Anal Fissures in Infants May Be a Pathognomonic Sign of Infants with Cow's Milk Allergy

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Objective: *To study the association between anal fissures and cow's milk allergy (CMA) in infants.*
Methods and Method: *In a prospective study, 72 confirmed cases of CMA in infants were examined for anal fissure by pediatricians with five years' experience. A positive finding was defined as when an anal fissure was detected by at least two out of three examiners.*
Results: *Of infants with CMA with and without gastrointestinal GI symptoms, 79% and 83% had anal fissures, respectively. The prevalence of anal fissure in these infants is significantly higher than in normal infants.*
Conclusion: *Anal fissure may be a pathognomonic sign of cow's milk allergy in infants.*

Keywords: *Anal fissure, Cow's milk allergy, Diagnosis, Pathognomonic sign*

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Diagnosing cow's milk allergy (CMA) in infants is challenging because symptoms suggestive of CMA are non-specific and reported in only 5 to 15% of CMA infants[1]. In addition, available diagnostic tests-such as cow's milk protein challenge, skin-prick tests, patch tests, and blood tests for specific IgE to cow's milk protein-yield positive results in less than 50% of cases[2,3]. Since delay in diagnosis of CMA can result in malnutrition and consequent sequelae[4], developing a method for early diagnosis is necessary[5].

In the presented study, the authors report on anal fissure as a pathognomonic sign of CMA. The authors were inspired by the frequency of anal fissures found in infants with CMA, regardless of their milk consumption habits. Traditionally, the presence of anal fissures has been associated with the degree of cow's milk consumption. Specifically, it was believed that infants with high cow's milk consumption have a tendency to develop chronic constipation and anal fissures[6]. Nevertheless, it was recently found that infants with CMA, who overall consume a lower amount of cow's milk, also have chronic constipation and anal fissures[7,8]. Therefore, cow's milk consumption and the development of anal fissure are likely unrelated. Furthermore, a recent study demonstrated no difference in the prevalence of anal fissure in infants aged 0-4 months, regardless of whether they were exclusively breast-fed, exclusively formula-fed, or fed with a combination of both[9]. Anal fissure therefore is very likely not associated with either the amount or type of milk consumed. Having excluded milk consumption habits as a possible confounder to the presence of anal fissure, the presented study aims to establish the association between anal fissure and CMA in infants.

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Material and Method

Seventy-two infants aged between 0 and 12 months who had been diagnosed with CMA by cow's milk protein challenge were recruited. Exclusion criteria were infants who were born prematurely, or with congenital gastrointestinal abnormalities, congenital birth defects, or inborn errors of metabolism. Parents of the infants gave written informed consent. The protocol was approved by the Ethics Committee for Clinical Research, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

Infants with CMA were divided into two groups. The first group consisted of infants with chronic or recurrent gastrointestinal (GI) symptoms, with or without respiratory and dermatological symptoms. The second group had no GI symptoms, but had respiratory or dermatological symptoms. GI symptoms included vomiting, colic, diarrhea, and constipation. Respiratory symptoms included stuffy nose, rhinorrhea, bronchial secretion, and hyper-responsive airways. Lastly,

dermatological symptoms included urticaria and eczema. Infants in both groups were then examined for anal fissure by members of our team with at least five years of experience in pediatrics. Each infant was placed in the prone position with knees pushed up against the abdomen. The anus was then cleaned with normal saline prior to examination under adequate light exposure. A positive finding was defined as when an anal fissure was declared by at least two out of three examiners.

Demographic data from the two groups of infants were analyzed using unpaired Student's t-tests for continuous data, and Chi-square test for discrete data. A Chi-square test was used to compare the prevalence of anal fissures in the two groups and the prevalence of anal fissure in this study group compared with those of normal infants in a previous study[9]. A p-value of less than 0.05 was statistically significant. Diagnostic test to confirm diagnosis of CMA in this study was open food challenge.

Results

Seventy-two CMA infants were included in the present study. Table 1 demonstrates similar baseline characteristics of both groups. Table 2 demonstrates the prevalence of anal fissure, 33 out of 42 (79%) in Group 1 and 25 out of 30 (83%) in Group 2. There was no statistically significant difference in the prevalence of anal fissure between the two groups. Table 3 shows the prevalence of anal fissure in these two groups (79% and 83%) to be significantly higher than the historical data of normal infants who were exclusively breast-fed, formula-fed, or who received mixed feeding (6%, 8%, and 11%, respectively) (p-value less than 0.001). When using anal fissure as a sign of CMA, the sensitivity and specificity of the test are 80.6% and 92.1%, respectively. The likelihood ratio of a positive test is 10.2.

Discussion

Nowadays, the gold standard for diagnosing food allergy, including CMA, is a double-blind, placebo-controlled food challenge (DBPCFC). This test detects the recurrence of CMA symptoms after the cow's milk protein is re-challenged. Although widely used, this test is costly and time-consuming, with the time interval between the elimination period and observation period being over 48 hours. In addition, food challenging may induce a life-threatening

Table 1. Baseline characteristics for 72 infants with cow's milk allergy, with GI symptoms (Group 1, n = 42) and without GI symptoms (Group 2, n = 30)*

Characteristics	Group 1 n (%)	Group 2 n (%)
Age (months, mean ± SD)	7.0±4.7	6.3±3.8
Sex		
Male	29 (69)	15 (50)
Female	13 (31)	15 (50)
Weight (g, mean ± SD)	7.4±1.4	7.3±1.5
Length (cm, mean ± SD)	66.3±6.1	66.0±6.0
Anemia (hematocrit <34%)		
Negative	14 (33)	12 (40)
Positive	28 (67)	18 (60)
Eosinophilia (>700/mm^3)		
Negative	35 (83)	25 (83)
Positive	7 (17)	5 (17)
Specific IgE to cow's milk protein (>0.3 KU_A/L)		
Negative	33 (79)	25 (83)
Positive	9 (21)	5 (17)

GI = gastrointestinal

* Symptoms Group 1 = chronic running noses, stuffiness, urticarial or eczema; Symptoms Group 2 = symptoms of vomiting, colic, diarrhea or constipation

Table 2. Prevalence of anal fissure in 72 infants with CMA, with GI symptoms (Group 1, n = 42) and without GI symptoms (Group 2, n = 30), 95% CI (0.67-0.88)

Anal fissure	Group 1, n (%)	Group 2, n (%)
Positive	33 (79)	25 (83)
Negative	9 (21)	5 (17)

CMA = cow's milk allergy; GI = gastrointestinal

Table 3. Comparison of prevalence of anal fissure between normal infants in a previous study of normal infants who were either exclusively breast-fed, formula-fed, or who received mixed feeding[9], and infants with CMA in this study, with and without GI symptoms

Infants	Prevalence of anal fissure n (%)
Normal infants	
Exclusively breast-fed	14/238 (6)
Formula-fed	7/93 (8)
Mixed-fed	19/173 (11)
CMA infants	
GI symptoms	33/42 (79)*
Non-GI symptoms	25/30 (83)*

CMA = cow's milk allergy; GI = gastrointestinal

* $p<0.001$ = significant differences from normal infants of all modes of feedings

anaphylactic reaction. Therefore, other diagnostic tests for CMA are being sought.

Other less commonly used diagnostic tests for CMA, such as a skin prick test (SPT) and an atopic patch test (APT), while being less costly and time-consuming than DBPCFC, still face a problem of low sensitivity and specificity. SPT is performed by using a 1-mm single-peak lancet, with histamine dihydrochloride (10 mg/ml) and isotonic saline solution as positive and negative controls, respectively. Reactions are recorded on the basis of the largest diameter (mm) of the wheal and flare at 15 minutes. The SPT result is considered "positive" if the wheal is 3 mm or larger, without a reaction of the negative control[10]. Hill et al, however, reported that the sensitivity and specificity of SPT are 58% and 91%, respectively, when the wheal size cut off is defined as 3 mm[11]. In addition, the test is not applicable to infants younger than six months of age due to its high false-negative rate. APT is performed in all children using freeze-dried purified food extracts contained in a commercial kit. The freeze-dried purified extracts are put on filter paper and applied with adhesive tape to the unaffected skin of the child's back, using 12-mm aluminum cups. Isotonic saline solution is the negative control. Seventy-two hours after the start of the test, reactions are classified as follows: negative, doubtful, weak positive, strong positive, and very strong positive[12]. Majamaa et al, however, reported the sensitivity and specificity of APT to be 44% and 71%, respectively; also, those of a radioallergosorbent (RAST) test yielded 25% and 94%, respectively[2].

Based on the results of the presented study, the authors propose using anal fissure as a novel, alternative way of diagnosing CMA in infants. As shown here in, using anal fissure as a pathognomonic sign of CMA, the sensitivity and specificity are 80.6% and 92.1%, respectively. In addition, the authors divided CMA infants into those with and without GI symptoms in order to test for the association of constipation with the development of anal fissure. Surprisingly, the prevalence of anal fissure in both groups is similarly high, suggesting that GI symptoms and constipation may not be correlated with anal fissures.

The mechanism of how anal fissure is developed in infants is yet to be elucidated. Currently, there are two competing hypotheses explaining how anal fissure is developed. One explains that milk intolerance causes constipation, which then leads to anal fissure development. However, as mentioned above, the presented study proves that this may not be true since the prevalence of anal fissure in CMA infants both with and without GI symptoms are similarly high, suggesting that constipation may not be the mechanism of anal fissure development. The second hypothesis suggests that allergic colitis is a cause of anal fissure. This mechanism is supported by cuboidal metaplasia of the epithelium, and lymphoid nodules found in rectal mucosa of CMA infants[13].

In summary, the presented report proposes the use of anal fissure as a novel way to diagnose CMA. More studies regarding the mechanisms of development of anal fissures in these infants are ongoing.

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Potential conflicts of interest

None.

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รอยแยกบริเวณทวารหนักของทารกอาจเป็นอาการบ่งบอกภาวะแพ้โปรตีนในนมวัว

พิภพ จิรภิญโญ, นฤมล เด่นทรัพย์สุนทร, ชนกานต์ กังวานพรศิริ

วัตถุประสงค์: *เพื่อศึกษาว่ารอยแยกบริเวณทวารหนักในทารกที่แพ้โปรตีนในนมวัวจะช่วยบ่งบอกภาวะแพ้โปรตีนในนมวัว*
วัสดุและวิธีการ: *ศึกษาความชุกของรอยแยกบริเวณทวารหนักในทารกที่ได้รับการวินิจฉัยภาวะแพ้โปรตีนนมวัว จำนวน 72 ราย โดยการตรวจของกุมารแพทย์ที่มีประสบการณ์ทางกุมารเวชศาสตร์มามากกว่า 5 ปี ซึ่งจะยืนยันจากกุมารแพทย์ 2 คน ในจำนวน 3 คน*
ผลการศึกษา: *ความชุกของรอยแยกบริเวณทวารหนักของทารกที่ได้รับการวินิจฉัยภาวะแพ้โปรตีนในนมวัวในกลุ่มที่มีอาการทางระบบทางเดินอาหารกับกลุ่มที่ไม่มีอาการทางระบบทางเดินอาหาร มีประมาณร้อยละ 79 และ 83 ตามลำดับ ซึ่งความชุกในทารกดังกล่าวมีค่ามากกว่าในทารกปกติอย่างมีนัยสำคัญ*
สรุป: *การตรวจพบรอยแยกบริเวณทวารหนักของทารกอาจจะช่วยบ่งบอกภาวะแพ้โปรตีนในนมวัวได้*