

Cow's Milk Protein Allergy in South Jordan

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Abstract

Cow's milk protein allergy (CMPA) is the most common food allergy during infancy. Clinical presentation is of tremendous importance for diagnosis. Data from our part of the world is scarce. Our aim is to study the spectrum of symptoms, management and outcomes of children with CMPA in Jordan. A pre-validated clinical definition of CMPA was adopted. All patients with CMPA followed at our clinic during the study period (Nov 2009-June, 2013) were identified. Patients who met the definition were included; their medical charts were reviewed, regarding their demographics, clinical presentations, therapeutic intervention and outcome. Data were analyzed and presented as averages and percentages. Over the study period, 40 patients were identified. Twenty-five patients met the adopted definition. Sixteen patients (64%) were males. The average age of presentation was 4.7 mo. Twenty-four patients (96%) had at least one or more gastrointestinal symptom, while dermatological and respiratory involvement were seen in 8 patients (32%). Three patients (12%) had elevated transaminases. The response rate to Soya-based formula was 76% while response to amino acid formula was 100%. CMPA is not uncommon. Clinical presentations are diverse. Gastrointestinal manifestations were the most common presentation in our cohort. Elevated liver enzymes can be unusual presentation of CMPA. Larger studies are needed to estimate the size of the problem in our population.

Keywords: Cow's milk protein allergy, Infants, formulas, Jordan.

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Introduction

Adverse reactions to milk affect about 15% of infants¹. Cow's Milk Protein Allergy (CMPA) defined as an immunological reaction to one or more milk proteins¹ represents less than half of these reactions². CMPA is the most common type of food allergy during the first year of life³. Prenatal sensitization during the fetal life and immaturity of the gastrointestinal defense mechanisms may contribute to the early susceptibility to this

condition⁴.

Clinical presentations depend on the underlying allergic reaction. CMPA could be an IgE-mediated, non-IgE-mediated or both⁵. Rhinoconjunctivitis, asthma, laryngeal edema, atopic dermatitis, urticaria, nausea, vomiting, and colic are mediated through IgE reaction. On the other hand, pulmonary hemosiderosis, dermatitis, gastroesophageal reflux, colitis, constipation, failure to thrive are mediated through non-IgE reaction.

Diagnosis is suspected on clinical

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background. Laboratory investigations are non-conclusive and play mainly a supportive role⁶. Skin prick test may be beneficial in IgE-mediated CMPA⁶. Confirming the diagnosis requires elimination of the suspected allergen (cow's milk protein), which leads to symptom relief, and reintroduction of the allergen leading to reappearance of the symptoms. Therefore, the gold standard for the diagnosis is by a double-blind placebo-controlled food challenge (DBPCFC) test⁷.

CMPA epidemiological and clinical data from Arab region are scarce. In this study we describe the spectrum of clinical symptoms, management and outcome of CMPA in Jordanian children followed in our pediatric gastroenterology clinic in south Jordan.

Patients and Methods:

Case Definition:

Pre-validated clinical definition of CMPA was adopted⁸. The definition included elimination of cow's milk formula resulting in improvement of symptoms, and recurrence of symptoms after reintroduction of cow's milk by oral challenge or by accidental ingestion.

All cases of Cow's milk protein allergy managed at our pediatric gastroenterology service at Alkarak teaching hospital between Nov 2009 and June 2013 were identified. Patients met the clinical definition of CMPA included in the study. Both patients with IgE and non-IgE suggestive symptoms were included.

The re-challenge was implemented after 2 weeks of management and resolution of symptoms. The home-based protocol involved slow introduction of the previous formula-to-formula-fed babies (over 5-7 days). In exclusively breast-fed babies, mothers were asked to have milk and dairy products back in their diet.

The author, who was the treating physician, reviewed the patients' medical charts. Data on demographic variables, clinical presentation, therapeutic intervention and outcome were collected. The data were analyzed using Microsoft Excel 2010, and were presented as ranges, means and percentages.

Results:

Over the study period, 40 patients were identified, of whom 25 met the clinical definition and were included. Patients whose families refused the re-challenge were excluded. Sixteen patients (64%) were male. The average age of presentation was 4.7 mo. (1-15 months). The average duration of symptoms before the first consultation was 3.2 mo. (0.5-12 months). The babies' formulas were changed 2.4 times on average (0-6 times) prior to presentation.

Twenty patients (80%) had a recurrence of their symptoms after uncontrolled re-challenge (accidental). None of the patients had a serious reaction. Sixteen patients (64%) received mixed feeding (breast feeding and formula), seven (28%) were formula fed, and two (8%) were exclusively breast-fed.

Twenty-four patients (96%) had at least one or more gastrointestinal symptoms. Vomiting was the most common presenting symptom (16/25, 64%). One patient (4%) had hematemesis. About half the patients had diarrhea (13/25, 52%), among whom four patients (30%) had bloody diarrhea. On the other hand, constipation was seen in three patients (12%). Twelve patients (48%) showed infantile colic and food refusal. Poor weight gain was noticed in eleven patients (44%). Skin manifestations (urticaria and eczema) were seen in eight patients (32%). Respiratory symptoms (runny nose, cough and wheezing) were also seen in eight patients (32%). One

patient (4 %) developed angioedema and three (12%) were found to have elevated liver enzymes (transaminases). The detailed clinical presentations and their prevalence appear in Table 1.

Table1. Clinical presentations and their prevalence in the study group

| Symptom / finding | Number (percentage %) |
|---|-----------------------|
| Vomiting | 16 (64) |
| - hematemesis | 1 (4) |
| Diarrhea | 13 (52) |
| - non-bloody | 9 (70) |
| - bloody | 4 (30) |
| Constipation | 3 (12) |
| Colic and refusal to feed | 12 (48) |
| Skin manifestations (urticaria, eczema) | 8 (32) |
| Respiratory (cough, wheezes , runny nose) | 8 (32) |
| Poor weight gain and failure to thrive | 11 (44) |
| Angioedema | 1 (4) |
| Elevated liver enzymes | 3 (12) |

None of our patients had immunological work-up, but one patient (who developed angioedema after receiving cow's milk formula by mistake) was transferred to an immunology service for controlled challenge at the age of 1 year.

Continuing breast-feeding with elimination of milk and dairy products was tried in six (24%) patients; four improved while the other two were lost to follow-up. Soya-based formulas were used in seventeen patients (68%), either in our facility or prior to referral. Thirteen (76%) of them improved. An amino acid based formula (Neocate ®) was used in nine (36%) patients (five after failure of the soya-based formula, one after the mother decided to stop breast feeding and the rest due to severe failure to thrive). All showed resolution of their symptoms (Table 2).

Discussion:

There are very few data on the presentation of CMPA in Jordan. To our knowledge, this is the first study to describe the clinical characteristics, management and outcome of CMPA in Jordanian children.

Table 2. Therapeutic intervention and outcome of CMPA

| Intervention | Number | Improvement (%) | Failure (%) | Lost to FU (%) |
|--|--------|--------------------|-----------------|-------------------------|
| Elimination diet and continue breast feeding | 6 | 4 improved (67 %) | 0 | 2 lost follow up (33 %) |
| Soya- based formula | 17 | 13 improved (76 %) | 4 failed (24 %) | 0 |
| Amino acid formula | 9 | 9 improved (100%) | 0 | 0 |

In our study, the diagnostic criteria for CMPA were based solely on clinical diagnosis, as validated in a previous study⁸. The

observation of significant clinical improvement in response to the elimination of cow's milk, and recurrence of symptoms

within 2 weeks after re-introduction of cow's milk, is a practical and applicable test for use by physicians in clinical practice, especially in areas with limited investigatory facilities, and particularly immunological services, as in our region. Basic laboratory investigations (stool work-up and basic hematological work-up) were used to exclude valid differential diagnoses, especially lactose intolerance and persistent parasitic infections.

In our cohort, accidental (uncontrolled) re-exposure to cow's milk protein was much more common than controlled re-challenge. Dairy products, especially yogurt, are among the most common weaning foods in our area; most of our patients were given yogurt as a substitute for formula by their parents, which led to the reappearance of symptoms.

Immunological work-up (specific IgE titer (RAST), skin-prick testing (SPT), etc.) was not available at our facility, and therefore was not performed for these patients. The absence of immunological parameters is the major limitation of this study. Although these tests cannot confirm or refute the diagnosis of CMPA in a child, RAST and SPT tests can guide the treatment and predict the prognosis⁸. One referral to an immunology service was made for a patient who developed angioedema after accidental exposure to cow's milk formula.

In this small cohort, the average age at presentation was 4.7 months, which is consistent with the findings of a large multicenter study⁹. An average delay of 3.2 months was observed between the appearance of the reaction and the first consultation, which is again similar to previously reported figures⁹.

Exposure to cow's milk protein is the prerequisite for the development of this form of allergy. It is known that bovine alpha-1-casein is a major allergen in cow's milk¹⁰. Alpha-1-

casein is also readily secreted into breast milk. The role of this protein in sensitization or tolerance to cow's milk in exclusively breast-fed infants needs further investigation¹⁰. In our study, two patients were exclusively breast-fed. The rate of CMPA in exclusively breast-fed babies was reported in one study⁸ to be as high as 13.2%. A diagnosis of CMPA should not be excluded if the baby is exclusively breast-fed.

Gastrointestinal manifestations are well known to be associated with CMPA, but our figures are much higher than reported rates¹¹. We believe that this reflects a referral bias. CMPA as a cause of gastrointestinal bleeding was found in four patients (16%). This diagnosis should be thought of in cases of upper and lower gastrointestinal bleeding in the vulnerable age groups. The incidence of infantile colic in patients with CMPA was reported to be as high as 44%¹², which is almost the same as our rate (48%).

The rate of poor weight gain and failure to thrive in our study was four times the reported rates⁸, while the rates of respiratory and dermatological manifestations were lower¹³. Again, we believe that referral bias is a contributor. In addition, most of the literature on CMPA is derived from immunological rather than gastrointestinal services.

An unusual finding in some of our patients was the presence of elevated liver enzymes (transaminases), although the basic work-up in all three cases was normal. After the patients started treatment (one with soya-based formula and two with amino acid formula), the liver enzymes normalized. Saito and colleagues reported hepatic dysfunction in three infants that was improved by the elimination of cow's milk formula. They concluded that CMPA might cause liver injury in infancy¹⁴. Taking this in consideration, it may worth to remove

cow's milk formula from the diet of infants showing isolated elevation of serum transaminases¹⁴.

The primary management of this condition involves elimination of the offending agent. In breast-fed babies, we encouraged mothers to use an elimination diet (i.e. avoiding milk, dairy products and eggs), with calcium and vitamin D supplementation¹⁵. In our study, six mothers agreed to try this regimen and the approach was successful in two-thirds of cases; the remaining one-third were lost to follow up. Dairy products are a major element of the food culture in Jordan and it is very hard to follow the elimination diet. Mothers who agree to try such a regimen are in need of good support.

Extensively hydrolyzed formula (eHF), which is considered by some authorities¹⁵ to be the first choice for treatment of CMPA, is not available in our facility. Some guidelines still consider soya-based formula to be hypoallergenic and that it should be considered for use in CMPA^{16, 17, 18}. In our cohort, soya-based formula was the first choice for patients with IgE-mediated suggestive symptoms, and patients who were referred while already on soya-based formula, and their symptoms improved. The response rate in patients on soya-based formula was 76%. All patients who failed to improve on soya-based formula or had severe symptoms (Gastrointestinal bleeding, severe Failure to thrive) were started on amino acid formula (Neocate®). All patients who received Amino acid formula showed resolution of their symptoms, giving a

response rate of 100%. Patients with poor weight gain showed significant improvement after 4 weeks of the new formula.

Although the small number of cases limits the statistical conclusions, the clinical presentation of CMPA reported here is consistent with larger studies from multiple areas of the world. However, elevated liver enzymes are an unusual finding in patients with CMPA, which resolved completely following a change of formula. This finding supports previous report, and should aware clinicians of this possibility when dealing with similar presentations.

Adoption of the clinical definition for CMPA used in this study will allow precise identification of cases. Misdiagnosis of patients could lead to unnecessary changes in infant formula, which might cause significant nutritional deficiencies¹⁹. However, shifting between formulas with similar constituents (cow's milk-based formulas) may lead to delayed referral and prolonged suffering. In our study, the infant formula was changed 2.4 times on average (range, 0–6 times) before referral. This caused a great deal of confusion and distress to the families and their babies. In addition, it involved a considerable financial burden. Increasing the awareness among primary care physicians and pediatricians of the diverse clinical presentations and modalities of treatment for CMPA will improve patient care, and will also reduce the amount of suffering and the financial costs of the condition.

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حساسية بروتين الحليب البقري لدى الأطفال في جنوب الأردن

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الملخص

إن الحساسية لبروتين الحليب البقري تعد الحساسية الغذائية الأكثر شيوعاً في مرحلة الطفولة. يعتمد التشخيص وبشكل أساسي على الأعراض السريرية التي تصيب المريض. إن المعلومات المتوفرة عن هذا المرض في بلادنا شحيحة جداً، ومن هنا جاء هدف هذه الدراسة وهو التعرف إلى طيف الأعراض السريرية، التداخلات العلاجية المتبعة ومدى فاعلية هذه التداخلات لدى الأطفال المصابين في جنوب الأردن. تم اعتماد تعريف سريري متحقق من دقته في دراسات سابقة لتشخيص الحالات. تم استخلاص جميع الحالات التي تعاني من حساسية لبروتين الحليب البقري والتي تمت متابعتها في عيادة أمراض الجهاز الهضمي لدى الأطفال خلال فترة الدراسة (تشرين الثاني 2009-حزيران 2013). المرضى الذين انطبق عليهم التعريف شملوا في الدراسة، فخضعت ملفاتهم الطبية للمراجعة وتم استخلاص معلوماتهم الخاصة بالأعراض السريرية، التداخلات العلاجية بالإضافة إلى مدى نجاعة هذه التداخلات.

تم معالجة المعلومات المستخلصة وتحليلها ومن ثم تقديمها بشكل معدلات ونسب مئوية. خلال فترة الدراسة تم تشخيص ومعالجة أربعين طفلاً. خمس وعشرون منهم انطبق عليهم التعريف المعتمد. ستة عشر مريضاً يشكلون أربعين بالمائة من المرضى كانوا من الذكور. كان المعدل العمري لدى المصابين 4.7 شهراً. أربعة وعشرون مريضاً يشكلون ستة وتسعون بالمائة عانوا على الأقل من عرض واحد في الجهاز الهضمي بينما الأعراض الجلدية والتنفسية فقد تم معاينتها في ثمان مرضى يشكلون اثنان وثلاثين بالمائة. فيما عانى ثلاثة مرضى من ارتفاع في أنزيمات الكبد.

كانت الاستجابة لحليب الصويا إيجابية في ستة وسبعين بالمائة من الأطفال الذين استخدموه، بينما كانت نسبة الاستجابة الإيجابية لحليب الأحماض الأمينية مئة بالمائة.

إن الحساسية لبروتين الحليب البقري ليست نادرة في مجتمعنا، كما أن الأعراض السريرية متنوعة جداً. في العينة المدروسة كانت أعراض الجهاز الهضمي هي الأكثر شيوعاً. إن الحساسية لبروتين الحليب البقري يمكن أن تتسبب بارتفاع أنزيمات الكبد. إن هذا المرض بحاجة إلى دراسات أوسع لتحديد حجم المشكلة في مجتمعنا.

الكلمات الدالة: الحساسية لبروتين الحليب البقري، رضع، حليب الرضع، الأردن.