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Cow's milk allergy related pediatric constipation: Appropriate time of milk tolerance

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Cow's milk allergy (CMA) has different clinical presentations according to age. The study aimed to evaluate the extent of CMA as a cause of pediatric constipation and determine the appropriate timing of tolerance to cow milk in such patients. The study included 60 patients suffering from chronic functional constipation, 27 of whom did not respond to 2 month laxative therapy (group I). Thirty age and sex matched apparently healthy infants and children were studied as a control group (group II). Serum specific IgE to cow milk proteins was measured. Withdrawal of cow milk and dairy products for a 1 month period was then followed by cow milk re-challenge over 2 wk. Patients were classified into: responders to this schedule (cow milk allergic = group Ia; n = 21) and non-responders (non-cow milk allergic = group Ib; n = 6). Eighteen CMA patients continued the study where nine of them underwent milk reinstitution after 6 months and another nine patients after 12 months of elimination. The frequency of CMA among constipated patients was 77.7%. Mean values of serum specific IgE to whole cow milk protein and β-lactoglobulins were significantly higher in constipated patients (0.82 ± 0.08, 0.79 ± 0.13 IU/ml, respectively) compared with controls (0.26 ± 0.14, 0.27 ± 0.14 IU/ml, respectively) and in group Ia (0.99 ± 0.08, 0.95 ± 0.14 IU/ml, respectively) compared with group Ib (0.39 ± 0.06, 0.37 ± 0.10 IU/ml, respectively). Serum specific IgE was positive in 85.7% of CMA group, predominantly in class 2. Tolerance to cow milk was achieved after 6 months in only 22.2% compared with 88.8% after 12 months of elimination. In conclusion, CMA is shown to be a significant etiologic factor for constipation in infants and young children. Serum levels of IgE to cow milk proteins are helpful although not definitive for diagnosis. Based on this limited study, tolerance is better achieved after 12 months of strict cow's milk elimination.

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Around 1–2% of adults and 5–7% of children suffer from some type of food allergy (1). Cow's milk allergy (CMA) is the most common food allergy in young children; with a prevalence of 2–5%. About 3% of all newborn infants will suffer from CMA within the first year of life (2). IgE-mediated CMA often persists to school age and is a risk factor for other atopic diseases. Non-IgE-mediated CMA, by contrast, is a benign infantile condition (3).

Constipation is responsible for an estimated 3–5% of physician visits by children (4). Patients with CMA may develop painful defecation, perianal erythema or eczema and anal fissures with possible painful fecal retention, thus aggravating constipation (5). The aim of the present study is to evaluate the extent of CMA as a cause of pediatric constipation and determine the appropriate timing of tolerance to cow milk in such cases.

Methodology

Patients

This study was conducted at the Pediatric Gastroenterology Unit, the Children's Hospital, Ain Shams University. Over the period from December 2006 to January 2008, 60 infants and children in total were diagnosed with chronic functional constipation. All received medical therapy (lactulose). Response to medical therapy was defined as disappearance or significant amelioration of constipation and the relevant symptoms (e.g., pain during defecation, abdominal distension) after 2 months.

Following 2 months of therapy, the non-responders (n = 27) were enrolled in the present study. They included 12 males and 15 females with ages ranging from 8 to 48 months (group I).

Inclusion criteria

- Infants and children with at least 2 months' history of passing firm or hard stools, less than three times per week.
- Non-responder to 2 months of medical therapy.
- Normal thyroid status.
- Normal serum levels of Ca, Mg, Na, K and creatinine.
- Normal barium enema study.

Exclusion criteria

- Patients with organic causes of constipation such as Hirschsprug disease and anal stenosis.
- Neurologic abnormalities including cerebral palsy, mental retardation or degenerative brain diseases.

A group of 30 age- and sex-matched clinically healthy infants and children were enrolled in this study as a control group. They were 13 males and 17 females with an age range of 8–48 months, recruited from infants and children presenting with non-relevant problems or following-up in the well-baby clinic (group II).

The study protocol was approved by the ethical committee of the Pediatric Department, in June 2006. Informed written consent was given by the parents/caregivers of all patients and controls. When parents/caregivers were illiterate, the consent was read to them by a hospital social worker who was not involved in the study, and the consent form was witnessed by an independent third party. The consent forms were prepared in both English and Arabic languages with illustration of all the procedures involved, any risk factors, the contact details of both the principal and co-principal investigators and the contact details for the head of the department in case of any inquiry or complaint.

Study design

- This study was designed as a case control follow-up interventional study.
- Plan of the work.

Phase I: pre-interventional evaluation for patients and evaluation of controls which included:

1. Proper history taking laying stress on frequency of bowel-motions per week, bleeding per rectum, associated symptoms (e.g., pain during defecation, anal fissure), drug history (including laxatives), age of onset of defecation problems, nasal problems, wheezy chest, skin rash and weight loss.
2. General examination with special emphasis on anthropometric measurements with estimation of *Z*-score, skin examination for rash, chest examination for wheezy chest, abdominal examination for abdominal distension as well as peri-anal and PR examination for eczema, erythema or fissure.
3. Laboratory work-up: A full blood count was performed with particular emphasis on total leucocytic count (TLC) and eosinophilic count. Quantitative determination of allergen-specific IgE concentration in serum against both whole cow milk protein and β-lactoglobulin (6) was performed by enzyme-allergo-sorbent-test (DR-Fooke, laboratories GmbH, Mainstrable 85). Serum IgE values were plotted as IU/ml and as classes (0–4) as shown in the following table.

Class	IU/ml	Specific IgE concentration
0	<0.35	Non-detectable
1	>0.35–0.7	Low
2	>0.7–3.5	Moderate
3	>3.5–17.5	High
4	>17.5–50	Very high

Phase II: Cow milk and dairy products were withdrawn from the diet of all 27 constipated non-responders (group 1). Laxative therapy was continued. Re-evaluation of the patients was carried out at the end of this phase.

Phase III: Patients were admitted to hospital and re-challenged with cow milk over a 2 wk period, starting with 10 ml in the first day, with 10 ml increments every day. Follow on formula

was used in infants between the ages of 6 and 24 months, and full cream powdered milk was used in older patients.

Patients showing clinical improvement after withdrawal and clinical worsening after re-challenge were considered to have CMA (group Ia = 21 patients). They were maintained on cow milk-free diet and followed-up. Patients who did not improve on withdrawal or who improved after withdrawal but were not worsened after re-challenge were not considered allergic to cow milk (group Ib = six patients). They underwent further investigations for diagnosis and treatment of the underlying cause of their constipation.

Phase IV: Re-institution of cow milk and dairy products for group 1a. Group 1a patients were randomly allocated to two subgroups according to the duration of withdrawal (either 6 or 12 months) before re-introduction of cow milk and dairy products. The shortest possible duration of elimination was chosen to ensure adequate compliance. Clinical reassessment was performed at the end of this phase. Three patients did not comply and were excluded from this phase of the study. The different clinical and epidemiologic variables of patients were not different between these two groups.

Statistical analysis

Standard computer program SPSS for windows, release 10.0 (SPSS Inc., Chicago, IL, USA) was used for data entry and analysis. All quantitative variables were expressed as mean ± s.d. Comparison of different variables in various groups was done using: Student *t*-test and Mann–Whitney test were used for the comparison of the normal and non-parametric variables, respectively between the groups. Chi-square and Fischer exact-test were used for the comparing qualitative normal and non-parametric variables between the groups. Spearman's correlation test was used for correlating non-parametric variables. For all tests a probability [(p) < 0.05] was considered significant. Graphic presentation of the results was also done.

Results

There were no significant differences in *Z*-scores of weight/age, height/age and weight/height between patients (0.04 ± 0.35, −0.12 ± 0.74 and −0.06 ± 0.40, respectively) and controls (0.01 ± 0.07, 0.09 ± 0.54 and 0.04 ± 0.31, respectively). Patients with CMA (group 1a) had significantly lower *Z*-scores for weight/age than patients without CMA (group Ib) (0.32 ± 0.65 and −0.3 ± 0.15, respectively; p = 0.02). *Z*-scores of height/age (−0.09 ± 0.78 and −0.26 ± 0.60, respectively) and weight/height (−0.10 ± 0.44 and 0.05 ± 0.10, respectively) were not statistically different between the two groups with constipation. The age of onset of defecation problems and the age of patients at presentation were significantly lower in the allergic group (6.67 ± 7.40, 19.48 ± 13.99 months, respectively) compared with non-allergic patients (17.17 ± 10.52, 36.17 ± 8.21 months, respectively) (p = 0.02).

Fecal soiling was present in 18% of constipated patients [14.3% of the CMA group (group Ia) compared with 33.3% of the non-allergic group (group Ib)], while abdominal distension was present in 74% (71.4% of the CMA group), blood in stools in 25% (28.6% of the CMA group), anal fissure in 18% (14.2% of CMA group), anal erythema or eczema in 41% (71.4% of CMA group), history of allergic symptoms in 25%, skin eczema in 14% (19% of CMA group), and wheezy chest in 22% of constipated patients (23.8% of CMA group).All patients who presented with history of allergic symptoms, skin eczema or wheezy chest were in the CMA group.

Mean values of total leucocytic count, eosinophilic count and Hb % were not significantly different between constipated patients and controls (p = 0.31, 0.08 and 0.75, respectively) or between CMA and non-CMA groups (p = 0.99, 0.77 and 0.45, respectively).

The mean values of IgE to whole cow milk protein and IgE to β-lactoglobulin were significantly higher in constipated patients compared with controls and in the allergic (Ia) subgroup compared with the non-allergic (Ib) subgroup (Table 1).

Quantitative evaluation of serum IgE to both whole cow milk protein and β-lactoglobulin according to class of positivity showed that significantly more controls were in the negative compared with constipated patients. Most of our patients were in class 2, with few patients in class 1. Constipated patients who were allergic to cow milk were predominantly class 2 compared with the non-allergic group who were predominantly negative and or in class 1 (Table 2).

Constipated patients showed a significant positive correlation between serum IgE to whole cow milk protein and eosinophilic count (r = 0.493, p = 0.009) Fig .1. Serum IgE to β-lactoglobulin

Table 1. Comparison of mean serum IgE to whole cow milk protein and to β-lactoglobulin between constipated patients vs. controls and between CMA vs. non-CMA subgroups

	Patients (I) n = 27 Mean ± s.d.	Control (II) n = 30 Mean ± s.d.	Sub-group Ia n = 21 Mean ± s.d.	Sub-group Ib n = 6 Mean ± s.d.	I vs. II p-value	Ia vs. Ib p-value
IgE to whole cow milk protein IU/ml	0.82 ± 0.08	0.26 ± 0.14	0.99 ± 0.08	0.39 ± 0.06	0.0002**	0.001*
IgE to β-lactoglubulin IU/ml	0.79 ± 0.13	0.27 ± 0.14	0.95 ± 0.14	0.37 ± 0.10	0.0003**	0.001*

*Significant; **Highly significant.

Table 2. Comparison of frequency of IgE classes between patients and controls and between CMA and non CMA sub-groups

		Patients (I) n = 27 (%)	Control (II) n = 30 (%)	Sub-group Ia n = 21 (%)	Sub-group Ib n = 6 (%)	I vs. II p-value	Ia vs. Ib p-value
Class 0	IgE to whole cow milk protein	6 (22.2)	24 (80)	3 (14.2)	3 (50)	0.001*	0.001*
	IgE to β-lactoglobulin	5 (18.5)	22 (73.3)	3 (14.2)	2 (33.3)		
Class 1	IgE to whole cow milk protein	5 (18.5)	4 (13.3)	2 (9.5)	3 (50)		
	IgE to β-lactoglobulin	5 (18.5)	5 (16.6)	2 (9.5)	3 (50)		
Class 2	IgE to whole cow milk protein	16 (59.2)	2 (6.6)	16 (76.1)	0		
	IgE to β-lactoglubulin	17 (62.9)	3 (10)	16 (76.1)	1 (16.6)		
Class 3	IgE to whole cow milk protein	0	0	0	0		
	IgE to β-lactoglobulin	0	0	0	0		
Class 4	IgE to whole cow milk protein	0	0	0	0		
	IgE to β-lactoglobulin	0	0	0	0		

*Significant.

showed significant negative correlations with both weight ($r = -0.509$; $p = 0.007$) and hemoglobin ($r = -0.58$; $p = 0.002$) and a significant positive correlation with eosinophilic count ($r = 0.671$; $p = 0.000$).

Reinstitution of cow milk after 6 months elimination showed significantly higher relapse rates compared with reinstitution after 12 months-elimination (p-value = 0.004) (Table 3).

Discussion

In the present work nutritional status as evaluated by the *Z*-scores of weight for age, height for age and weight for height was not statistically different between patients with constipation and controls. However, *Z*-score of weight for age was significantly lower in the constipated cow milk allergic subgroup of patients compared with the non-allergic subgroup. Field, (7) reported that infants who suffer from constipation have anorexia, absorb fewer nutrients and refuse food because they are afraid to defecate; hence their height and weight may drop down several growth percentiles.

Abdominal distention and anal erythema or eczema were very commonly encountered in our constipated patient group. Moreover, encopresis, presence of blood in stools, anal fissure, and other allergic manifestations (skin eczema and wheezy chest) were not uncommon. These findings are similar to other studies (3, 8, 9).

Cow milk allergy was diagnosed in 21 patients of the constipated group (group 1) (77.7%). This percentage is identical to that demonstrated by

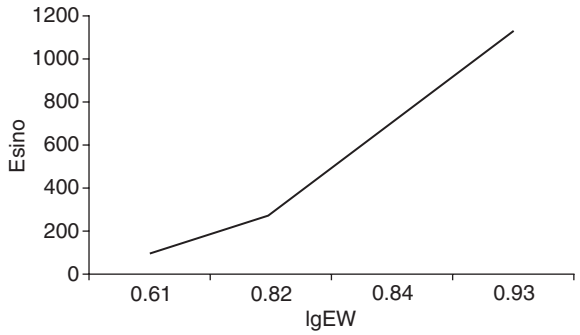

Fig. 1. Correlation between Serum IgE to whole cow milk protein in constipated patients and eosinophilic count ($r = 0.493$ and $p = 0.009$).

Table 3. Relapse rate in relation to duration of strict cow milk elimination

	Re-institution after 6 months; n = 9 (%)	Re-institution after 12 month; n = 9 (%)	χ^2	p-Value
No relapse	2(22.2)	8(88.8)	8.1	0.004*
Relapse	7(77.7)	1(11.1)		

*Significant.

Iacono et al., (10). Carrocio et al., (11) found that 52% of their constipated patients had CMA. The slightly lower frequency may be attributable to inclusion of older age groups as the mean age of their patients was 51.2 ± 18 m.

Serological evaluation showed significantly higher values of serum IgE to both whole cow milk protein and β-lactoglobulin in the constipated group (group q) compared with controls (group 2), and in the CMA subgroup compared with the non-allergic subgroup. Furthermore, 85.7% of our CMA subgroup who showed positive RAST results were predominantly in class 2 (Table 2). These findings concur with the results of Iacono et al. (10) who reported that 15 of 21 (71.4%) CMA constipated patients (proven by withdrawal-re-challenge test) had one or more positive laboratory tests (specific IgE, IgG, anti-β-lactoglobulin, circulating eosinophils). Similarly, Castro et al., (12) showed that 75% of CMA patients had positive RAST results. On the other hand, Daher et al., (13) found that 71% of their CMA constipated children had high serum levels of total IgE with only 29% of them being positive specific IgE tests. This may be attributed to the wide age range in their series (3 months-11 yr). The variability of allergic mechanisms according to age has been previously described by Crittenden and Bennett,(14) who found that IgE-mediated reactions are common in infancy, while non-IgE-mediated reactions predominate in adults.

The most appropriate timing of reinstitution of cow milk or dairy products to cow milk allergic constipated children (i.e., cow milk tolerance) was judged according to the relapse rate on trial. It is evident that a 6 months elimination period was not sufficient to achieve cow milk tolerance as the relapse rate was 77.7%. On the other hand, cow milk elimination for 1 yr was associated with tolerance in 88.8%. The exact timing of tolerance to cow milk is a matter of debate. Levy et al., (15) found that less than half of the children diagnosed with IgE-mediated CMA during the first 9 yr of life outgrew it. Furthermore, Saarinen et al., (3) found that IgE-mediated CMA was detected in 73% of children at the age of 8.6 yr, and 15% had persistent CMA, while all children with IgE-negative CMA became tolerant by the age of 5.0 yr. Vanto et al., (16) reported that by the age of 2, 3, and 4 yr, CMA children with delayed reactions developed tolerance to CM faster than those with immediate reactions (64%, 92%, and 96% versus 31%, 53%, and 63%, respectively). Iacono et al., (17) studied the characteristics of patients with persistent CMA by performing a CM challenge each year, and comparing those patients with others who had CM tolerance within 1–2 yr (controls). They found that a family history of atopic diseases was present in 10/12 patients with persistent CMA and in 10/26 controls. The clinical presentation was predominantly gastrointestinal at the beginning of the study, but by the end of the study there was an increased frequency of atopic diseases; asthma, rhinitis and eczema (nine/12 infants with persistent CMA and in 2/26 controls).

In conclusion, cow milk allergy is considered a common etiologic factor for constipation in infants and children. Serum levels of IgE to cow milk proteins are helpful although not definitive for the diagnosis. Cow's milk tolerance is better achieved at least after 12 months of strict cow's milk elimination.

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