastrointestinal tract manifestation n (%)**	**Respiratory tract manifestation n (%)**	**P value**
Age (month, mean)	15,9 (± 1,66)	10,4 (± 1,81)	
Age (month) • 1-6 • > 6-12 • > 12-60	 19 (65,5) 16 (53,3) 35 (87,5)	 10 (34,5) 14 (46,7) 5 (12,52	 **0,006**
Gender • Male • Female	 42 (66,7) 28 (75,7)	 20 (32,3) 9 (24,3)	 0,401
Anthropometry Measurement • *Underweight* • Normal • *Stunted* • Normal • *Wasted* • Normal	 42 (60) 28 (40) 37 (52,9) 33 (47,1) 46 (65,7) 24 (34,3)	 11 (37,9) 18 (62,1) 17 (58,6) 12 (41,4) 7 (24,1) 22 (75,9)	 **0,045** 0,600 **0,000**

p significant < 0.05

The effect of growth disorders in children with cow's milk protein allergy to have underweight and wasted is higher in clinical manifestation of GI tract compared to clinical manifestation of respiratory tract (OR 2.455 for underweight (95% CI 1,008-5,974) and OR 6.024 for wasted (95% CI 2,253-16,104) (Table 3).

Table3. Effects of gastrointestinal and respiratory tract clinical manifestations on the occurrence of underweight, stunted, and wasted in children with cow's milk allergy

Clinical manifestations of the gastrointestinal and respiratory tract	**p value**	**OR**	**95% CI**
Underweight	0,045	2,455	1,008-5,974
Stunted	0,600	0,791	0,330-1,899

Wasted	0,000	6,024	2,253-16,104

p significant < 0.05

4. Discussion

In this study, most of the children who were allergic to cow's milk protein were> 12-60 months as many as 51 children (40.2%),> 6-12 months as many as 30 children (30.3%), 1-6 months as many as 29 children (29.3%). This study has different results from study conducted by Vieira that children with cow's milk protein allergy aged ≤ 6 months obtained 79 children,> 6-12 months obtained 51 children, aged> 12-24 months obtained 29 children, this can be due to the age ranges of the samples in different studies[7].

The subjects were male compared to female, namely 62 children (62.6%), while the female subjects were 37 children (37.4%). The most clinical manifestations found in children allergic to cow's milk protein are the digestive tract, namely 70 children (70.7%) and the respiratory tract of 29 children (29.3%). The results of this study are in line with the previous findings that children with cow's milk protein allergy ≤ 6 months found 79 consisting of 39 boys and 40 girls,> 6-12 months, 51 consisting of 30 boys and 21 girls, aged> 12-24. months were obtained 29 consisting of 16 men and 13 women. Of the 159 children studied, 141 children (88.7%) had gastrointestinal and respiratory tract manifestations of 31 children (19.5%) [7].

Anthropometric measurement of 99 children allergic to cow's milk protein was found to be underweight in 53 children (53.5%), stunted in 54 children (54.5%), and wasted in 53 children (53.5%). Similar results were also obtained in previous studies that showed growth disorders in children allergic to cow's milk protein were measured from anthropometry, namely 24 children (15%) were underweight, 38 children (24%) were stunted, 18 children (11%) experienced wasted. The smaller number of growth disorders in Vieira's study could be due to the different age ranges of the sample so that growth disorders could be diagnosed earlier [7].

This study found that the average age of children allergic to cow's milk protein was 15.9 months ± 1.66 in the clinical manifestations of the digestive tract and 10.4 months ± 1.81 in the respiratory tract. In previous studies, it was explained that most of the incidence of allergy to cow's milk protein at an average age was experienced before the age of 1 month. In this study, the clinical manifestations of the digestive tract were found to be more than the respiratory tract for each age and sex. This is in line with previous studies that at each age found more digestive tract manifestations than respiratory tract[7].

Cow's milk protein allergy is most common in children in the first year with an incidence of 2-3%, and under 1% in children over 6 years of age.[13]. Cow's milk protein allergy affects between 1.9-4.9% of infants and children, of which 50-60% present with digestive and skin symptoms, about 20-30% have respiratory symptoms[14].

Allergy to cow's milk protein can cause growth problems because the variety of food and beverage choices is reduced, because cow's milk and its derivatives must be eliminated from the daily menu. However, it is also explained that cow's milk protein allergy can also increase energy requirements due to inflammation and impaired absorption of nutrients[15,16].

Growth disturbances often occur in children allergic to cow's milk, because of the less variety of food that can be given and the length of time elimination diet therapy. In addition, the inflammatory state that characterizes allergic disease can result in reduced bioavailability of nutrients. Another possible explanation is the increased caloric requirement, as indicated indirectly due to the anatomical and functional restoration processes of wound healing. Certain clinical manifestations of cow's milk protein allergy such as gastroenteritis which is a manifestation of the digestive tract are often accompanied by loss of appetite and early satiety, which can reduce nutrient intake. There are many risk factors for poor growth in children with allergies (a) late diagnosis, (b) disease in the active phase, (c) persistent (subclinical) intestinal inflammation, (d) restriction of menu choices due to elimination diet, (e) associated with atopic disease (asthma, eczema) or with chronic disease. Nutritional interventions, if properly monitored, have been shown to be effective in treating growth disorders[17].

Previous studies divided the symptoms of cow's milk protein allergy into digestive, skin and respiratory tracts. In that study, cow's milk protein allergy was associated with dietary restriction as an elimination diet as assessed by anthropometric parameters, but no significant value was found for any of these parameters on growth. All children were evaluated by a pediatrician and explained about the proper and correct elimination diet. However, some children still experience growth problems. Growth disturbances in allergic children mainly associated with dietary elimination of food therapy have been described in previous studies but common atopic comorbidities such as asthma, severe eczema are currently rarely considered in etiology. Inflammatory cytokines, particularly interleukin-6 produced by macrophages and tumor necrosis factor-α, are thought to play a role in allergic inflammation common in atopic disorders. Children with food allergies appear to be thinner than the general population of children[18].

In the clinical manifestations of the gastrointestinal tract, namely chronic diarrhea, the most common was at the age> 12-60 months, namely 17 children (60.7%), the mostbloodydiarrhea was at the age> 12-60 months, namely 3 children (60%), while in acute diarrhea. and vomiting was found more frequently at the age of 1-6 months, as many as 20 (58.8%) children. In the clinical manifestations of the respiratory tract, namely under-five asthma, the most was found at the age of> 6-12 months, namely 6 children (50%), recurrent pneumonia was mostly found at the age> 6-12 months, namely 8 children (40%). This is in accordance with the previous study of 159 children studied, there were gastrointestinal manifestations in 141 children, respiratory tract in 31 children, systemic in 39 children, and cutaneous manifestations in 29 children. A total of 85 children with complaints of vomiting and regurgitation, 54 children had abdominal colic, 30 children had diarrhea without bleeding, 25 children had constipation, 23 children had bowel movements with normal consistency but accompanied by blood, 10 children had bloody diarrhea, but in this study not compared between age with clinical manifestations [7]. Another study also explained similar results, among 280 children clinical manifestations of diarrhea in 171 children (61.1%), hematochezia in 149 children (53.2%), vomiting in 71 children (25.4%), eczema in 57 children. (20.4%), and constipation in 13 (4.6%). The clinical manifestations of diarrhea were the most common, but the clinical manifestations of the respiratory tract were not explained[19]**.**

In this study, the clinical manifestations of the digestive tract had a greater influence on the occurrence of underweight 2.455 times, stunted 0.791 times, wasted 6.024 times compared to the respiratory tract. This is in line with previous study that 38 toddlers (95%) had comorbidities, which was the largest proportion in the growth disorders group with a value of p = 0.000, which means that comorbidities had a significant relationship with the incidence of growth disorders. In addition, it was obtained that 35,286 comorbidities were greater to cause growth disorders [20].

A study conducted by Diaferio on 33 of 43 infants had growth problems due to allergy to cow's milk protein. Growth impairment correlated with cow's milk protein allergy at 6 months of age (98% of children had gastrointestinal symptoms in non-IgE-mediated cow milk protein allergy, p <0.001)[6].

5. Conclusion

The effect of gastrointestinal clinical manifestations is greater on the occurrence of underweight and wasted in children allergic to cow's milk protein compared to breathing. The clinical manifestations of the digestive tract are more common than in respiratory children allergic to cow's milk protein. Children allergic to cow's milk protein from anthropometry underweight, stunted and wasted were found to be more common in clinical manifestations of the gastrointestinal tract.

6. References

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