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Probiotics Provoked D-lactic Acidosis in Short Bowel Syndrome: Case Report and Literature Review

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Abstract D-lactic acidosis is a rare complication of short bowel syndrome. Clinically there are episodes of encephalopathy and metabolic acidosis with an increased anion gap. Formation of D-lactic acid by the abnormal gut flora, together with its impaired metabolism results in its accumulation and subsequent effect on the central nervous system. In this article we reported a boy with short bowel syndrome and D-lactic acidosis provoked by ingestion of probiotics. The probiotics are in the form of capsules and probiotic-containing formula. We had also reviewed the paediatric cases of D-lactic acidosis and discussed its biochemistry, pathogenesis, clinical features, diagnosis and treatment. With more understanding of its mechanism, we stated that D-lactic acidosis can be treated as well as provoked by probiotics.

Key words D-lactic acidosis; Paediatric; Probiotics; Short bowel syndrome

Introduction

D-lactic acidosis has been well recognised by the veterinarians as a cause of metabolic acidosis in the ruminants.[1] It occurs in ruminants overfed with grains or other readily fermentable carbohydrates. The gut floras ferment the carbohydrates with production of D-lactic acid and it is subsequently absorbed into the bloodstream. It was first described in human in 1979 by Oh et al.[2]

D-lactic acidosis is a rare complication of short bowel syndrome which may result from surgical resection of the intestine or intestinal bypass surgery for treatment of obesity.[3] Clinically there are episodes of encephalopathy and metabolic acidosis with an increased anion gap.

In this report we presented a boy with short bowel syndrome who presented with repeated episodes of D-lactic acidosis following administration of a probiotic and a probiotic-added formula. We have also reviewed other reported cases of D-lactic acidosis in the literature. The clinical features, biochemical results and the modality of treatment were reviewed. Finally we will discuss on the use of probiotics and prebiotics in the management of short bowel syndrome and D-lactic acidosis.

Case Report

Our patient is a Chinese boy who was born in Hong Kong in June 1996. At the age of two he was diagnosed to have stage III right adrenal neuroblastoma. The tumour was inoperable on presentation so he was commenced on chemotherapy. He was given a course of N6 protocol for neuroblastoma, which comprised of combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, cisplatin, etoposide) plus monoclonal antibody 3F8. He could not tolerate the side effect so was switched to then OPEC combination chemotherapy (vincristine, prednisolone, etoposide, chlorambucil). After four months the tumour decreased in size and was resected with right nephrectomy and partial hepatectomy, followed by chemotherapy and tumour bed irradiation. The

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chemotherapy was completed in February 1999.

In March 1999, he complained of sudden onset of abdominal pain, with bilious vomiting and shock. He underwent an emergency laparotomy and found there was mid-gut volvulus with only 50 centimeters of jejunum and the most distal three centimeters of terminal ileum viable. The ileocaecal valve was preserved. Post-operatively he was put on total parenteral nutrition and elemental diet (Neocate, SHS International Ltd). He developed severe diarrhoea which required octreotide (Sandostatin, Novartis). He also suffered from hypomagnesemia which required weekly intravenous magnesium infusion and daily oral magnesium supplement. In June 2000, there was central line problem so the parenteral nutrition was stopped. The elemental diet (Neocate, SHS International Ltd) was continued while he was allowed to start diet as tolerated.

Nocturnal parenteral nutrition was restarted in September 2000 because of failure to thrive. In July 2001 there was central line problem again so the central line was removed. He was allowed to have diet as tolerated in addition to the elemental formula (Neocate, SHS International Ltd.). He was also started with a probiotic capsule Infloran Berna (Berna Biotech) which contained *Lactobacillus acidophilus* and *Bifidobacterium infantis* hoping to reduce his diarrhoea.

Started from November 2001, he experienced repeated episodes of lethargy, weakness, slurred speech and ataxia. Physical examination showed Kussmaul's breathing, confusion, generalised weakness and ataxia. There was no fever. Blood tests included complete blood picture, electrolytes, blood urea nitrogen, creatinine, liver function tests, and blood glucose were all normal. Serum magnesium level was decreased. During each episode he was put on intravenous fluid and the oral feeding was suspended. The hypomagnesemia was corrected with intravenous magnesium infusion. Each time the neurological condition resolved with the aforementioned management. The encephalopathic symptoms were initially thought to be due to hypomagnesemia, but the encephalopathy could not be completely explained by the low serum magnesium level.

He was admitted to the hospital again on 25th February 2002, presented with malaise, confusion and slurred speech for one day. Blood tests showed normal full blood count, normal liver and renal function tests with normal sodium, potassium and chloride level. Magnesium was 0.37 mmol/L (normal range 0.67 to 1.01 mmol/L). Plasma ammonia was 25 umol/L (normal range 21 to 50 umol/L). Blood gases showed pH 7.20, bicarbonate 10 mmol/L, and base excess -17 mmol/L. Anion gap was 26.6 mmol/L. The computer tomography of the brain was normal, and the electroencephalogram was also normal.

The hypomagnesemia was corrected with magnesium infusion, but the encephalopathy persisted. In view of the presence of short bowel syndrome, with widened anion gap metabolic acidosis, D-lactic acidosis was suspected. Blood lactate level was 1.1 mmol/L (normal range 0.7 to 2.1 mmol/L) as measured by conventional assay method, which would only detect L-lactate. Serum D-lactate assay was unavailable at that time. In the urine there was large amount of lactic acid detected by gas chromatography. There were also presence of other organic acids in the urine including 4-hydroxy-phenyl-acetic acid, 4-hydroxy-phenyl-lactic acid, and phenyl-lactic acid. The discrepancy of lactic acid between blood and urine was compatible with D-lactic acidosis. Upon review of the previous attacks, the episodes of acidosis usually presented after an increase in oral intake, particularly of carbohydrates. The metabolic acidosis was corrected with intravenous bicarbonate, and he was given oral metronidazole for two weeks to eradicate the abnormal gut flora which produced the D-lactate. The probiotic was also stopped.

He continued to have attacks of D-lactic acidosis once every few months time precipitated by increased oral feeding. Each time the attack was treated with intravenous bicarbonate, suspension of oral feeding and oral metronidazole. Different regimes of oral antibiotic prophylaxis including neomycin, metronidazole, ampicillin and trimethoprim-sulfamethoxazole were started; but they failed to prevent further episodes of D-lactate acidosis. He was started on oral vancomycin prophylaxis for five consecutive days per month since September 2003, which prevented further episodes of D-lactic acidosis. The oral vancomycin was stopped in May 2004 because of profuse diarrhoea and worry of development of drug resistance organisms.

He remained well and was taking three main meals, supplemented with Neocate (SHS International Ltd.) 1000 ml per day. We tried to switch the formula to Pediasure (Abbott Laboratories) as it was less expensive and more palatable. He tolerated well without any diarrhoea. His body height was maintained along the 10th percentile, and his body weight along the 3rd percentile. He remained free from attack of D-lactic acidosis until June 2005. He presented again with an episode of encephalopathy. Blood test showed high anion gap metabolic acidosis with serum D-lactate level up to 11.4 mmol/L. He was managed with intravenous bicarbonate and nil by mouth.

His mother revealed the patient had been taking the Pediasure formula with a new packing (Pediasure Protect,

Abbott Laboratories) since May 2005, after exhausted the old packing stock. The new packing stated that probiotics were added. Abbott Laboratories Hong Kong confirmed that the probiotics were added into the Pediasure formula since March 2003, with the new packing and named Pediasure Protect. The probiotics were *Lactobacillus acidophilus* and *Bifidobacterium spp.* which were same as the probiotic capsule Infloran Berna (Berna Biotech) he took in 2001. It was likely that his gut was colonised with the D-lactate forming bacteria again and leading to the D-lactic acidosis. The bacteria were eradicated with a three-day course of oral vancomycin.

For the neuroblastoma, he remained in remission without recurrence of the tumour.

Literature Review

The computerised Medline database was searched using the headings "D-lactic acidosis" and "D-lactate encephalopathy" from 1979 until 2005. The reference lists of the articles were also reviewed, to search for any cases missed in the Medline search. From the above search we were able to collect 43 cases from 38 reports.

There was a case described in 1977 in which the D-lactic acidosis was thought to be due to inborn error of metabolism in a mentally retarded infant without any intestinal disease.[4] A nine-year old boy with short bowel syndrome and D-lactic acidosis was reported in a German literature in 1994, the case was not included as English translation of the report was unavailable.[5] There were several cases in which the clinical features were suggestive of D-lactic acidosis but the diagnosis was not confirmed as the authors were not aware of the diagnosis of D-lactic acidosis.[3,6-9]

We further selected patients who were 18 years old or younger at presentation for further analysis. There were 21 children of D-lactic acidosis from 15 reports.[10-24] Each report was analysed for the following parameters: sex and age of the patient, cause of short bowel syndrome, time between onset of D-lactic acidosis and intestinal operation, clinical presentations, precipitating factors, blood pH, anion gap, peak serum D-lactate level, treatment and outcome. The result of stool culture was also reviewed if available.

Results

The patients' information was shown in Table 1. The condition of D-lactic acidosis was more frequent in boys than in girls, with the ratio of 15:5 in our series (in one report the sex of subject was not stated). The average age at presentation was 6.4 years old (standard deviation 4.8 years), with the range of 18 months to 18 years old. The cause of short bowel syndrome was intestinal resection in all cases, either as a result of volvulus or congenital gastroschisis in the majority of cases (18 cases). In one case there was necrotizing enterocolitis requiring gut resection (patient 12), another one with thrombosis of mesenteric vessels (patient 2). There was an eighteen years old boy suffered from stabbed injury with post-operative bowel ischaemia requiring bowel resection (patient 1). The average time eclipsed from the intestinal surgery to the time of presentation of D-lactic acidosis was 32 months, with the range from two months to ten years.

The clinical features were given in 15 patients (Figure 1). The most common manifestation was impaired conscious level, which ranged from somnolence, lethargy, drowsiness, to lost of consciousness and coma. It was present in 13 (87 percent) of the 15 patients. In the remaining two patients, one of them has stupor (patient 4), another one has confusion (patient 6). In other words, all of the cases had impaired mental status. Other clinical features included ataxia, gait disturbance, slurred speech, tachypnoea, hyperventilation, weakness, headache, aggressive behaviour, inability to concentrate, agitation, carbohydrate craving, "unhappy", pallor, vertical nystagmus, bruxism, opisthotonus, irritability, and nausea.

The attacks were precipitated by increased oral intake, particularly carbohydrates. In two patients there was ingestion of yogurt containing Lactobacillus and/or Lactobacillus tablets before the acidosis (patients 6 and 18). There was also intake of trimethoprim-sulfurmethoxazole for treatment of otitis media and bowel bacterial overgrowth respectively in these two patients prior to the attack.

Blood pH was reported in 13 patients, in which all of them had acidosis (Table 1). The mean pH was 7.19 with the range of 7.01 to 7.28 (standard deviation 0.08). The serum anion gap was also increased, the mean value was 22.2, with the range of 16.9 to 28.0 (standard deviation 3.32). The mean peak serum D-lactate level was 6.58 mmol/L, with the range of 4.0 to 10.0 mmol/L (standard deviation 1.95 mmol/L). We have excluded two values of serum D-lactate level during our calculation. In patient 3 the peak serum D-lactate was 0.85 mmol/L, while the fecal D-lactate was high (13.11 mmol/L). In patient 10 the serum D-lactate level was 1.1 mmol/L, but it was measured twelve months after the start of treatment. Three patients was reported to have abnormal urinary organic acid profile (patients

Table 1 Review of paediatric patients with short bowel syndrome developing D-lactic acidosis

Patient No.	Reference No.	Age (yr)	Sex	Time from surgery (months)	pH	Serum Anion gap (mmol/L)	Serum D-lactate (mmol/L)	Stool Culture
1	10	17	M	5	7.26	28	6.7	
2	11	3	M	24	7.23	27.2	‡,§	
3	12	2.5	F	18	7.28		†	*Lactobacillus buchneri*
4	12	5.75	M	24	7.12		8.5	*Lactobacillus fermenti IVa/ fermentum*
5	13	18	M	6	7.24	23.5	5.1	*Bacteroids ruminicola*
6	14	5	M	2	7.11	21	10	*Lactobacillus acidophilus*
7	14	1.5	M	12	7.25	21	7	
8	15	9	F	15				*Lactobacillus acidophilus, Lactobacillus fermenti IVa/ fermentum*
9	16	8	M	28	7.13	21.1	‡,§	*Lactobacillus spp.*
10	17	1.67	M	10	7.17	22	†	
11	18	10	M	120			6.1	*Lactobacillus plantarum, Lactobacillus salivarius*
12	19	2.5	NS	30				
13	19	4	M	48				
14	19	4	F	48				
15	19	2	F	24				
16	19	11	M	72				
17	10	4	F	24				
18	21	5	M	60	7.01	16.9	§	*Lactobacillus spp.*
19	22	12	M	12	7.21	24	5.23	
20	23	2.5	M	26	7.21	18.5	4	
21	24	5.5	M	66	7.25	21.4	‡	
Mean		6.38		32.10	7.19	22.24	6.58	
SD		4.83		28.44	0.08	3.32	1.94	

NS = not stated; SD = standard deviation; †low serum lactate level; ‡abnormal urine organic acid profile; §elevated urine D-lactic acid

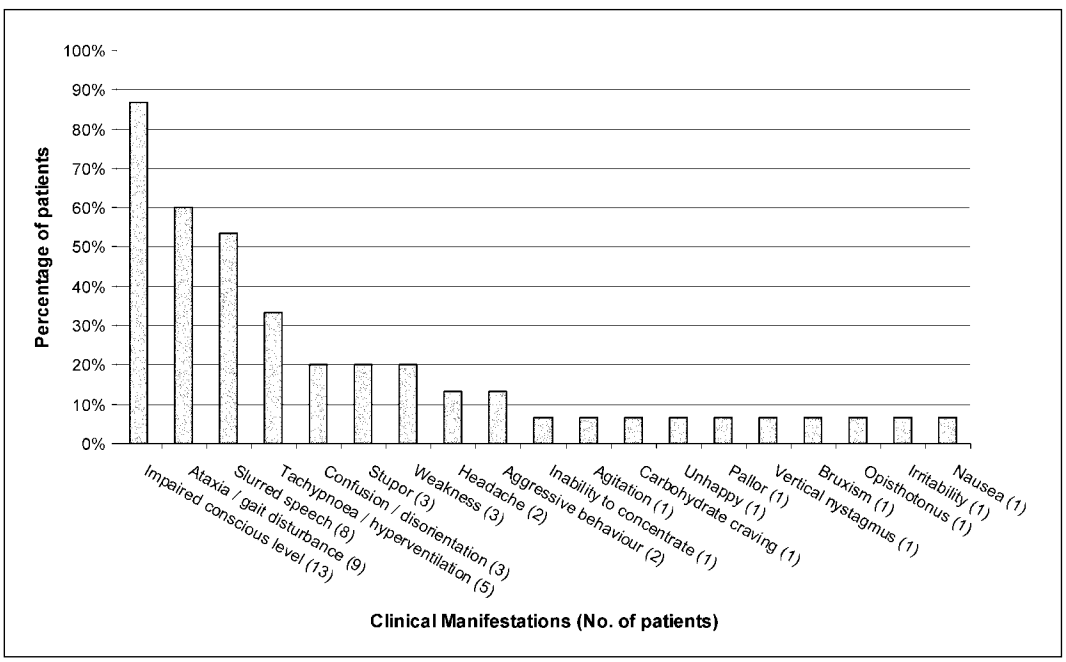

Figure 1 Clinical manifestations of the 15 reviewed paediatric D-lactic acidois cases.

2, 9 and 21) consisting of phenyl-lactic acid, 4-hydroxy-phenyl-lactic acid and 4-hydroxy-phenyl-acetic acid. In two of them (patients 2 and 9) the urinary D-lactic acid were elevated. In patient 18 the urinary D-lactic acid was measured only.

Stool culture result was given in eight patients (Table 1). In those patients nearly all (seven of eight) of their stool grew Lactobacilli of different species, while the remaining patient's stool was positive for Bacteroids, in which all have been shown to produce D-lactate in vitro. The production of D-lactate by the stool organisms was demonstrated in a number of cases (patients 3, 4, 6, 8 and 11).

For the treatment, 13 patients were given oral antibiotics, including neomycin, kanamycin, vancomycin and metronidazole. The treatment period ranged from five days to 14 months. Oral neomycin and another antibiotic (name was not given) were reported to be ineffective in two patients (patients 15 and 21). Dietary carbohydrate was restricted in five patients (patients 1, 5, 19, 20 and 21), in another patient the carbohydrate was given in polymeric form (patient 8). Three patients were given probiotics, including "Julia flora" (patient 2), Lactobacillus plantarum 299V and Lactobacillus GG (patient 16), Bifidobacterium breve Yakult and Lactobacillus caesei Shirota (patient 17). Galactooligosaccharides was given as a prebiotic with the latter two probiotics. Other treatment modalities included oral or intravenous bicarbonate, bisacodyl suppositories, intestinal washout with hypertonic polyethylene glycol solution, hypertonic saline enemas and Bianchi procedure. The follow up period ranged from two months to three years.

Discussion

Biochemistry of D- and L-lactic Acid

D- and L-lactic acids are optical isomers of each other. In humans L-lactic acid is produced by the anaerobic carbohydrate metabolism forming pyruvic acid and then subsequently converted into L-lactic acid by the enzyme lactic dehydrogenase. The enzyme is isomer specific, and mammals only possess L-lactic dehydrogenase, which will produce L-lactic acid. D-lactic acid, although can be generated in small amount by the methyl-glyoxal pathway in the human body,[25] is mainly produced by the intestinal bacteria or obtained from an exogenous source. The exogenous source can be from dietary intake of yogurt, fermented fruits and vegetables such as prickles or sauerkrauts. Lactated Ringer solutions and peritoneal dialysis fluids contain both D- and L-lactic acids. Jorens et al has reported a case of D-lactic acidosis resulted from incidental massive oral ingestion of propylene glycol.[26] The propylene glycol was converted into D-lactate via the methyl-glyoxal pathway.

Formation of D-lactic Acid in Short Bowel Syndrome

In normal human subjects D-lactic acid is absent or only present with minimal amount in the blood stream. The carbohydrate is nearly completely absorbed by the intact small intestine. In patients with short bowel syndrome, especially with small bowel resection and an intact colon, the unabsorbed carbohydrates become available to the colonic bacteria. Similar condition is also present in those patients with intestinal bypass for management of obesity.[27] With the carbohydrates as a substrate, large amounts of lactic acid will be formed if the colonic bacteria are lactic acid producers. Both D- and L-lactic acids are formed but only the D-lactic acid accumulates because of its slower metabolism, resulting in D-lactic acidosis. The carbohydrate load may be increased after a big meal, or resulting from a transition from a parenteral diet or strictly controlled elemental diet to a more liberal oral diet. The presence of abnormal intestinal flora is also essential for the development of D-lactic acidosis. In patients with D-lactic acidosis, it was found that their intestinal flora changed from the normal gram negative colonic bacteria to gram positive anaerobes such as Lactobacillus species. Some of the Lactobacillus has been shown to produce D-lactic acid in vitro, including *Lactobacillus acidophilus, Lactobacillus buchnori, Lactobacillus fermenti IVa, Lactobacillus plantarum*, and *Lactobacillus salivarius*.[12,14,18] Bacteroids ruminicola produces D-lactic acid as well.[13]

There are three mechanisms of the flora change. Firstly, carbohydrate fermentation in the colon will cause a decrease in the colonic pH. The acid resistant bacteria such as the Lactobacillus species will be selected out and become predominant. They continued to produce lactic acid and maintained a low pH environment in the colon, to favor their growth.[18] Secondly, administration of antibiotics can select out the resistant bacteria. Coronado[28] reported a case of D-lactic acidosis in a 50 year old man with jejunoileal bypass after taking 14 days of doxycycline and 3 days of trimethiprom-sulfamethoxazole. His stool culture grew *Lactobacillus acidophilus* which was resistant to doxycycline and trimethiprom-sulfamethoxazole. A boy in our case series (patient 6)[14] was also treated with a course of trimethiprom-sulfamethoxazole for otitis media one week before the onset of D-lactic acidosis. His stool culture also

grew *Lactobacillus acidophilus*. Thirdly, there may be direct ingestion of the Lactobacillus. Lactobacillus containing foods include yogurt, other fermented diary products, Lactobacillus tablets, probiotics containing Lactobacillus or probiotics-added milk formula.

The time lag from the intestinal surgery to the presentation of D-lactic acidosis observed in our case series may represent the time needed for the intestinal flora to change.[13] It ranged from two months to ten years in our paediatric case series. In an adult patient, D-lactic acidosis had been reported to occur 23 years after a jejuno-ileal bypass surgery.[29]

In our reported case there was intestinal resection as a result of volvulus, and a transition from parenteral nutrition to an oral diet. He had taken the probiotic Infloran Berna (Berna Biotech) which contained *Lactobacillus acidophilus* and *Bifidobacterium infantis* before he started to experience recurrent episodes of D-lactic acidosis. It was three years and eight months after the intestinal surgery and four months after taking the Lactobacillus-containing probiotic. Each attack was precipitated by an increase in oral intake, particularly with carbohydrates. Stool culture result during the attacks was not available; otherwise it might demonstrate the presence of Lactobacillus in the stool. Further episodes of D-lactic acidosis were prevented by prophylactic oral vancomycin. However, the D-lactic acidosis recurred as a result of ingesting milk formula containing Lactobacillus.

Metabolism of D-lactic Acid

When the condition of D-lactic acidosis was first described in human by Oh et al in 1979,[2] it was thought that the metabolism of D-lactic acid is very slow in human. Subsequent studies showed that healthy human subjects can metabolise D-lactic acid rapidly.[30] The L-lactic acid is metabolised by the L-lactate dehydrogenase (L-LDH). Although humans do not possess D-lactate dehydrogenase (D-LDH), they can still metabolise D-lactic acid with the D-2-hydroxyacid dehydrogenase (D-2-HDH).[31] The D-2-HDH is an intramitochondrial flavoprotein with highest activity in the kidney and liver. Experiments showed that in healthy human subjects, they can metabolise the intravenously or orally administrated D-lactic acid efficiently.

However, when D- and L-lactic acids are present in high concentration they will cross inhibit each other's metabolism.[31] D-lactic acidosis results from its over-production and accumulation. The formation of organic acids during bacterial carbohydrate fermentation also inhibits the oxidation of D-lactic acid, which is prerequisite for its metabolism.[31] These may explain why administration of D-lactic acid to healthy human subjects fails to produce D-lactic acidosis.

Mechanism of Neurological Manifestations

The neurological manifestations in D-lactic acidosis cannot be explained by the acidosis alone, as patients with acidosis resulting from other causes do not demonstrate the clinical features of D-lactic acidosis. In some patients with D-lactic acidosis the correction of acidosis with bicarbonate failed to improve the neurological symptoms. There are two proposed mechanism for the encephalopathy. The first one is the direct toxic effect of D-lactic acid to the brain.[8,32] D-lactate can diffuse into the brain cells, causing decrease in intraneuronal pH, inhibits the pyruvate decarboxylation by the pyruvate dehydrogenase comlpex. Subsequently the production of acetyl CoA and adenosine triphosphate is impaired, resulting in altered neurotransmitter production. The cerebellum has particularly little reserve of pyruvate dehydrogenase complex, thus the cerebellar symptoms such as ataxia and slurred speech is prominent in D-lactic acidosis. The activity of pyruvate dehydrogenase complex is also impaired by thiamine deficiency. This may explain the difference in susceptibility to D-lactic acid in different subjects.

Another theory is the presence of unidentified by-products produced along with the D-lactic acid in the intestine by the gut flora. In the cattle there are different substances identified such as ethanol, histamine, tyramine, formate and endotoxins.[1] Organic acids such as hydroxyl-phenyl-lactic acid and phenyl-acetic acid were shown in patients with D-lactic acidosis.[2,11,16,24] However, it is not clear whether these substances or the presence of other unknown compounds is causative of the neurological features.

Clinical Manifestations of D-lactic Acidosis

Upon review of the patients in our case series, impaired mental status was a universal feature in D-lactic acidosis. Patients could present with confusion, stupor, or impaired conscious level ranging from somnolence, lethargy, drowsiness, to lost of consciousness and coma. There were cerebellar symptoms with ataxia, nystagmus, slurred speech and gait disturbance. Higher cognitive function impairment included aggressive behaviour, inability to concentrate, agitation, carbohydrate craving, "unhappy" and irritability. Other neurological manifestations were weakness, headache, bruxism and opisthotonus. The metabolic acidosis led to hyperventilation and tachypnoea. There were non-specific symptoms including nausea or pallor.

In our patient the presenting symptoms were lethargy, weakness, slurred speech and ataxia. Initially it was thought to be due to the hypomagnesemia. Clinical features of hypomagnesemia include generalised weakness, anorexia, hypokalemia, hypocalcemia, positive Trousseau and Chvostek signs, tetany, and generalised convulsions.[33] The neurological symptoms could not be completely explained by the low serum magnesium level, there were absence of hypokalemia and hypocalcemia, and the symptoms persisted despite correction of the hypomagnesemia. The diagnosis of D-lactic acidosis should be suspected in a patient with short bowel syndrome presenting with unusual neurological features.

Diagnosis and Laboratory Investigations

In patients with D-lactic acidosis, blood test shows a metabolic acidosis with increased anion gap. The serum lactate level as measured by conventional assay can be normal, because the L-lactate dehydrogenase used in the assay is isomer specific which will only measure L-lactate.[34] The serum D-lactate can only be measured by a specific kit utilising D-lactate dehydrogenase (Boehringer Mannheim).[2]

In our reviewed cases, serum D-lactic acid level was reported in ten patients. There is no consensus of the normal value of serum D-lactic acid level, but most studies used 3 mmol/L as a reference value. In two of the above patients the measured D-lactic acid levels were low (patients 3 and 10). One of them had high fecal D-lactate (patient 3) while another patient the D-lactate measurement was delayed.

D-lactate has a much lower renal threshold than L-lactate, so a significant amount of D-lactate will appear in the urine if the serum level is elevated; while L-lactate should not appear in the urine until a significantly high serum level (6 to 10 mmol/L) is attained.[30] Urinary lactate level is measured by gas chromatography, which will detect both D- and L-lactate.[2] Thus in the setting of a normal serum lactate level as measured by conventional assay, the elevated lactate in the urine detected by gas chromatography should be D-lactate.

Abnormal urinary organic acid profile was observed in three cases, consisting of phenyl-lactic acid, 4-hydroxy-phenyl-lactic acid and 4-hydroxy-phenyl-acetic acid. These organic acids, together with the lactic acid, were produced by the abnormal gut flora.[2,11,16,24] Although in one case (patient 21) as well as our patient the isomeric configuration of the urine lactic acid was not been determined, but as L-lactic acid only excreted in the urine when serum level exceeds 6 to 10 mmol/L, with the normal serum L-lactate level, the lactic acid appeared in the urine must be the D-optical isomer. Actually in two patients with abnormal urinary organic acid profile the lactic acid was confirmed to be D-lactic acid (patients 2 and 9). The presence of a high serum D-lactate level was also confirmed in our patient.

Treatment

As discussed in the section of D-lactic acid formation, the presence of abnormal bacterial flora, abundant carbohydrate substrate, with a short gut environment are essential in causing D-lactic acidosis. The treatment modalities are targeted on the above aspects. The treatment can be grouped into the following modalities: 1) Elimination of the abnormal D-lactic acid producing intestinal flora using antibiotics. 2) Replacement of the abnormal intestinal flora with a "good" bacteria population - the probiotics. 3) Suspension of carbohydrate substrate to the bacteria by oral restriction or use of polymeric carbohydrate. 4) Wash out of intestinal bacteria and carbohydrate substrate using saline, polyethylene glycol solution or suppositories. 5) Attempt to neutralise the acidosis using oral or intravenous bicarbonate. 6) Correction of the short gut by Bianchi procedure.

There have been no single large studies or systemic review of the treatment of D-lactic acidosis. Use of oral non-absorbable antibiotics was most commonly used, including neomycin, kanamycin, vancomycin and metronidazole. However, it was reported to be ineffective in some patients (Patients 15 and 21), and with prolonged use there is risk of evolvement of drug resistant bacteria, particularly worrisome is vancomycin resistant enterococci. Some patients experience diarrhoea with the oral antibiotics, while it was also reported to precipitate D-lactic acidosis.[28] The optimal duration of antibiotic treatment is also unclear. In some patients the symptoms recurred shortly after stopping the antibiotic, while in other patients they remained symptom free many years without antibiotics.

One of the most effective and simple treatment during the attack is suspension of oral feeding. In long term management, a carbohydrate restricted diet together with non-absorbable antibiotics seems to be effective. In one report[15] the patient remained free from attack for 30 months while on a polymeric carbohydrate diet.

The use of probiotics seems to be a potential field of further exploration. With identification of specific L-lactic acid forming bacteria, we can use it to replace the D-lactic acid producing organisms in the intestine. Nevertheless, not all probiotics are beneficial. The D-lactic acidosis can even be provoked if the probiotic contains D-lactic acid

forming organisms. It has been reported the attack was precipitated by intake of Lactobacillus tablets.[2,21] In our patient he had taken the probiotic capsule Infloran Berna (Berna Biotech) which contained *Bifidobacterium infantis* and *Lactobacillus acidophilus* four months before the onset of D-lactic acidosis. There was also recurrence of D-lactic acidosis after ingesting Lactobacillus-containing milk formula.

There were different reports regarding the beneficial effect of probiotics. Strain of *Lactobacillus GG* had been reported to be an effective treatment of rotavirus associated acute diarrhoea.[35] In one of our reviewed patient (patient 16) he was given a probiotic with Lactobacillus plantarum 299V and Lactobacillus GG (CAG Nutrition), he remained symptom free during the follow up period.[19] Kanamori[20] reported the effective treatment of a four-year girl using a probiotic containing *Bifidobacterium breve* and *Lactobacillus casei*, together with a prebiotic galactooligosaccharides. The organisms were proven to produce L-lactic acid only. The prebiotic is a non-digestive food ingredient that selectively targets the growth of a particular population of intestinal bacteria. Uchida[36] also reported the use of the above probiotic together with kanamycin in treatment of D-lactic acidosis, while Candy[37] used it in management of small bowel bacterial overgrowth in an infant. From the information provided by the literatures, the latter probiotic and prebiotic were manufactured by the Yakult Company Limited, Japan. We have contacted the Yakult Company Limited in Japan to ask for the availability of the products in Hong Kong. The probiotic is a licensed healthy food in Japan, with the liaison of Yakult Hong Kong, they were able to import the probiotic and prebiotic. We have discussed with the parents of our case for the possibility of using the above substances and they have agreed for the trial. Our patient was given a three-day course of oral vancomycin after the recurrence of D-lactic acidosis in June 2005. We plan to use the probiotic and prebiotic if the D-lactic acidosis recurs, preferably with stool culture before and after the treatment.

Conclusion

We have reported a case of probiotics provoked D-lactic acidosis in a boy with short bowel syndrome, followed by a review of all reported paediatric cases of D-lactic acidosis. The lesson to learn in our illustrative case is the need to suspect D-lactic acidosis in a patient with short bowel syndrome presenting with peculiar neurological symptoms. Another point worth to note is not all probiotics are beneficial, for example, they may precipitate D-lactic acidosis in patients with short bowel syndrome. Nowadays probiotics have been added into many different milk formulas, so they should be used with caution in patient with short bowel syndrome. On the other hand, with the identification of L-lactic acid forming bacteria, they may be utilised as a safe and effective treatment for D-lactic acidosis.

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