

Role of Cow's Milk Allergy in Children with Chronic Constipation

KRONİK KONSTİPE ÇOCUKLARDA İNEK SÜTÜ ALLERJİSİNİN ROLÜ

Tümay DOĞANCI, MD,^a Reha CENGİZLİER, MD^b

Departments of ^aGastroenterology, and ^bAllergy, Dışkapı Children's Hospital, ANKARA

Abstract

Objective: Since cow's milk allergy was reported to be a factor in chronic childhood constipation, reference centres have been reporting high percentages of such cases including those of persistent nature. We aim to evaluate the frequency of chronic constipation related to cow's milk allergy in untreated cases.

Material and Methods: In this prospective study, 100 consecutive children with chronic constipation were studied. Initially, organic causes were excluded. The personal and familial history of atopic diseases was noted and daily consumption of cow's milk was recorded for each children. After obtaining consents from the parents, skin prick tests to cow's milk and a circulating eosinophil count were performed in each case. Afterwards, a two-week elimination diet was given to all cases. The patients who were responsive to elimination diet were given cow's milk for two weeks as a challenge.

Results: In 11 cases, constipation resolved during the elimination diet phase and reappeared during the challenge phase. In five out of eleven cases, skin prick test was positive.

Conclusion: In conclusion, 11% of randomized cases of untreated, chronic functional constipation in children may be associated with cow's milk allergy.

Key Words: Childhood, chronic constipation, cow's milk allergy

Türkiye Klinikleri J Pediatr 2007, 16:8-12

Özet

Amaç: İnek sütü allerjisinin çocukluk çağı kronik konstipasyonunda rolü olabileceği belirtildikten sonra, referans merkezlerinde inatçı olanlarda kapsayan bu tür vakaların yüksek oranlarda görüldüğü bildirilmeye başlanmıştır. Amacımız tedavi edilmemiş vakalarda inek sütü allerjisi ile ilişkili kronik konstipasyon sıklığını araştırmaktır.

Gereç ve Yöntemler: Bu prospektif çalışmada kronik konstipasyonu olan 100 ardışık vaka değerlendirildi. Daha önce organik nedenler ekarte edilmişti. Her vakaya ait kişisel ve ailesel atopik hastalık öyküsü ve günlük tüketilen inek sütü miktarı öğrenildi. Ailelerden onay alındıktan sonra tüm vakalara inek sütü için deri testi ve periferik eozinofil sayımı yapıldı. Daha sonra bu vakalara iki haftalık inek sütü eliminasyon diyeti uygulandı. Eliminasyon diyetine cevap veren hastalara iki hafta süreyle inek sütü provokasyon amacıyla tekrar verildi.

Bulgular: Tüm vakaların 11'inde eliminasyon sırasında konstipasyon düzeldi, provokasyonla tekrar başladı. Bu vakaların 5'inde inek sütüne ait deri testi pozitifliği saptandı.

Sonuç: Çocukluk çağında tedavi edilmemiş ve randomize kronik fonksiyonel konstipasyonun %11'inin inek sütü allerjisi ile ilişkili olabileceği düşünüldü.

Anahtar Kelimeler: Çocukluk çağı, kronik konstipasyon, inek sütü allerjisi

Chronic constipation, which is common in childhood, is generally defined as defecation occurring with difficulty and/or less than 3 times a week for more than two months. Reports indicate that patients referred to medical centres due to problems related with defecation consti-

tute 3% of all cases in pediatric outpatient clinics and 25% in pediatric gastroenterology units.¹

The association between cow's milk and chronic constipation was reported in 1954. After that, few reports were published on this subject.^{2,3} In 1995, a research was made by eliminating cow's milk from the diets of 27 children, and a resolution of constipation was noted in 78% of the cases. However, constipation problems reappeared within 48-72 hours when cow's milk was reintroduced.⁴ Various studies on the relation between cow's milk and chronic constipation were reported.⁵⁻⁸ Most of those studies were carried out at various referral

Geliş Tarihi/Received: 07.12.2005 Kabul Tarihi/Accepted: 18.09.2006

Yazışma Adresi/Correspondence: Tümay DOĞANCI, MD
Dışkapı Children's Hospital,
Department of Gastroenterology, ANKARA
tumaydoganci@hotmail.com

Copyright © 2007 by Türkiye Klinikleri

centres and they involved children not responding or partially responding to treatment. In the literature, the prevalence of constipation caused by cow's milk is still questioned and the need for carrying out studies in different centres is emphasized.

The aim of this study was to evaluate the correlation of cow's milk allergy in untreated cases with chronic functional constipation. Elimination and provocation methods as well as skin prick test to cow's milk protein and a circulating eosinophil count were performed in all cases.

Material and Methods

In this prospective open-label study, we evaluated the children who were managed in the pediatric gastroenterology unit of our hospital due to chronic constipation starting from January 2001, and whose families gave permission to perform skin prick tests with cow's milk proteins. The diagnosis of chronic constipation was based on history of difficult defecation with hard feces less than 3 times in a week for a period of at least 3 months.

The cases were questioned for the presence of atopic diseases such as bronchial asthma, allergic rhinitis and conjunctivitis, atopic dermatitis, etc., in addition to chronic constipation in their personal or family history. The duration of feeding with breast milk, the time they switched to cow's milk, and their daily consumption of cow's milk were also recorded. In addition to physical and rectal examination, complete blood counts, urine analyses, serum electrolyte and calcium levels, and liver and kidney function tests were also evaluated. More than 400 eosinophiles per cubic millimetres were considered elevated. When necessary, thyroid function tests, sweat tests, barium colon graphies, and sacral tomographies were also performed. Thus, the cases due to organic causes (drugs, structural defects of gastrointestinal tract, metabolic and endocrine disorders, collagen and muscle diseases affecting gastrointestinal tract, spinal cord defects, abnormalities of myenteric ganglion cells, neurogenic and psychiatric conditions and others) were excluded from the study.

Skin prick tests to cow's milk (Center Lab., USA) were performed by the same physician on all the cases. The diluent was used as negative control while histamine 10 mg/ml was used as positive control. A wheal diameter at least 3 mm wider than of the negative control was accepted as positive.⁹

In all cases, before laxative treatment and dietary arrangement, a two-week strict diet excluding cow's milk was started. Patients aged less than 12 months were fed with a formula containing soy protein. At the end of the two-week period, painless defecations with normal hardness of at least 3 times a week were accepted as the indication of the fact that the constipation had resolved. In all cases, a two-week provocation test was performed by using cow's milk again. A positive challenge was defined as the reappearance of constipation with painful passage of hard stool less than three times a week during the challenge period.

Informed consent was obtained from the parents of all patients involved in the study.

Results

The baseline characteristics of study subjects are shown in Table I. The ages of the 100 consecutive cases consisting of 38 girls and 62 boys ranged between 4 and 60 months. Their mean age (\pm SD) was 23.5 ± 12.9 months and the period of constipation (\pm SD) was 12.9 ± 12.6 months (range, 1 to 55 months). Thirty-two cases had histories of rectal bleeding. The duration of feeding on breast milk was shorter than 6 months in 39 cases and was equal to or longer than 6 months in 61 cases. Daily consumption of cow's milk was less than 500 ml in 56 cases, and more than 500 ml in 44 cases. None of the cases had a history of familial atopic diseases, though 2 of the cases had atopic diseases resembling allergic bronchitis and atopic dermatitis in their medical histories.

The rectal examination of the cases revealed that 31 had fecal impaction, 58 had perianal erythema and 18 had anal fissure. Twelve cases had hemoglobin levels below 10 g/dl and average erythrocyte volumes below 75 fl. Five cases had

positive skin prick tests. In 9 cases, the circulating eosinophil count was more than 400 eosinophils per cubic millimetre.

Based on the clinical response to cow's milk free diet and the challenges, the cases were divided into 2 groups: Those who improved with a cow's milk free diet, and those who did not improve. Clinical characteristics of both groups were also shown in Table 1.

Discussion

The occurrence of functional constipation, which is the most common cause of chronic constipation, depends on various factors like genetic tendency, motility disorders, emotional factors, inappropriate toilet training and insufficient amounts of dietary fibre.^{1,9,10}

On the other hand, adverse reactions to cow's milk protein are observed in 0.3-7.5% of healthy infants.⁹ Such reactions linked with abnormal immune response are called allergy or hypersensitivity, which may or may not be mediated by IgE.⁸ Adverse food reactions may also be mediated by non immune mechanisms (enzymatic, pharmacol-

ogical, hormonal, etc.). However, the interpretation of such reactions is difficult due to the dependency of the studied factors.

Constipation is considered a special syndrome of IgE sensitivity to cow's milk. It is well established that cow's milk with its more than 30 structural proteins, may stimulate an IgE response. Beta lactoglobulin, alpha lactalbumin, bovine serum immunoglobulin, albumin and casein are the most important antigens.^{11,12} High incidence of food allergy in infants is associated with the introduction of numerous food allergens into the circulation due to their immature systems. As the intestinal systems get mature, the T-cell sensitivity caused by nutrients decreases.¹³

Currently accepted tests for diagnosing food allergy include skin prick test, prick-to-prick tests, patch tests, specific IgE tests and elimination diets followed by food challenges. Skin prick tests have a positive predicted accuracy of 50% but the negative predictive value is in excess of 95%. Therefore, skin prick tests should be considered beneficial for excluding immediate food hypersensitivity.

Table 1. Clinical and laboratory characteristics of study subjects and improved and unimproved cases with cow's milk free diet.

Characteristics	All cases (n:100)	Improved cases (n:11)	Unimproved cases (n:89)
Age (mo)	23.5 ± 12.9	22.6 ± 10.3	24.2 ± 15.8
Sex (M/F)	62/38	10/7	52/31
Duration of cons. (mo)	12.9 ± 12.6	11.3 ± 10.2	14.3 ± 15.9
Rectal bleeding	32	12	20
Duration of breast feeding (mo)	<6 ≥6	39 61	5 12
Daily consumption of cow's milk (ml)	<500 ≥500	56 44	9 8
History of atopy			
Familial	0	0	0
Personal	2	2	0
Fecal impact	31	11	20
Perianal erythema	58	6	5
Anal fissure	18	3	15
Hemoglobin <10 g/dl with MCV<75 fl	12	2	10
Eosinophilia	9	3	6
Skin prick test positivity	5	5	0

ity.¹⁴ The results of skin prick test and radioallergen sorbent test (RAST) may only be indicative of the possibility that children with constipation will respond to an elimination diet.¹⁵ The sensitivity and specificity of specific IgE test (RAST) are reduced compared to skin prick test.¹⁴

International working group states that food intolerance cannot be diagnosed exclusively by immunologic tests. They recommend food elimination and provocation test for the diagnosis of allergy causing significant gastrointestinal symptoms.^{15,16} The double-blind, placebo controlled food challenge is still considered the gold standard for diagnosing food allergies, if performed properly.¹⁷ However, it is also noted that double-blind, placebo controlled food challenges are time-consuming, not very cost-effective and not without risk.¹⁸ Besides, children may notice the different taste of different formulas.

Iacono et al⁴ in their study investigating the role of cow's milk in childhood constipation, reported that through the elimination of cow's milk, constipation was resolved in 78% of 27 children of 5-36 months of age, and that provocation caused reappearance of constipation. They concluded that constipation in infants might be a symptom of cow's milk protein intolerance. The same authors performed another double-blind crossover study of cow's milk as compared with soymilk in 65 children with constipation who were unresponsive to laxative treatment. The results revealed that 68% of the cases who were not given cow's milk were responsive. The ratio of accompanying rhinitis, dermatitis, bronchospasm, anal fissure, erythema, and edema was higher in cases who were cured. Besides, positive results in the dermal tests as well as the IgE test specific to cow's milk was detected more frequently in the same group, though no statistical difference was observed.¹⁹

In another study including 20 children with persistent constipation, 11 out of 14 children with a history of atopy, constipation resolved through a cow's milk elimination diet.⁷ Recently, 28% of 25 children between 3 and 11 years old with chronic constipation were determined to have cow's milk

protein intolerance, after performing elimination-provocation tests.⁸

In the literature, the prevalence of constipation cases caused by cow's milk is still questioned. As most of the reported constipation cases are of persistent nature and most studies are from the same referral centres, new studies to be carried out by different centres are necessary.¹⁴

In this study, we aimed to evaluate the frequency of chronic functional constipation due to cow's milk allergy in our population. Taking into consideration the recommendations stated in recent reports to challenge food elimination and provocation, we performed elimination-provocation test as an open controlled food challenge as well as skin prick tests in cases with untreated chronic functional constipation. Although it was not a double-blind placebo controlled food challenge, single blind, open-label challenges are also recommended. It is noted that the least time-intensive procedure is the open-label challenge.²⁰ In daily clinical practice, the challenge may be performed as an open controlled food challenge when objective reactive reactions are expected.²¹ As a result, we found out that 11% of the randomized cases of untreated, chronic functional constipation in children might be associated with cow's milk allergy and a half of such cases might be related to IgE mechanisms.

Our rates are lower, compared to those in other studies. Particularly high rates were reported by tertiary reference centres dealing with refractory cases unresponsive to laxatives.^{7,19} In the study with a reported rate of 68%, the frequency of personal and familial histories of atopy was also high.¹⁹

Our study may be helpful in determining the frequency of cow's milk allergy in childhood chronic functional constipation. Unfortunately, the study is not population based and only referred patients were investigated. However, it included a sufficiently high number of randomized cases with a wide age range and it did not cover selected cases like those unresponsive to laxatives or those with a high allergy rate.

It is generally accepted that being exposed to allergens intensively early in life is an important factor for the development of food allergies and being fed on breast milk for longer periods may prevent the development of cow's milk protein allergy. However, recent reports show that cow's milk protein allergy may be observed due to the antigens in breast milk.²² In our study, the ratio of daily consumption of cow's milk was similar in improved and unimproved cases fed with cow's milk free diet, so it was difficult to make a comment on the relation between cow's milk allergy and daily consumption of cow's milk.

A number of studies indicate that a history of atopy is more common in children with cow's milk protein allergy and in their family members.^{7,19,22,23} In our study, two cases who improved with a cow's milk diet had a history of atopic disease.

Conclusion

In conclusion, the results of this study suggest that allergy to cow's milk may be related to chronic functional constipation in children who were not treated with laxatives previously and who do not have a clear personal or familial history of atopy. New studies to be carried out by different centres covering a wide spectrum of cases are necessary for the development of new approaches in this subject.

REFERENCES

- Baker SS, Liptak GS, Coletti RB, et al. Constipation in infants and children: evaluation and treatment. *J Pediatr Gastroenterol Nutr* 1999;29:612-26.
- Buisseret PA. Common manifestations of cow's milk allergy in children. *Lancet* 1978;1:304-5.
- Chin KC, Tarlow MJ, Allfree AJ. Allergy to cow's milk presenting as chronic constipation. *Br Med J* 1983;287:1593.
- Iacono G, Carroccio A, Cavataio F, et al. Chronic constipation as a symptom of cow's milk allergy. *J Pediatr* 1995;126:34-9.
- Vanderhoof JA, Perry D, Hanner TL, et al. Allergic constipation: association with infantile milk allergy. *Clin Pediatr* 2001;40:399-402.
- Daher S, Sole D, de Morais MB. Cow's milk and chronic constipation in children. *N Engl J Med* 1999;340:891.
- Shah N, Lindley K, Milla P. Cow's milk and chronic constipation in children. *N Engl J Med* 1999;340:891-2.
- Daher S, Tahan S, Sole D, et al. Cow's milk protein intolerance and chronic constipation in children. *Pediatr Allergy Immunol* 2001;12:339-42.
- Eigenmann PA, Zamora SA, Belli DC. Cow's milk and chronic constipation in children. *N Engl J Med* 1999;340:891.
- Di Lorenzo C. Childhood constipation: finally some hard data about hard stools. *J Pediatr* 2000;136:4-7.
- Hill DJ, Firer MA, Ball G, et al. Natural history of cow milk allergy in children: immunological outcome over 2 years'. *Clin Exp Allergy* 1993;23:124-31.
- Hide DW, Gant C. Hypoallergenic formulae have they a therapeutic role? *Clin Exp Allergy* 1994;24:3-5.
- Sampson HA. Adverse reactions to foods. In: Adkinson NF, Yunginger JW, Busse WW, eds. *Middleton's Allergy Principle and Practice*, 6th ed. Philadelphia: Mosby Co.; 2003. p.1619-43.
- Holgate ST, Arshad SH. *The Year in Allergy 2003*. London: Clinical Publishing Services Ltd; 2003. p.121-40.
- Daher S, Sole D, de Morais MB. Cow's milk and chronic constipation in children. *N Engl J Med* 1999;340:892.
- Loening-Baucke V. Constipation in children. *N Engl J Med* 1998;339:1155-6.
- Moneret-Vautrin DA. Cow's milk allergy. *Allergy Immunol* 1999;31:201-10.
- Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for allergen challenges in young children: a comparison of in vitro with in vivo tests. *Clin Exp Allergy* 2001;31:1031-5.
- Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998;339:1100-4.
- Spergel JM, Pawlowski NA. Food Allergy. *Pediatr Clin North Am* 2002;49:73-95.
- Host A, Adrae S, Charkin S, et al. Allergy testing in children: why, who, when and how? *Allergy* 2003;58:1-11.
- Isolauri E, Tahvanainen A, Pertola T, et al. Breast-feeding of allergic infants. *J Pediatr* 1999;134:27-32.
- Iacono G, Cavataio F, Montalto G, Soresi M, Notarbartolo A, Carroccio A. Persistent cow's milk protein intolerance in infants: the changing faces of the same disease. *Clin Exp Allergy* 1998;28:817-23.