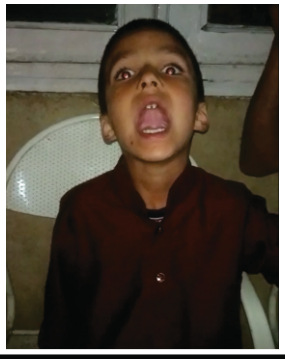
ISSN: 2772-5170

Indian Pediatrics Case Reports IPCaRes

VOLUME 2 • ISSUE 1 • JANUARY-MARCH 2022 www.ipcares.org

Academics



Social Pediatrics

Humanities

HIGHLIGHTS OF THIS ISSUE

An Official Publication of the Indian Academy of Pediatrics

Wolters Kluwer Medknow

Case Report

An Unusual Cause of Acute Encephalopathy: D-Lactic Acidosis Secondary to Short Bowel Syndrome

Prashant Jain, Ashish Prasad, Rachna Sharma[1], Vibin Vasudevan[1]

Departments of Pediatric Surgery and Pediatric Urology and [1]Pediatric Intensive Care, BLK-MAX Super Speciality Hospital, New Delhi, India

Abstract

Background: Blood D-lactate levels increase in short bowel syndrome (SBS) and may lead to neurological manifestations. **Clinical Description:** A 5-year-old boy, postoperative case of SBS, presented with loose stools, generalized weakness, and lethargy for 2 days. The child had undergone significant intestinal resection in the past. On examination, he had some dehydration, and was drowsy, but arousable. Remaining examination was normal. Metabolic abnormalities detected included metabolic acidosis (pH of 7.1, HCO_3 7 mmol/L), high anion gap (20 mmol/l), and normal lactate levels (2 mmol/L). Other baseline investigations were normal. He was treated as a case of acute gastroenteritis with some dehydration and metabolic acidosis and improved. He was discharged after 5 days. After 2 months, he was readmitted with drowsiness and unsteady gait. This time there was no diarrhea or dehydration. Investigations again revealed severe metabolic acidosis, high anion gap, and normal lactate levels. **Management:** We considered SBS induced D-lactate encephalopathy but were unable to prove it by assay due to unavailability of tests. The child was kept nil per orally and given bicarbonate infusion, on which he showed dramatic improvement. He was also given a low carbohydrate diet and oral metronidazole. The family was counseled at discharge 5 days later regarding dietary modifications and microsupplementation. The patient had 6 admissions for D-lactic encephalopathy over 4 years that coincided with dietary lapse. **Conclusion:** D-lactate acidosis is an underrecognized condition and its diagnosis and management is challenging. A high index of suspicion should be kept in patients with history of intestinal resection presenting with acute encephalopathy and unexplained metabolic acidosis.

Keywords: Carbohydrate restricted diet, D-lactic acidosis, encephalopathy, enteral nutrition, short bowel syndrome

Short bowel syndrome (SBS) is essentially the loss of length of the small intestine (either due to a congenital malformation or following surgical resection), which leads to inadequate absorption of enteral nutrients.[1] It is not defined only in terms of length of residual bowel length, as the function of the remnants is also dependent on the site of the resected bowel and quality of function of the remnant bowel.[1] The diagnostic criterion of SBS is the need for parenteral nutrition for >60 days after intestinal resection, or a bowel length of <25% of the expected length.[2] The cause of SBS depends on the age of the patient. In infants and older children, the common causes include malrotation with volvulus, intestinal gangrene secondary to mesenteric vein thrombosis, hernia, or intussusception. Other causes include Crohn's disease, abdominal tumors, and radiation enteritis.[2] SBS is characterized by an inability to maintain protein–energy, fluid, electrolyte, and micronutrient balance, resulting in diarrhea, dyselectrolytemia, and deficiencies.[1-3] The short length of the remnant small bowel decreases the transit time, causing unabsorbed carbohydrates (CHO) to reach the colon and undergo fermentation by the colonic bacteria.[1-3] This causes bacterial overgrowth which results in more malabsorption, metabolic acidosis, and the likelihood of sepsis, and mortality.[1-3]

Metabolic acidosis occurs due to multiple causes such as sepsis, hypoxemia, cardiogenic shock, and liver failure. It is mainly due to overproduction of L-lactic acid, the predominant form of lactate found in the blood whenever there is increased anaerobic metabolism, which can be detected in specific laboratory tests, namely lactic acid assay.[4] In contrast, its enantiomer, D-lactic acid, is produced in very small quantities, due to fermentation of unabsorbed CHO in the colon by commensal bacteria.[4,5] This usually remains undetected, as D-lactic acid cannot be detected by the aforementioned assay

Address for correspondence: Dr. Ashish Prasad, Consultant, Paediatric Surgery and Paediatric Urology, BLK-MAX Center for Child Health, BLK-MAX Super Speciality Hospital, New Delhi - 110005, India.
E-mail: prasadaashish@gmail.com

Submitted: 22-Nov-2021 **Revised:** 31-Jan-2022
Accepted: 03-Feb-2022 **Published:** 25-Feb-2022

Access this article online

Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_347_21

How to cite this article: Jain P, Prasad A, Sharma R, Vasudevan V. An unusual cause of acute encephalopathy: D-lactic acidosis secondary to short bowel syndrome. Indian Pediatr Case Rep 2022;2:52-5.

used to estimate L-lactic acid. As explained earlier, there is increased CHO fermentation in SBS, which means the levels of D-Lactate will increase. This results in a variety of neurological symptoms (slurred speech, ataxia, gait disturbances, weakness, lethargy, tachypnea, and rarely acute encephalopathy),[5] and a typical metabolic profile (metabolic acidosis, high anion gap, but with normal lactate levels).[5]

We describe a postoperative case of SBS who got repeatedly hospitalized for neurological presentations, and was subsequently diagnosed as D-lactic acidosis. We also present a brief systemic review of literature. The goal of sharing this case is to sensitize pediatricians to ask about previous surgery and explore the possibility of SBS in the setting of acute encephalopathy with unexplained metabolic acidosis.

Clinical Description

A 5-year-old boy, postoperative case of SBS presented to our emergency department with progressively increasing lethargy for 2 days. The mother said that though responding to all the commands, the child was displaying excessive sleepiness throughout the day. There were no associated seizures, abnormal movements, sudden onset of abnormalities in vision and hearing, deviation of eyes, difficulty in swallowing or chewing, drooling, facial asymmetry, and neck stiffness. There was no history suggestive of decreased movement or use of limbs, cranial or focal neurological deficits, or sensory impairments. There was no history of fever, trauma, dog bite, accidental drug ingestion, vomiting, emanation of any unusual odor, abdominal pain, abdominal distention, jaundice, pallor, or difficulty in breathing. The clinical phenotype appeared to be of acute, noninfectious, and nontraumatic encephalopathy. Further probing revealed that the child had diarrhea for the last 2 days. He had multiple watery stools, small amount, without any blood. The child was passing urine with the same frequency as before the onset of illness. The child was born to a nonconsanguineous couple with immunization appropriate for age. The family history was unremarkable. There was no significant or similar complaints in other family members or neighbors. The child was not on any chronic medication. The child had a significant past history of undergoing extensive small bowel resection 8 months earlier at our center, for intestinal gangrene secondary to superior mesenteric vein thrombosis (for which low molecular weight heparin [LMWH] was started), diagnosed when the child presented with abdominal pain and bleeding per rectum. Initially approximately 110 cm of jejunum and 10 cm of ileum had been preserved along with ileocecal junction. The postoperative period had been stormy: the child had required mechanical ventilation for 72 h and developed peritonitis that warranted exploratory laparotomy and requiring further resection of small bowel due to areas of fresh gangrene identified in the terminal ileum. After the second operation, around 95 cm of jejunum and 5 cm of terminal ileum including the ileocecal junction were left. The child required prolonged nutritional rehabilitation comprising total parenteral nutrition and hydrolyzed feeds. Enteral autonomy was achieved after 2 months of hospitalization, and he was discharged on a normal diet, vitamin and mineral supplementation, and continuation of LMWH. Thrombophilia workup had been done as per standard protocol, and found to be normal.

Management and Outcome

At present admission, it was noted that the airway, breathing, and circulation were not compromised. The preliminary impression was that of a drowsy child who was transiently arousable on painful stimulation. The heart rate was 120 beats/minute, respiratory rate 22/min, capillary filling time <2 s, blood pressure of 100/70 mmHg (90th centile), temperature 98.5°F, and saturation 98% at room air. The weight and height of the child were 14.5 kg and 91 cm, respectively, while the body mass index (BMI) was 16.9, all of which were within the normal range. There were signs of some dehydration. General physical examination did not reveal presence of pallor, rashes, cyanosis, jaundice, or signs of external trauma. There was no pedal edema and other signs of nutritional deficiencies. Salient central nervous system findings were a Glasgow Coma Scale (GCS) score of 11/15 (E3, M4, V4), bilateral pupils of normal size and reaction, normal fundus, and absence of focal cranial or peripheral neurological deficit. The tone, power, and deep tendon reflexes appeared normal as far as could be tested. There were no meningeal signs. Cerebellar signs could not be tested due to the lethargy. The remaining systemic examination was normal.

Based on the above, we managed to exclude acute infectious or traumatic encephalopathy. The differential diagnoses that was actively considered to explain the acute encephalopathy was mainly metabolic, like hypoglycemia and dyselectrolytemia or uremia, given the setting of diarrhea. We planned hematological, biochemical, and microbiological workup of the child, accordingly. The child was resuscitated with isotonic intravenous (IV) fluids, calculated as per standard protocol.

The first tier biochemical tests were within normal limits. {blood sugar (110 mg/dl), serum electrolytes (serum sodium, potassium, and chloride were 137 meq/L, 3.7 meq/L, and 109 meq/L, respectively), renal and liver function tests (urea 28 mg/dl, creatinine 0.5 mg/dl, total/direct bilirubin 0.2/0.19 mg/dl, respectively, albumin 3.8 g/dl, serum aspartate transaminase and serum alanine transaminase 35 IU/L and 28 IU/L, respectively)}. Thus, we excluded hypoglycemia, dyselectrolytemia, uremia, and hepatic derangement. A blood gas analysis showed severe metabolic acidosis with respiratory compensation (pH 7.24, pCO_2 22 mmHg, HCO_3 7 mmol/L, with high anion gap [21 mmol/l; normal level 12–16 mmol/L] and lactate 1.5 mmol/L [normal range <2 mmol/L]). Serum ammonia was within normal limits (76 ug/dl;

normal <100 ug/dl). Routine urine examination showed normal pH and was negative for ketones.

The sepsis workup was negative: Hb 12 g/dl, total leukocyte count 12,000/cmm with 64% neutrophils and 44% lymphocytes, total platelet count 2.5 lakh/cmm, C-reactive protein 3.5 mg/dL, and sterile blood and urine cultures. Stool routine microscopy was normal. A lumbar puncture was not done as there was no history of fever, the workup for sepsis was negative, and the sensorium improved markedly within a few hours. The child's dehydration and metabolic acidosis resolved within the next 48 h, respectively. Based on the clinical phenotype, a final diagnosis of acute gastroenteritis with some dehydration and metabolic acidosis was kept. The child was discharged after 5 days of admission.

After 2 months, he was readmitted with excessive drowsiness for 1 day. This time parents noticed that he had slurring of speech, was unable to walk steadily since morning, and was frequently falling down. Apart from this, and the fact that he did not have diarrhea, the presentation was the same as the first one. At admission vitals were stable, there was no dehydration, and GCS score was 10/15 (E2M4V4). No other abnormalities were identified on examination. The investigations again revealed severe metabolic acidosis with respiratory compensation (pH 7.15, pCO_2 25 mmHg, HCO_3 10 mmol/L with high anion gap of 24 mmol/L, and normal lactate of 1 mmol/L). The routine first tier hematological, biochemical, and microbiological investigations were normal.

The findings of unexplained severe metabolic acidosis with a high anion gap and normal lactate levels, in a setting of a child with previous extensive intestinal resection, prompted us to suspect a diagnosis of D-lactic acidosis secondary to SBS. We revisited the history to look for specific clues like excessive intake of sweetened beverages and sweets. It emerged that he had attended a family function at the time of the first episode, and currently, he had just celebrated his birthday. Further investigations were planned accordingly. The stool was positive for reducing substances and fat globules. Vitamin B12 (296 pg/ml) and Vitamin D (45 ng/ml) were normal, probably since he was receiving supplements.

Once SBS was established clinically, we tried to objectively prove that the metabolic acidosis was due to D-lactic acid, by estimating the levels. However, this test was not available in standard laboratories. Since no other diagnostic alternatives were available, we decided to keep the child nil per orally (stop enteral CHO) and start IV bicarbonate to correct the metabolic acidosis, as per standard protocol. A dramatic improvement in sensorium was seen over the next 12 h. The metabolic acidosis resolved within 48 h (pH 7.3, HCO_3 16.5 mmol/L, pCO2 32 mmHg, and lactate 1.0 mg/dl). The child was started on a low CHO diet and oral metronidazole (to counter bacterial overgrowth). There was no recurrence of lethargy or concurrent metabolic acidosis, and the child was discharged after 5 days. A low CHO diet was planned in consultation with a dietician, the goals being prevention of future recurrences, and maintenance of adequate calories, proteins, and micronutrients.

The child was kept under regular follow-up. He subsequently had 6 admissions for D-lactic encephalopathy over a period of 4 years. Each time it occurred when there was a dietary lapse for some reason. The child is otherwise doing well. He is now 9 years old, is active, studying in class 4, and has a good academic performance. His height (100 cm), weight (16 kg), and BMI (16) are all normal. Although a formal assessment of his intelligence quotient or psychometric testing has not been undertaken, till date he does not exhibit any clinical symptom or sign of any permanent neurological sequelae.

Discussion

D-lactic acidosis causing D-lactate encephalopathy is an uncommon metabolic complication of SBS.[4-6] The short length of the postoperative small bowel remnants leads to CHO being incompletely digested. These undigested macronutrients reach the colon and undergo fermentation by the colonic bacteria.[6-8] This results in excessive production of organic acids that exceeds the amount that can be normally metabolized by the body. Thus, there is an accumulation of organic acids, short chain fatty acids, and D-lactate, all of which result in metabolic acidosis and an increased anion gap.[7,8]

The increased acidity of the gut environment favors the growth of acid-resistant bacteria like lactobacillus species, which in turn produce D-lactate.[6] Another reason for an increase in D-lactate levels is the inhibition of D-2-hydroxydehydrogenase (the primary enzyme that metabolizes D-lactate) by the acidic environment.[7] Other factors which can contribute to increased levels are poor colonic motility, dehydration, and renal and hepatic failure.[7,8] However, although the D-lactate levels are increased, paradoxically the lactate levels will remain normal, due to failure of routine tests to detect this form.

The body can deal with excess L-lactate as it is metabolized quickly, but has limited capacity to deal with accumulation of its "D" isomer, due to the inhibition of D-2-hydroxydehydrogenase (the primary enzyme that metabolizes D-lactate) by the acidic environment.[6,8] The pathogenesis of encephalopathy is complex and poorly understood. The two main mechanisms that have been proposed are: (1) a direct toxic effect of D-lactate on the brain since it crosses the blood–brain barrier; and (2) low levels of D-2-hydroxydehydrogenase in the brain.[7,8] A poor correlation between the D-lactate levels and clinical presentation has been reported in some cases.[8] In our case, there was no other identifiable cause for the acute encephalopathy or the characteristic acid-base abnormalities (metabolic acidosis with increased anion gap, in the presence of normal lactate and ketone levels). Although we were unable to demonstrate increased levels of D-lactate by laboratory tests, it can be argued that the child responded well to the trial of decreased

CHO in the diet by exhibiting resolution of metabolic acidosis. The recurrence of symptoms and metabolic acidosis whenever there was noncompliance can in a way also be considered failure of a therapeutic trial.

The clinical manifestation of D-lactic acidosis includes recurrent episodes of encephalopathy. Clinical manifestations include altered mental status, slurred speech, ataxia, gait disturbances, and confusion. Cerebellar signs are prominent in D-lactic acidosis as the cerebellum metabolizes D-lactate poorly.[4] A systemic review of 45 pediatric cases with SBS and D-lactic acidosis,[7] observed that the mean age group was 5.1 years (2.8–9 years), and the most common presentation was altered mental status (78%) and Kussmaul breathing (24%).

The diagnosis of D-lactate encephalopathy is challenging because of the various other causes of noninfectious and nontraumatic encephalopathy that need to be excluded (especially at initial presentation). In the high-income countries, the diagnosis is confirmed by a serum level of D-lactate levels >3 mmol/L (normal undetectable or <0.2 mmol/L) that is estimated by D-lactate assay. However, as was seen in our case despite the best of our efforts and availability of finances, we were unable to get these levels estimated in India.[4] In these circumstances, when no other option is available and there is a setting of SBS, indirect evidence like improvement of clinical and laboratory parameters with treatment should be used to clinch the diagnosis.

The goals of therapy are correction of acidosis, dietary modification (restriction of CHO intake to approximately 1/3rd the recommended dietary allowance), frequent and low volume meals, and measures to prevent further episodes. The acute phase is managed by correction of dehydration with lactate free IV fluids and IV bicarbonate along with restricting oral intake of CHO.[8] The role of antibiotics and probiotics is still controversial.[6,8] Nonabsorbable oral antibiotics (clindamycin, vancomycin, metronidazole, neomycin, etc.) may reduce D-lactic acidosis by altering some of the gut microbial flora, but may paradoxically also lead to overgrowth of the D-lactate producing bacteria.[6] A similar observation has been made with the use of probiotics.[6,7] Prevention of recurrence can be attempted by restricting simple CHO (since these get metabolized to D-lactate very rapidly). Ensuring strict compliance in children will always remain a major challenge, as was evident in this case.

Lessons learnt

- Children who have undergone any surgical intervention involving resection of the small intestines should be monitored for short bowel syndrome
- D-lactate encephalopathy should be considered in such children presenting with acute encephalopathy in the presence of metabolic acidosis, high anion gap, and normal levels of blood lactate and urinary ketones
- The diagnosis D-lactate encephalopathy is challenging because of non-availability of D-lactate estimation
- Clinical and biochemical response to therapeutic trials may be considered helpful in establishing diagnosis when laboratory tests are not available.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parent. The legal guardian has given his consent for the images and other clinical information to be reported in the journal. The guardian understands that the name and initials will not be published, and due efforts have been made to conceal the same, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Batra A, Keys SC, Johnson MJ, *et al*. Epidemiology, management and outcome of ultrashort bowel syndrome in infancy. Arch Dis Child Fetal Neonatal Ed 2017;102:F551-6.
2. Chandra R, Kesavan A. Current treatment paradigms in pediatric short bowel syndrome. Clin J Gastroenterol 2018;11:103-12.
3. Höllwarth ME, Solari V. Nutritional and pharmacological strategy in children with short bowel syndrome. Pediatr Surg Int 2021;37:1-15.
4. Zhang DL, Jiang ZW, Jiang J, *et al*. D-lactic acidosis secondary to short bowel syndrome. Postgrad Med J 2003;79:110-2.
5. Obando Pacheco P, Navas López VM, Yahyaoui Macías R, *et al*. D-lactic acidosis in a ten months old infant with short bowel syndrome: Early suspicion equals early treatment. An Pediatr (Barc) 2016;84:56-7.
6. Uchida H, Yamamoto H, Kisaki Y, *et al*. D-lactic acidosis in short-bowel syndrome managed with antibiotics and probiotics. J Pediatr Surg 2004;39:634-6.
7. Bianchetti DG, Amelio GS, Lava SA, *et al.* D-lactic acidosis in humans: Systematic literature review. Pediatr Nephrol 2018;33:673-81.
8. Kowlgi NG, Chhabra L. D-lactic acidosis: An underrecognized complication of short bowel syndrome. Gastroenterol Res Pract 2015;2015:476215.