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The "Red Umbilicus": A Diagnostic Sign of Cow's Milk Protein Intolerance

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ABSTRACT

Introduction: Red umbilicus is considered to be an infectious disease typical of neonates. In our experience, umbilical erythema could be due to cow's milk protein intolerance (CMPI).

Aims: To evaluate the frequency and clinical significance of umbilical erythema in a series of consecutive children referred for suspected CMPI.

Patients and Methods: Seven hundred ninety-six consecutive patients (median age, 18 months) referred for suspected CMPI diagnosis were studied. CMPI diagnosis was based on the disappearance of symptoms on elimination diet and their subsequent reappearance on double-blind placebo-controlled cow's milk challenge.

Results: CMPI was diagnosed in 384 patients: 120 with respiratory, 75 dermatologic and 198 gastroenterological symptoms. Although some patients showed more than 1 type of symptom, whether gastroenterological, dermatologic or respiratory, they were classified in 1 category only according to the main reason for referral to the outpatients clinic. Umbilical erythema was observed in 36 patients (median age, 10 months): 16 (8%) with gastroenterological symptoms, 9 (7.5%) with recurrent asthma and 11 (15%) with atopic dermatitis. None of the symptomatic controls without CMPI had umbilical erythema. On elimination diet, the erythema disappeared within the second week. On CMPI challenge, it reappeared within 24 hours.

Conclusions: Umbilical erythema can be a sign of food intolerance and can be a useful diagnostic tool for CMPI. ***JPGN 42:531–534, 2006.*** **Key Words:** umbilicus—food intolerance—cow's milk protein intolerance. © 2006 by Lippincott Williams & Wilkins

INTRODUCTION

Cow's milk protein intolerance (CMPI) is a common clinical problem in children, with a reported frequency of between 3% and 5% in the general population (1–3). Diagnosis is often difficult because immunologic tests cannot be considered absolutely predictive. In patients with gastroenterological symptoms in particular, exclusively clinical criteria must be adopted, based on response to an elimination diet followed by a double-blind placebo-controlled (DBPC) food challenge (4). Because this diagnostic procedure is cumbersome and sometimes dangerous for the patient, identifying clinical signs that clearly indicate a CMPI diagnosis is a very important goal.

In our experience, the presence of umbilical and periumbilical erythema in children can be a sign of CMPI, and this prospective study was designed to evaluate (*a*) the frequency of umbilical erythema in a series of consecutive patients referred for suspected CMPI and (*b*) its clinical significance.

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PATIENTS AND METHODS

The study included 796 consecutive patients (356 boys; age range, 1 month to 10 years; median, 18 months) referred for suspected CMPI to the outpatients clinic of Pediatric Gastroenterology at the "Di Cristina" Hospital in Palermo, between January 2001 and June 2002. Inclusion criteria were (*a*) clinical history and/or physical signs compatible with CMPI diagnosis and, (*b*) regular consumption of cow's milk and its derivatives. Exclusion criteria were (*a*) prior clinical evaluation for CMPI and (*b*) referral for reasons other than probable CMPI.

Although some patients showed more than 1 type of symptom, whether gastroenterological, dermatologic or respiratory, they were classified in 1 category only according to the main reason for referral to the outpatients clinic. Consequently, 510 were classified as showing gastroenterological symptoms (the main symptom leading to consultation being: gastroesophageal reflux in 123 cases, chronic constipation in 89, chronic diarrhea with malabsorption syndrome in 82, bloody diarrhea in 81, infantile colic in 80, loss of appetite and failure to thrive in 55); 200 showing respiratory symptoms (rhinitis and/or bronchial asthma with wheezing) and 86 eczema. All underwent detailed physical examination and clinical history and routine hematochemical and immunology assays. Furthermore, physicians started a diagnostic workup according to the individual laboratory data, which may have included serology for celiac disease diagnosis, fecal clinitest and occult blood test, chest radiography, 24-hour esophageal pH-metry, esophagogastroduodenoscopy with duodenal biopsy,

colonoscopy with multiple biopsies, small intestine barium examination, abdominal ultrasonography and/or computed tomography scan. Diagnoses other than CMPI were based on standard recognized criteria, and the patients were followed up for 12 to 24 months (median 18 months) to confirm the initial diagnoses.

Umbilical erythema was defined as the presence of erythematous skin in the umbilical and periumbilical region, with or without secretion. The presence of erythema was evaluated by 3 authors (A.C., L.D.P. and D.D.) unaware of the clinical symptoms, diagnoses and diets. Each of them evaluated the patients separately, and the concordance rate in judging the presence or absence of umbilical erythema was calculated.

Criteria for CMPI Diagnosis

CMPI diagnosis was based on the disappearance of symptoms on elimination diet and their subsequent reappearance on DBPC cow's-milk challenge. Because in our experience CMPI can be associated with intolerance toward other foods (5), the elimination diet excluded all the following: cow's milk and its derivatives, wheat, tomato, cocoa, egg and fish. During this period, the infants younger than 15 months received a semielemental formula based on oligopeptides (Polilat; Mellin, Milan, Italy), whereas the children older than 15 months received a commercially available soy milk. After 12 weeks, all the patients who were cured on the oligoantigenic diet underwent cow's milk challenge. The challenges were begun in hospital according to the procedure previously described (6,7); the same milk prescribed during the CM-free diet period was used as a placebo in the DBPC challenge, and the children were randomly assigned to receive cow's milk or placebo. If no clinical reactions were observed within 12 hours after the beginning of the challenge, the patient was discharged and the challenge continued at home with bottles coded A or B. During the 2-week challenge period, the parents recorded any clinical symptoms, and the patients were reexamined in hospital for any adverse reactions. The challenge was stopped when a clinical reaction occurred. The challenges for foods other than cow's milk were performed in an open fashion as described elsewhere (8).

Laboratory Test

At entry to the study routine hematochemical and immunologic tests were performed. Immunologic assays were performed with commercial kits, and the respective cutoff values were used as previously described (7–9). They included serum levels of total IgE, radioallergosorbent tests (RASTs) and skin prick tests for the main foods and serum IgG anti–β-lactoglobulin assay. In all patients with umbilical erythema, a culture assay on the umbilical skin was performed.

The children's parents gave their informed consent to all the diagnostic and therapeutic procedures described in this study. The study protocol was approved by the Ethics Committee of the University Hospital of Palermo.

Statistical Analysis

Frequency analysis was performed using Fisher exact test. The Mann-Whitney *U* test was used for data comparison between the different groups.

RESULTS

CMPI was diagnosed in 384 patients (185 boys; age range, 1 month to 8 years; median, 18 months) after the disappearance of the symptoms on elimination diet and their subsequent reappearance on DBPC challenge. In detail, CMPI was diagnosed in 120 (60%) of the 200 showing respiratory symptoms, 75 (87%) of the 86 with eczema and 198 (39%) of the 510 with gastroenterological symptoms.

Umbilical and periumbilical erythema were observed in 36 patients (14 boys; age range, 1–25 months; median, 10 months). The 3 blinded independent observers agreed on the presence of umbilical erythema in all cases. Erythema was associated with a serous, sometimes badly smelling secretion in 20 cases (Fig. 1). Culture assays on the umbilical skin were all negative for pathogen bacteria and fungi. Table 1 shows the frequency of gastrointestinal symptoms in the study patients, divided according to whether they were with or without CMPI. Sixteen patients had umbilical erythema, and it was always associated with gastroenterological symptoms of CMPI. It was a specific sign of CMPI, as it was never present in the patients without CMPI. No other erythematous lesions were observed in other areas of the skin, with the exception of subjects with chronic constipation, who presented erythema in the perianal region. Furthermore, umbilical and periumbilical erythema were also observed in 9 (7.5%) of 120 CMPI patients with recurrent asthma and in 11 (15%) of 75 with atopic dermatitis. None of the patients with respiratory or dermatologic symptoms not due to CMPI showed umbilical erythema.

In summary, erythema was observed in 9.3% (36/384 cases) of the patients with CMPI and in none of the symptomatic controls without CMPI. Clinical history indicated that the umbilical erythema had appeared after the appearance of the "main" symptom of CMPI (the

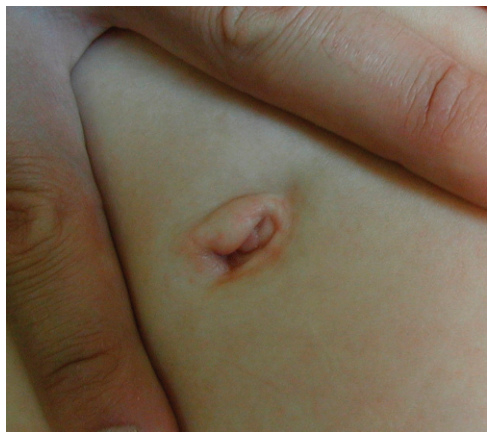

FIG. 1. Picture of umbilical erythema in a pediatric patient included in the study.

TABLE 1. *Number of gastrointestinal symptoms in patients with a gastroenterological clinical presentation (n = 510), divided according to the final diagnosis into CMPI and non-CMPI patients*

	CMPI Patients (n = 198)	Non-CMPI Patients (n = 312)	Symptom due to CMPI	Symptom not due to CMPI
Umbilical and periumbilical erythema	16/198 (8)	0/312 (0)	16/16 (100)	0/16 (0)
Chronic constipation	32/198 (16)	57/312 (18)	32/89 (36)	57/89 (64)
Gastroesophageal reflux	49/198 (25)	74/312 (24)	49/123 (40)	74/123 (60)
Chronic diarrhea with malabsorption	23/198 (12)	59/312 (19)	23/82 (28)	59/82 (72)
Bloody diarrhea	42/198 (21)	39/312 (13)	42/81 (52)	39/81 (48)
Failure to thrive	28/198 (14)	27/312 (8)	28/55 (51)	27/55 (49)
Infantile colic	24/198 (12)	56/312 (18)	24/80 (30)	56/80 (70)

The percentage of cases due or not due to CMPI is given for each symptom (in parentheses).

Several patients showed more than 1 symptom, but they were classified only according to the main symptom (the one leading to the clinical consultation).

symptom leading to referral) in 24 cases (67%), at the same time in 9 cases (25%) and beforehand in 3 cases (8%). In the latter patients, the subsequent clinical manifestations of CMPI were atopic dermatitis (2 cases) and proctocolitis with bloody diarrhea.

On elimination diet, umbilical erythema disappeared within the second week (range, 2–12 days; median, 5 days). On CMPI challenge, it reappeared within 24 hours (range, 1–24 hours; median, 3 days), often before the reappearance of the "main" associated CMPI symptom. In detail, umbilical erythema reappeared before the reappearance of constipation, hyporexia and gastroesophageal reflux, whereas it reappeared at the same time as diarrhea and respiratory and dermatologic symptoms.

Table 2 shows the clinical and laboratory characteristics of the patients with CMPI divided according to the presence or absence of umbilical erythema. The patients with umbilical erythema had a lower age at CMPI diagnosis and a shorter duration of the disease than the other CMPI subjects. RASTs for food antigens were more frequently positive in the subjects with umbilical erythema than in the other CMPI patients. The most sensitive assays were RASTs and IgG anti–β-lactoglobulin, but neither of these was highly specific as they were positive in many non-CMPI patients included in the study (data not shown).

DISCUSSION

Omphalitis is a problem that is not rare in infants (10,11) but sometimes causes severe complications (12,13). It is always considered a consequence of infection, also in the much rarer cases reported in adult patients (14).

Our data demonstrated that umbilical and periumbilical erythema can be a sign of food intolerance. In fact, we found a symptomatic inflammation of the umbilical skin in approximately 9% of 384 consecutive children with CMPI. None of them showed skin pathogen bacteria as a cause of the inflammation, and in all cases, the relationship between the clinical signs and food intolerance was demonstrated by the disappearance of the erythema on elimination diet and its reappearance on food

TABLE 2. *Clinical and laboratory characteristics of the CMPI patients studied, divided according to the presence (n = 36) or absence (n = 348) of umbilical erythema*

Characteristic	Patients with umbilical erythema	Patients without umbilical erythema	*P*
Age at diagnosis (mo), mean ± SD	11.4 ± 9.1	21.5 ± 19.3	0.005
Sex (males/females)	15/21	163/185	NS
Breast feeding at birth (n)	33/36	310/348	NS
Refused food at weaning (n)	1/36	16/348	NS
Duration of illness (mo), mean ± SD	3.5 ± 2.2	10.3 ± 12.2	0.01
Family history of food intolerance (n)	14/36	134/348	NS
Presence of multiple food intolerance (n)	7/36	71/348	NS
Abnormal test results (n)			
Serum IgE level	12/36	115/348	NS
Skin test with food antigens (prick)	12/36	124/348	NS
Specific IgE antibodies to food antigens	21/36	113/348	0.01
Serum IgG anti–β-lactoglobulin	20/36	248/348	NS

Reference values were total serum IgE of less than 60 KU/L (mean value ± 2 standard deviation [SD] recorded in age-matched healthy children by our laboratory); skin prick tests: any wheal diameter that exceeded that of the control and was more than one fourth the size of the histamine wheal was regarded as positive; specific IgE for food antigens of less than 4 sorbent units per milliliter; serum IgG anti–β-lactoglobulin of less than 36% (value with the highest diagnostic accuracy in a large study performed on more than 200 healthy controls and more than 200 CMPI patients).

challenge. Such clinical criteria are the only ones accepted for food intolerance diagnosis in patients with predominantly gastroenterological symptoms (4,15). Furthermore, the 100% concordance rate of the 3 blinded observers in evaluating the presence of the periumbilical erythema is worthy of note.

In the literature, there is a previous report of 3 cases of pruritic periumbilical papules in children with atopic dermatitis (16). However, that article described more severe skin lesions than those we found in our patients, as we never observed papular lesions. Furthermore, those authors described periumbilical papules only in patients with atopic dermatitis who had a typical symmetric eczematous involvement of other skin areas (arms, legs, etc). On the contrary, we found that periumbilical erythema can be associated with all the possible clinical presentations of food intolerance: not only dermatologic, but also respiratory and gastroenterological ones. In most of our patients with umbilical erythema, no other skin area was affected; erythematous skin lesions in other areas were found only in patients with atopic dermatitis or in patients with chronic constipation due to CMPI (in the perianal region). In patients with gastroenterological symptoms of CMPI, the presence of umbilical erythema can be a very useful aid in diagnosing food intolerance. In fact, many of the gastroenterological symptoms connected with suspected food intolerance (ie, chronic diarrhea, constipation, gastroesophageal reflux) can be due to a great variety of diseases, and it is often difficult to decide whether an elimination diet should be attempted. Furthermore, the presence of multiple food intolerance can cause symptoms to persist during the diet, thus making diagnosis difficult. Although, in general, the "red umbilicus" was not a frequent symptom of CMPI (it was present in less than 10% of the cases), it is very interesting that none of the over 400 patients without CMPI had umbilical erythema. In this study, as in many other studies by our group and by other authors (7,17,18), none of the immunology tests commonly performed to validate the diagnosis of food intolerance had a high sensitivity and specificity. This aspect further highlights the importance of finding clinical signs, such as umbilical erythema, which can indicate a diagnosis of food intolerance. Furthermore, we also observed the appearance of umbilical erythema due to intolerance toward foods other than cow's milk: wheat, tomato and fish (data not shown). The patients with umbilical erythema showed a higher frequency of positive RASTs for food antigens than the other CMPI patients, but because of the absence of IgE-specific antibodies in some of them and to the clinical relapse time after food challenge (1–24 hours), we cannot affirm that the umbilical erythema was based on an IgE-mediated mechanism.

In conclusion, we showed that umbilical erythema is a sign of food intolerance in children, and its presence can be an important diagnostic aid.

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