An unusual cause of secondary capillary leak syndrome in a child: rotavirus diarrhea

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SUMMARY: Aldemir-Kocabaş B, Karbuz A, Çiftçi E, Demir M, İnce E. An unusual cause of secondary capillary leak syndrome in a child: rotavirus diarrhea. Turk J Pediatr 2013; 55: 90-93.

Secondary capillary leak syndrome is characterized by loss of fluid and proteins to the interstitial space due to different causes, which are related to endothelial damage. Rotavirus is the most common pathogen of diarrhea in childhood, especially during the first years of life. This virus is generally responsible for severe diarrhea and electrolyte imbalance in children. Some complications can also occur during the course of the rotavirus diarrhea. An eight-month-old girl with rotavirus diarrhea admitted to our clinic with severe dehydration. After restoring the intravascular volume, hypoalbuminemia and generalized edema were seen in the recruitment phase of the treatment, which was attributed to secondary capillary leak syndrome. She was successfully treated with prednisolone and discharged from the hospital without any sequelae. Herein, we report an infant with rotavirus diarrhea complicated with secondary capillary leak syndrome, which is an unidentified complication of the disease. To our knowledge, this is the first such case in the literature.

Key words: capillary leak syndrome, rotavirus diarrhea, dehydration, children.

Capillary leak syndrome (CLS) is defined as increased capillary permeability due to several etiological conditions and causes loss of fluid and proteins from the intercellular to interstitial space. Consequently, hemoconcentration, hypoalbuminemia and edema occur[1-3]. Two types of this syndrome have been described: primary CLS, which is generally seen in the adult population, and secondary CLS, which can occur due to various reasons accompanying vessel damage[1,4,5]. There is no case in the literature reported as having CLS attributed to rotavirus gastroenteritis. Rotavirus causes severe electrolyte deficiency and dehydration when not treated immediately with fluid replacement. However, in this case report, we emphasize that CLS may develop during replacement therapy of severe dehydration due to rotavirus enteritis.

Case Report

An eight-month-old girl was admitted to our emergency department with complaints of vomiting, fever and diarrhea. There was a history of watery diarrhea 10-12 times and vomiting 2-3 times per day, for three days. Despite her oral intake being adequate before the presentation day, she had lost 750 g in body weight upon admission to the hospital. Her body temperature increased to 38.5°C on the day of presentation. Her physical examination revealed the following: physical growth parameters were normal (length: 64.5 cm, weight: 7200 g, head circumference: 44 cm), blood pressure 90/60 mmHg, pulse rate 136 beats/minute, respiratory rate 28 breaths/minute, and temperature 36.4°C. Her general condition was poor and she was confused. She was dehydrated with a sunken anterior fontanel (2x1 cm), no tears, sunken eyes, dry lips and mouth, and poor skin turgor. Laboratory findings revealed blood urea nitrogen (BUN): 2 mg/dl, creatinine 0.2 mg/dl, sodium 132 mmol/L, potassium 2.6 mmol/L, total proteins 4.7 g/dl, albumin 3 g/dl, and positive stool rotavirus antigen. Urinalysis was normal except for a high specific gravity (1025). Further, arterial blood gas values revealed pH: 7.37, pO_2: 110, pCO_2: 24.9, SPO_2: 98.1, base excess: -9.6, and HCO_3: 16.4. Despite the patient

having received a bolus infusion of 0.9% saline (20 ml/kg) in the emergency room, she was administered second and third boluses because of ongoing severe dehydration findings on the physical exam and anuria. After restoring the intravascular volume, her fluid treatment was adjusted as dextrose 5% in one-third normal saline with 40 mEq/L KCl. A urinary catheter was used for monitoring the urine output, which increased to 4.1 ml/kg/h during the follow-up, and her potassium level returned to normal ranges. Therefore, the urinary catheter was removed on the second day. The patient's dehydration signs and symptoms resolved and she achieved her previous body weight, as measured before the illness. On the third day of the hospital admittance, the patient deteriorated and intravenous (IV) ceftriaxone (75 mg/kg/day, divided 2 doses) was initiated empirically after blood and urine cultures were obtained. Diffuse pitting edema, which was more prominent on the hands and feet, occurred on the fourth day and generalized on the following day (Fig. 1). Urine output decreased when edema occurred. The patient gained 300 g of weight in two days while she was administered maintenance fluid treatment. Despite generalized edema, there were no signs of congestive heart failure including tachycardia, tachypnea or hepatomegaly. Laboratory findings were BUN 1 mg/dl, creatinine 0.3 mg/dl, sodium 136 mmol/L, potassium 4.6 mmol/L, total proteins 4.8 g/dl, and albumin 2.9 g/dl. It was considered as CLS developed in the recruitment phase of the severe hypovolemic shock. IV prednisolone 1.5 mg/kg/dose (total 2 doses) was administered immediately. On the second day of the prednisolone treatment, urinary output of the patient increased and the edema disappeared. Because the cultures were sterile, we discontinued the ceftriaxone treatment on the third day. On the sixth day of the admission, all the physical examination findings, activity and nutrition normalized. However, we found bulging and pulsation of the anterior fontanel on the following day and performed lumbar puncture to exclude meningitis. The patient's head circumference did not increase, and she had no findings of increased intracranial pressure. All the cerebrospinal fluid examinations were normal and the culture was sterile. Because the patient had improved clinically and all her vital signs were stable, this situation was considered as a result of the CLS. She was discharged from the hospital on the ninth day with no complications.

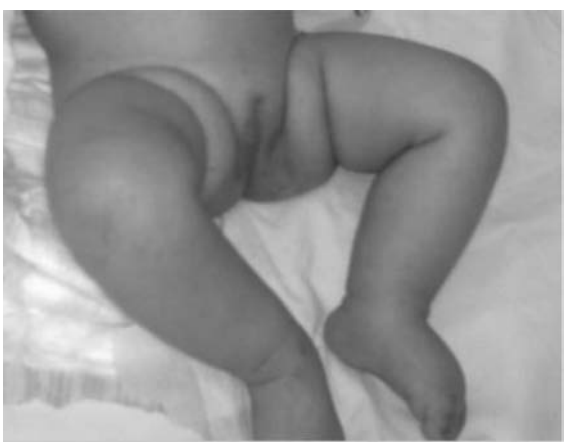

Figure 1. Diffuse edema on the legs and feet caused by capillary leak as a complication of Rotavirus diarrhea.

Discussion

Rotavirus is the most common cause of severe diarrhea among infants and young children in all socioeconomic groups and in all regions of the world. Gastroenteritis due to this virus is responsible for severe fluid and electrolyte loss and may be life-threatening in untreated patients. Although the pathogenesis of rotavirus diarrhea is not completely understood, it is thought that viral enterotoxin is responsible for malabsorption related to mucosal damage and depression of disaccharidases. The severity of diarrhea correlates with the degree of mucosal damage. In vitro studies revealed that disruption of tight junctions by VP8 or NSP4, which are viral proteins, plays an important role for increased permeability causing secretion of fluid, sodium and chloride from intestinal segments. The enterotoxin inhibits glucose-coupled sodium transport and stimulates phospholipase C, resulting in elevated intracellular calcium level[2,6-8].

The pathogenesis of CLS remains unclear, but cytokines, leukotrienes, vascular endothelial growth factor (VEGF), and complement have been implicated[1]. Generally, primary CLS is described in the fourth and fifth decades and rarely in childhood[1,2,9]. Secondary CLS can occur due to various reasons accompanying endothelial damage, which is related to

endotoxin exposure, ischemia-reperfusion, vessel injury with platelet deposition, or mechanical stress. On the other hand, sepsis, multiorgan failure, trauma, shock, cardiac surgery, C1q esterase deficiency, C4A deficiency, and acute gastroenteritis are known as the most common causes of secondary CLS in childhood[4,5,9]. It has been reported in the literature that treatment with tumor necrosis factor (TNF), interferon-α and β, acitretin, epoprostenol, gemcitabine, clofarabine, interleukin (IL)-2, denileukin diftitox, and filgrastim is associated with secondary CLS[1,10-13]. When ischemia-reperfusion occurs oxidized phospholipids released from endothelial membrane vesicles may serve as stress signals, triggering both pro- and anti-inflammatory cascades. Finally, released mediators, such as TNF-α and IL-1β, play an important role in vascular endothelial damage[5,14]. We suggest that this damage in our patient was a result of severe dehydration due to rotavirus causing hypovolemic shock. After aggressive fluid replacement therapy, CLS occurred in the recruitment phase of hypovolemic shock because of ischemia-reperfusion damage. As a result of altered capillary and blood–brain barrier permeability, shift of fluid and protein to the interstitial space, generalized edema and bulging of the anterior fontanel occurred.

The treatment of secondary CLS is based mainly on managing the underlying cause. Increased microvascular permeability generally results from sepsis and systemic inflammatory response syndrome. Therefore, it is reported in the literature that a number of therapies including prednisone, indomethacin, methylxanthine, terbutaline, montelukast, angiotensin-converting enzyme inhibitor, and anti-VEGF antibody bevacizumab were given[1,9,15]. It is possible that secondary bacterial infections can be seen during rotavirus gastroenteritis. Because our patient clinically deteriorated, we started antimicrobial therapy empirically, but neither blood nor cerebrospinal fluid cultures revealed any microorganism. The patient responded to the steroid therapy dramatically; thus, we think that CLS was responsible for the clinical picture.

We could not find any report of CLS related to rotavirus infection in children in the published literature. However, Onal et al.[9] described a five-month-old child with intractable diarrhea that led to secondary CLS. She had severe edema that was not responding to treatment with methylprednisolone and IV immunoglobulin infusion. They reported that the patient had a good response to the cessation of breastfeeding, a lactose-free diet, restriction of IV fluids, and aminophylline infusion. Although the patient had severe diarrhea, all the viral and bacterial examinations were negative for etiological screening.

In conclusion, CLS is quite a rare entity in children. We report a patient who had secondary CLS associated with rotavirus gastroenteritis and severe dehydration and who was treated successfully with prednisolone. To our knowledge, this is the first such case in the literature.

REFERENCES

1. Bressan AL, Gripp A, Oliveira EF, Silva RS. Systemic capillary leak syndrome. An Bras Dermatol 2011; 86: 593-595.
2. Dormitzer PR. Rotaviruses. In: Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (7th ed). Vol. 2. Philadelphia: Elsevier, Churchill Livingstone; 2010: 2105-2115.
3. Druey KM, Greipp PR. Narrative review: the systemic capillary leak syndrome. Ann Intern Med 2010; 153: 90-98.
4. Fishel RS, Are C, Barbul A. Vessel injury and capillary leak. Crit Care Med 2003; 31: S502-511.
5. Gallagher DC, Bhatt RS, Parikh SM, et al. Angiopoietin 2 is a potential mediator of high-dose interleukin 2-induced vascular leak. Clin Cancer Res 2007; 13: 2115-2120.
6. Kapoor P, Greipp PT, Schaefer EW, et al. Idiopathic systemic capillary leak syndrome (Clarkson's disease): the Mayo clinic experience. Mayo Clin Proc 2010; 85: 905-912.
7. Bhutta ZA. Acute gastroenteritis in children. In: Kliegman RM, Behrman RE, Jenson HB (eds). Nelson Textbook of Pediatrics (18th ed). Philadelphia: Saunders Elsevier; 2007: 1605-1618.
8. Hyser JM, Estes MK. Rotavirus vaccines and pathogenesis: 2008. Curr Opin Gastroenterol 2009; 25: 36-43.
9. Onal H, Aktuglu-Zeybek C, Altun G, et al. Capillary leak syndrome in a 5-month-old infant associated with intractable diarrhoea. Ann Trop Paediatr 2007; 27: 81-86.
10. Nakagawa N, Ota H, Tanabe Y, et al. A case of idiopathic systemic capillary leak syndrome with high serum levels of G-CSF on exacerbation. Intern Med 2011; 50: 597-600.

11. Karagol BS, Erdeve O, Arsan S, et al. Status epilepticus and capillary leak syndrome in a neonate related to perinatal hypoxic-ischemic encephalopathy. Indian J Pediatr 2010; 77: 439-441.

12. Dagdemir A, Albayrak D, Dilber C, et al. G-CSF related capillary leak syndrome in a child with leukemia. Leuk Lymphoma 2001; 42: 1445-1447.

13. Baytan B, Ozdemir O, Gunes AM, et al. Clofarabine-induced capillary leak syndrome in a child with refractory acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010; 32: 144-146.

14. Nooteboom A, Van Der Linden CJ, Hendriks T. Tumor necrosis factor-alpha and interleukin-1beta mediate endothelial permeability induced by lipopolysaccharide-stimulated whole blood. Crit Care Med 2002; 30: 2063-2068.

15. Takabatake T. Systemic capillary leak syndrome. Intern Med 2002; 41: 909-910.