D-Lactic Acidosis in Humans : Review of Update

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D-Lactic acidosis has been well documented in ruminants. In humans, D-lactic acidosis is very rare, but D-lactic acidosis may be more common than generally believed and should be looked for in a case of metabolic acidosis in which the cause of acidosis is not apparent. The clinical presentation of D-lactic acidosis is characterized by episodes of encephalopathy and metabolic acidosis. The entity should be considered as a diagnosis in a patient who presents with metabolic acidosis accompanied by high anion gap, normal lactate level, negative Acetest, history of short bowel syndrome or malabsorption, and characteristic neurologic manifestations. Low carbohydrate diet, bicarbonate treatment, rehydration, and oral antibiotics would be helpful in controlling symptoms.

Key Words : D-lactic acidosis, Metabolic acidosis, Humans

Introduction

D-Lactic acidosis has been well documented in ruminants. In humans, however, D-lactic acidosis is very rare and usually only L-lactic acidosis is identified in clinical laboratories. In 1979, Oh et al.[1] first described the D-lactic acidosis in short bowel syndrome that presented with neurological manifestations and severe metabolic acidosis. However, D-lactic acidosis may be more common than generally believed and should be looked for in a case of metabolic acidosis in which the cause of acidosis is not apparent.

Short bowel syndrome is a disorder of malabsorption and malnutrition due to congenital or acquired loss of a large portion of the small intestine. Nutritional impairment develops in these cases because of carbohydrate malabsorption, steatorrhea, and inadequate absorption of fluid and electrolytes[2].

We reviewed the literature on D-lactic acidosis in humans in regards to its pathophysiology, diagnosis and proper management.

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Clinical presentations

A typical clinical presentation of D-lactic acidosis is recurrent episodes of encephalopathy and metabolic acidosis occurring in a patient with the short bowel syndrome. These episodes often last from a few hours to several days. The patients have short bowel syndrome, mainly due to surgical resection of intestine or intestinal bypass for treatment of obesity. Another underlying condition is chronic exocrine pancreatic insufficiency. D-lactic acidosis can be present in a few months to several years after the underlying conditions mentioned above established. D-lactic acidosis has been defined as metabolic acidosis accompanied by an increase in serum D-lactate ≥3 mmol/L.

The acidosis is always accompanied by various neurologic manifestations. Common features are slurred speech, confusion, inability to concentrate, somnolence, hallucination, clumsiness, weakness, ataxia, unsteady gait, nystagmus, irritability, and abusive behavior[3, 4]. The serum anion gap is usually high at the onset of symptoms. The increase in the anion gap in

D-lactic acidosis tends to be disproportionately less than the decrease in the serum bicarbonate concentration, while in L-lactic acidosis the increase of the anion gap is usually greater than the degree of reduction in bicarbonate. The discrepancy could be explained following; the significantly lower renal threshold for D-lactate (<1 mmol/L) than for L-lactate, and the loss of the sodium salt of D-lactic acid in the stool[4].

Biochemistry and metabolism of D-lactate

L-lactate is rapidly metabolized to pyruvate by L-lactate dehydrogenase in the liver. Meanwhile, because of lack of D-lactate dehydrogenase in mammals, D-lactate is thought to be metabolized to pyruvate by the enzyme d-α-hydroxy acid dehydrogenase, which metabolizes D-lactate at about one-fifth the rate that L-lactate dehydrogenase metabolizes L-lactate[5]. D-lactate dehydrogenase had been isolated only in lower organisms, but recently, some researchers identified putative human and murine mitochondrial D-lactate dehydrogenase[6, 7]. In human, parenteral infusion of D-L-lactate causes increases in pyruvate, alanine, 3-hydroxybutyrate, and acetoacetate[8].

The transport of D-lactate from cytosol to the mitochondrial matrix allows D-lactate to be oxidized by the putative D-lactate dehydrogenase. Three novel transporters that shuttle D-lactate across the mitochondrial membrane have been identified : the D-lactate/H^+ symporter, the D-lactate/oxoacid antiporter, and the D-lactate/malate antiporter[6].

There are many controversies regarding the metabolism and excretion of D-lactate in mammals. Conventional opinion is that D-lactate is not well metabolized by mammals and is excreted mainly in the urine. However, recent experiment using either D-lactate or ^{14}C-labeled D-lactate, established that D-lactate is indeed readily metabolized and excreted in urine[9].

At high doses, reabsorption of L-lactate exceeds 70%, while that of D-lactate never exceeds 50%, even at low dose[9]. At the plasma levels of D-lactate higher than 3.0 mmol/L, renal tubular reabsorption of D-lactate decreases by as much as 30%. Lactates, both L- and D-lactate, are reabsorbed actively against an electrochemical gradient in renal tubule, probably using the same sodium cotransport system. This sodium cotransport system may contribute to the mutual interference between L- and D-lactate reabsoprtion[9]. Renal tubular reabsorption of lactate is reduced by the increase in urine volume.

D-lactate is transported to various tissues via eight proton-dependent monocarboxylate transporters (MCT-1 to MCT-8). MCTs are expressed in most tissue such as retina, muscles, kidneys, brain capillary endothelial cells, cardiac myocytes, enterocytes, hepatocytes erythrocytes, thymocytes, placenta, and nervous tissue. D-lactate is absorbed by the small intestinal and colonic epithelial cells by MCT-1[10].

D-lactate is normally produced by the fermentative organisms of the gastrointestinal tract, mainly by lactobacilli and bifidobacteria. Under normal condition, lactate is not produced in acid-base imbalance because it is converted by other microbes to acetate and fatty acids. The major benefit of these organic acids in the gastrointestinal tract is to provide a fuel for oxidative metabolism and ion pumping for mucosal cells of the colon[11]. The colon is protected from large influxes of carbohydrate, being regulated by gastric emptying and effective small intestinal digestion and absorption.

Pathophysiology of D-lactic acidosis

D-lactic acidosis is a rare metabolic complication in humans, but is occasionally observed as a consequence of short-bowel syndrome. Because of its slower metabolism, only D-lactate accumulates and remains distributed in the human body as a low molecular weight organic acid until it is excreted unchanged in the urine. In patients with short bowel syndrome, carbohydrates that normally undergo sterile digestion in the

small bowel reach the colon in undigested or partially digested form and are fermented to produce organic acid, causing a progressive decrease in intraluminal pH. This acid state alters the intestinal microenvironment into the overgrowth of acid resistance bacteria such as *Lactobacillus acidophilus, Lactobacillus fermenti*, and streptococcus. The majority of Colonic floras are Gram positive anaerobes, which are the major lactate producers. The symptoms of D-lactic acidosis may occur when patients with short bowel syndrome ingest a large amount of carbohydrate. A short or bypassed small intestine causes poor digestion of carbohydrate, which leads to the delivery of sugars to the colon. Acid resistance bacteria produce both the D- and L-lactate, making the D-lactate to accumulate systemically after absorption[3].

Various mechanisms for neurologic symptoms in D-lactic acidosis have been postulated. D-lactate itself and other unknown compounds produced along with D-lactate are toxic to the brain[4]. The brain apparently lacks D-2-hydroxyacid dehydrogenase, and this may lead D-lactic acid to accumulate excessively in the brain. High D-lactic acid level may alter intraneuronal pH.

Short bwel sndrome and D-Lactic aidosis

Short bowel syndrome is a disorder of malabsorption and malnutrition secondary to congenital or acquired loss of a large part of the small intestine. Carbohydrate malabsorption, steatorrhea, and inadequate absorption of fluid and electrolytes characteristically cause diarrhea, resulting in failure to thrive. D-lactic acidosis is a serious complication in patients with short bowel syndrome[2]. In healthy condition, the small bowel, although not sterile, hosts only a population of aerobic gram-negative microflora in concentration of less than 10^5/mL, without any strictly anaerobic microflora. The cecum and large bowel, by contrast, host concentrations of anaerobic microflora from 10^9 to 10^{12}/mL. Proper intestinal motility and an intact ileocecal valve appear to be the most important mechanisms for the maintenance of the normal small bowel microflora. For the short bowel syndrome patient who maintains a part or the entire portion of large bowel, overgrowth of small bowel bacteria is likely to occur, particularly in the absence of the ileocecal valve. In short bowel syndrome, carbohydrates reach the colon in an undigested form. Colonic bacteria ferment the carbohydrate, producing organic acids that lower the intestinal pH. This acidic environment favors the suppression of normal gut microflora and allows for the overgrowth of acid-resistance flora. Lactobacillus contains an enzyme that produces D- lactate. When high amount of D-lactate are absorbed into the bloodstream, exceeding the metabolic and renal excretory capacity, a syndrome of D-lactic acidosis can occur. In these cases, treatment with a short course of oral antibiotics, targeting the acid-resistant flora, is effective[12].

Diagnosis

Increased anion gap and rapid onset and recovery from clinical manifestations are characteristic features seen in D-lactic acidosis. The critical elements of diagnosis are 1) increased serum anion gap with normal lactate levels measured by conventional laboratory techniques and negative Acetest, 2) presence of short bowel syndrome, 3) acidosis that is preceded by food ingestion and that improves after discontinuation of oral intake of food, and 4) characteristic neurologic symptoms[4]. Any patient presenting with acidosis and one or more of the above clinical clues should be strongly considered to have D-lactic acidosis. The diagnosis of D-lactic acidosis is confirmed by demonstrating high levels of D-lactate in urine and/or in serum. D-lactic acid level is usually greater than 3 mmol/L in D-lactic acidosis. D-lactate level is measured enzymatically using a D-lactic dehydrogenase specific assay.

Treatment

Main treatments are: 1) changing the abnormal intestinal flora with the administration of oral antibiotics, 2) attempt to diminish the quantity of substrate for intestinal fermentation by using the low-carbohydrate diet or enteral formulas containing fructose or starch instead of glucose as the main source of carbohydrate, 3) correction of the underlying abnormality by reanastomosing the intestine in case of intestinal bypass, 4) nonspecific therapy of acidosis with high doses of bicarbonate, 5) correction of the acidosis and simultaneous clearance of D-lactate with hemodialysis[3, 4].

Antibiotics control symptoms and prevent recurrence of the syndrome in most patients, but in some patients acidosis recurs despite the antibiotic use. Antibiotics that have been tried include neomycin, vancomycin, ampicillin, kanamycin, and metronidazole. The optimum duration of antibiotic therapy is uncertain because the symptoms may recur in a few days after discontinuation of antibiotics in some patients, while others may remain without symptoms for several years in the absence of oral antibiotics[4].

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