

## Cow's milk induced proctocolitis in full term dizygotic twin neonates

*Alergijski proktokolitis na kravlje mlijeko u dizigotnih blizanaca u neonatalnom razdoblju*

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### Summary

Allergic proctocolitis in the neonatal period has rarely been reported in twins. We report on a case of an allergic proctocolitis to cow's milk in dizygotic twin neonates during the early neonatal period. Full-term dizygotic twins presented with rectal bleeding and severe anemia. Investigation supported diagnosis of cow's milk protein allergy and they responded positively to the elimination of offending antigen. Allergic colitis should be considered in the differential diagnosis of any newborn with rectal bleeding after the exclusion of infectious and anatomic disorders common in this age group.

**Key words:** allergic proctocolitis, cow's milk protein allergy, newborn, twin

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### Sažetak

Alergijski se proktokolitis rijetko pojavljuje u neonatalnom razdoblju. Prikazujemo slučaj alergijskog proktokolitisa na kravlje mlijeko u novorođenih dizigotnih blizanaca u neonatalnom razdoblju. Prikazuju se dizigotni blizanci rođeni u punom terminu s rektalnim krvarenjem i teškom anemijom. Istraživanje je otkrilo alergiju na protein kravljega mlijeka s pozitivnom reakcijom na uzročni antigen. Treba uzeti u obzir alergijski kolitis kod diferencijalne dijagnoze bilo kojeg novorođenog djeteta s rektalnim krvarenjem nakon isključenja infekcija i poremećaja koji su uobičajeni u ovoj dobnj skupini.

**Ključne riječi:** alergijski proktokolitis, alergija na proteine kravljega mlijeka, novorođenče, blizanac

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### Introduction

Cow's milk protein allergy (CMPA) is the most common food allergy in young children with incidence from 2 to 3% in the first year of life.<sup>1</sup> Allergic proctocolitis is non-IgE mediated food allergy which frequently occurs in exclusively breast-fed infants.<sup>2</sup> Blood stained stools usually develop between 2 and 6 weeks of age.<sup>3</sup> Allergy tests have a low diagnostic value and diagnosis is based on clinical features. Rectal bleeding resolves within 72-96 hours of cow's milk protein (CMP) elimination.<sup>4</sup>

In breast-fed infants, breast feeding should be encouraged with maternal cow's milk protein avoidance. In nonbreast-fed infants, the elimination diet usually starts with an extensively hydrolyzed infant formula (eHF) or with amino acid-based formula (AAF) in infants with no clinical improvement.<sup>5</sup> Patients should be reevaluated every 6 to 12 months to assess tolerance to CMP. Children routinely tolerate cow's milk protein by their first birthday.<sup>2</sup> The aim of this case report is to highlight the possibility of CMPA in a full term, otherwise healthy neonates after excluding other possible causes.

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### Case report

Twins born from the second pregnancy of non-consanguineous parents were delivered at term by Cesarean section. The family history was positive for allergic rhinitis and their older brother had cow's milk allergy. The parents provided informed consent.

#### The girl (1<sup>st</sup> twin)

The girl's birth weight was 2,540 g. Apgar scores were 10 respectively. On the first neonatal day breastfeeding supplemented by cow's milk protein-based formula was initiated. Empirical antibiotic treatment (ampicillin and netilmicin) was initiated for suspected perinatal infection. The girl started to pass blood

stained stools on the 2<sup>nd</sup> day of life and the mother had no nipple fissures. Physical examination revealed normal temperature, blood pressure, respiratory and heart rates. Her abdomen was soft and mildly distended, without palpable masses or anal fissures. The bowel sounds were normal. Laboratory tests showed hemoglobin 137 g/L, hematocrit level of 0.410, normal coagulation screening results, platelets of  $356 \times 10^3/\mu\text{L}$ , white cell count  $24,4 \times 10^3/\mu\text{L}$  and absolute eosinophil count 1,140/  $\mu\text{L}$ . C-reactive protein was 4.2 mg/L. Blood sugar was 1.9 mmol/l. Apt test was positive for fetal hemoglobin. Total serum immunoglobulin E (IgE) was negative (<0.100 IU/mL) and specific IgE-antibodies to cow's milk protein were negative (< 0.35 kU/L). Blood and urine cultures were sterile.

Table 1 Patient characteristics

Tablica 1. Karakteristike pacijenata

Patient characteristics <i>Karakteristike pacijenta</i>	1 <sup>st</sup> twin <i>1. blizanac</i>	2 <sup>nd</sup> twin <i>2. blizanac</i>		
Sex <i>Spol</i>	Female <i>žensko</i>	Male <i>Muško</i>		
Birth weight, g <i>Težina pri porodu</i>	2,540	2,850		
Apgar score, points <i>Apgar bodovi</i>	10/10	10/10		
Onset of initial symptoms, days <i>Nastup početnih simptoma, dani</i>	2	9		
C-reactive protein, mg/L <i>C-reaktivan protein</i>	4.2	22.5		
White blood cells, $\times 10^3/\mu\text{L}$ <i>Bijela krvna zrnca</i>	24,4	29,4		
	2 <sup>nd</sup> day of life <i>2. dan života</i>	lowest level <i>najniža raz.</i>	2 <sup>nd</sup> day of life <i>2. dan života</i>	lowest level <i>najniža raz.</i>
Hemoglobin, g/L <i>Hemoglobin</i>	137	83	155	78
Hematocrit <i>Hematokrit</i>	0.410	0.237	0.470	0.277
	2 <sup>nd</sup> day of life <i>2. dan života</i>	highest count <i>najveći broj</i>	2 <sup>nd</sup> day of life <i>2. dan života</i>	highest count <i>najveći broj</i>
Platelets, $\times 10^3/\mu\text{L}$ <i>Trombociti</i>	356	977	325	729
Absolute eosinophil count <i>Apsolutni broj eozinofila</i>	1,140	629		
Total serum immunoglobulin E, IU/L <i>Sveukupni serumski imunoglobulin</i>	< 0.100	< 0.100		
Specific serum Immunoglobulin E, kU/L <i>Specifičan serumski imunoglobulin</i>	< 0.35	< 0.35		

Abdominal ultrasound was normal. Breast-feeding was continued and cow's milk protein was eliminated from the mother's diet. The patient was fed with eHF from day 3. She responded negatively with occult blood in stools, progressive anemia with hemoglobin 83 g/L, hematocrit level of 0.237 and thrombocytosis of  $977 \times 10^3/\mu\text{L}$ . The AAF and iron supplementation were introduced. The girl responded positively with gaining weight and passing normal stools. Hemoglobin and hematocrit level improved. She was discharged home on day 25 with a weight of 3,100 g. Oral challenge test performed at 12 months of age was negative.

#### *The boy (2<sup>nd</sup> twin)*

The second twin was a boy with birth weight 2,850 g. Apgar scores were 10 respectively. On the first neonatal day, breast-feeding supplemented by cow's milk formula was started. Physical examination was normal. Laboratory tests showed hemoglobin 155 g/L, hematocrit level of 0.470, normal coagulation, platelets of  $325 \times 10^3/\mu\text{L}$ , white cell count  $29,4 \times 10^3/\mu\text{L}$  with 60% segmented and 12% band neutrophils. C-reactive protein was 22.5 mg/L. Blood urea nitrogen and serum creatinine were mildly elevated. Treatment with ampicillin and netilmicin was initiated. Blood and urine cultures were sterile. From the 9<sup>th</sup> day of life, he gradually developed severe anemia with hemoglobin 78 g/L, hematocrit level of 0.277 and thrombocytosis of  $729 \times 10^3/\mu\text{L}$  with occult blood in stools. Apt test was positive for fetal hemoglobin. Stool cultures were negative. Rota- and Adenovirus were negative in the stool. Abdominal ultrasound was normal. Total serum IgE and specific IgE-antibodies to cow's milk protein were negative. Absolute eosinophil count was  $629/\text{mm}^3$ . The child was breastfed and fed with eHF, then AAF. Iron supplementation was introduced from day 21. He responded positively and started to gain weight passing normal stools negative for occult blood. Hemoglobin and hematocrit level improved. He was discharged home on day 25 with a weight of 3,580 g. Oral challenge test performed after his first birthday was negative.

### **Discussion**

We report on a case of allergic proctocolitis to cow's milk in dizygotic twin neonates during the early neonatal period. Reports of early-onset CMPA with gastrointestinal bleeding in the neonatal period are increasing.<sup>6,7,8,9</sup> Although it is well recognized that there is genetic predisposition towards allergy, few

described the condition in twins. Watanabe and colleagues reported a case of milk-induced enterocolitis in monozygotic twin neonates.<sup>10</sup> There have been two reported of allergic proctocolitis to cow's milk protein described in premature twin neonates.<sup>11,12</sup>

Diagnosis of milk protein-induced proctocolitis is usually made on clinical grounds alone, as initial symptoms are nonspecific and the results of cow's milk-specific IgE antibody and skin prick tests are not always positive. Eosinophilia, defined as absolute eosinophil count  $>700/\mu\text{L}$ ,<sup>13</sup> seems to be useful in suggesting allergic origin, but non-specific. Marked peripheral eosinophilia was noted in our first case with normal total IgE and specific IgE-antibodies in both cases. Atopy patch test (APT) cannot be recommended at the present time, due to difficulties with standardization of the preparation and interpretation of the results, although there may be a role for it in the future.<sup>5</sup> Atopy patch test might become useful to identify infants with multiple gastrointestinal allergies involving delayed non-IgE immune mechanisms.<sup>4</sup> The most definitive approach to establish the diagnosis is the following response to specific food elimination and rechallenge.<sup>14</sup> If CMPA is suspected by history and examination, diagnostic elimination diet is initiated for a limited period of time, as 1 to 2 weeks in children with delayed reactions.<sup>5</sup> In breast-fed infants, the mother should start a CMP-free diet and breast-feeding should be encouraged. Non-breast-fed infants should receive an eHP. Soy protein formula is an option beyond 6 months of age. Standardized oral challenge with CMP should be performed if symptoms improve. Infants should be maintained on an elimination diet for at least 6 months, or until 9 to 12 months of age, if CMPA is confirmed. Patients should be reevaluated every 6 to 12 months to assess tolerance to CMP.<sup>5</sup> Diagnostic rectosigmoidoscopy with biopsies should only be performed in selected cases refractory to a maternal diet.<sup>4</sup> Due to the focal nature of mucosal eosinophilic infiltration, diagnosis could be missed.<sup>15</sup> Gastrointestinal blood loss is common in the neonatal period and can be benign or life threatening. Other causes of rectal bleeding had to be considered such as an anal fissure, swallowed blood and lymphonodular hyperplasia. In clinically unstable neonates necrotizing enterocolitis, sepsis, volvulus, intussusception, Meckel diverticulitis and colitis complicating Hirschsprung disease should be considered.<sup>16</sup> Vitamin K was administered in the delivery room to both of our patients and coagulation disorders were excluded. Absence of peritoneal signs argued against a vascular disorder as the cause of gastrointestinal bleeding.

Infection causes were unlikely because of negative stool cultures. The clinical course with healthy appearance of affected neonates, despite of severe anemia with normalization of stools negative for occult blood within 72 hours after feeding with elementary milk formula, indicated that CMPA may have been the cause of the symptoms. Abdominal x-ray and rectosigmoidoscopy were not performed because both of our cases were full term and responded to withdrawal of the offending antigen. Our patients had significant bleeding and severe anemia, so the challenge test was delayed for ethical reasons due to potential severe allergic reaction. At 12 months of age, oral food challenge was performed and they showed tolerance to the dairy formula used. During the follow-up period of 3 years, patients tolerated cow's milk and dairy products without gastrointestinal symptoms. Allergic colitis should be considered in otherwise healthy neonates with rectal bleeding after the exclusion of infections and atonic disorders common in this age group.

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