Severe Lactic Acidosis Associated with a Suspected Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency in a Young Chihuahua Dog

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ABSTRACT

This report describes a case of severe lactic acidosis associated with a suspected succinic semialdehyde dehydrogenase (SSADH) deficiency in a 5-month-old Chihuahua. The dog was presented for obtundation and "drunk-like" behavior of 1 month duration. Venous blood gas analysis revealed a severe lactic acidosis (blood pH 6.938; reference interval 7.35-7.45; lactate concentration 18.27 mmol/L; reference interval 0.8-2.0 mmol/L). As other causes of encephalopathy and hyperlactatemia were ruled out, an inborn error of lactate metabolism was suspected. Quantitative organic acid analysis showed marked elevations of urine lactic acid, pyruvic acid and gamma-hydroxybutyric acid (or 4-hydroxybutyric acid) concentrations. Activity level of SSADH, measured in the dog's cultured lymphoblasts, was 30% of that recorded in three healthy dogs, suggesting SSADH deficiency. The dog initially responded to treatment, but eventually deteriorated, and was euthanized. Organic acidurias are being increasingly recognized in veterinary medicine; however SSADH deficiency has never been reported in dogs. Early identification of inherited organic aciduria in domestic animals might facilitate prompt, appropriate treatment, and potentially facilitate modelling of corresponding human pathologies.

Keywords: Inborn Errors of Metabolism; Lactate; Encephalopathy; Canine; Chihuahua.

CASE PRESENTATION

A 2.5 kg, 5-month-old, intact male Chihuahua dog was presented for encephalopathy of 1-month duration. The dog was acquired from a breeder at the age of 6 weeks, and was reported to be apparently healthy until 4 months of age, after which episodes of obtundation and "drunk–like" behavior were noted, particularly following meals. In addition, the dog showed a selective appetite, and after several trials, refused to eat various different commercial diets. The history excluded exposure to toxins. Prior to presentation, the dog was examined by his regular veterinarian, as well as in a referral practice, where complete blood count (CBC), serum chemistry (including serum bile acids), urinalysis and abdominal ultrasound were performed. Abnormalities included absolute monocytosis (1650 cells/μL, reference interval [RI] 0-840 cells/μL) and mild hyperphosphatemia, which was attributed to the dog's young age. Urinalysis abnormalities included proteinuria (3+), a moderate amount of granular casts, and

a urine pH of 5.0. Pre- and post-prandial serum bile acid concentrations were within RI.

At presentation, the dog was responsive, with a body condition score of 3/9, and normal vital signs; however, he was obtunded and ataxic. Neurological examination revealed dull mentation, generalized ataxia and dysmetria, and excessive blinking. Postural reactions and cranial nerve examination were normal. Venous blood gas analysis (I-stat, Heska laboratories, USA) showed severe metabolic acidosis (pH 6.938, HCO_3^- 6.4 mmol/L; $PvCO_2$ 30.1 mmHg; RIs, 7.34-7.45; 22±2 and 35-45, respectively). Blood glucose at presentation was 96 mg/dL (RI 81-133 mg/dL). Plasma lactate concentration was markedly elevated (18.27 mmol/L; RI, 0.8-2.0 mmol/L; I-stat, Heska laboratories, USA). Fasting ammonia concentration was unremarkable (18.8 µmol/L; RI, 0.0-45.0 µmol/L). Pulse oximetry saturation and systolic blood pressure were 98% and 110 mmHg, respectively, and did not support hypoxic causes of hyperlactatemia.

Due to the dog's young age, the exacerbation of clinical signs following meals and the severe lactic acidosis, a congenital defect in lactate metabolism was suspected. Urine was collected for quantitative organic acid analysis by gas chromatography-mass spectrometry (Comparative Neuromascular laboratory, San-Diego, CA) (Table 1). Urine lactic acid, pyruvic acid and 4-hydroxybutyric acid (GHB) concentrations were all markedly increased.

Pending urine organic acid analysis, the dog was treated with intravenous (IV) crystalloids (Normosol-R, Abbot laboratories, Chicago, IL, USA; 4 ml/kg/hr), supplemented with 2.5% dextrose (50% Dextrose, Hospira Inc., Lake Forest, IL, USA) and KCl (Potassium chloride, American Pharmaceutical Partners, Schaumburg, IL, USA; 30 mEq/L). Bicarbonate deficit was calculated using the formula 0.3 x BW (kg) x (normal bicarbonate – patient bicarbonate) and was corrected over 24 hours intravenously (sodium bicarbonate, Hospira Inc., Lake Forest, IL, USA). Vitamin B complex and cyanocobalamin (Vedco Inc., St. Joseph, MO, USA) were administered (250 µg and 500 µg, IM, respectively).

The following morning, the dog appeared improved. Carnitine (generic; 125 mg PO, BID) was added to the treatment regimen. Repeat venous blood gas analyses throughout hospitalization are shown in Table 2. On day 3, the dog ate willingly, and was fed a low protein diet (Hill's k/d, St. Louis, MO, USA). Lactate levels decreased as long as the dog was receiving bicarbonate. However, over the next three days, as bicarbonate therapy was tapered, the dog progressively lost appetite, became ataxic, and hyperlactatemia reoccurred.

Table 1: Quantitative urine organic acid analysis and related metabolites concentration in a 5-month old male Chihuahua with suspected succinic semialdehyde dehydrogenase (SSADH) deficiency

Urine organic acid (µmol/mol creatinine)	Result	Reference interval
Lactic acid	>31,379	0 – 200
3-hydroxybutyric acid	475	0 – 22
4-hydroxybutyric acid	812	NA
Methylmalonic acid	3	0 – 9
Malonic acid	0	0 – 2
2-ethyl-3-OH propionic acid	27	0 – 14
Succinic acid	0	0 – 17
Propionylglycine	0	0 – 1
Adipic acid	0	0 – 17
Pyruvic acid	>2262	0 – 26
Tiglylglycine	1	0 – 1
2-OH glutaric acid	1	0 – 3
Acetoacetic acid	90	0 – 1
Suberic acid	0	0 – 4
Orotic acid	0	0 – 2
Citric acid	0	0 – 190
Methylcitric acid	0	0 – 1
2-oxoglutaric acid	0	0 – 22
Urine Lactate:Pyruvate	~14	NA

NA – Not available

Magnetic resonance imaging (MRI) and cerebrospinal fluid analysis were declined by the owners. On day 6, a percutaneous gastrostomy (PEG) tube was placed endoscopically, and muscle biopsy for histopathology to detect mitochondrial or storage disorders, and skin biopsy for fibroblast culture were obtained under general anesthesia. Recovery from anesthesia was uneventful. Due do the progressive increase of serum lactate concentration, therapy with IV fluids, supplemented with bicarbonate and dextrose, was reinstituted. Dicholoroacetate (DCA; Received from Dr. Barshop and Shelton's laboratory, manufacturer unknown; 150 mg PO, q24h) and hydromorphone (hydromorphone-HCl, Hospira Inc., Lake Forest, IL, USA; 0.22 mg IV, q8h) were added to the treatment regimen. PEG-tube feedings were initiated on day 7. Although serum lactate concentrations improved, the dog remained obtunded and developed abdominal discomfort. Abdominal radiographs, performed on day 9, revealed a mild amount of free abdominal gas suggesting leakage from the gastrostomy site. The owners declined surgical exploration. On day 11, repeat radiographs revealed an increased

Table 2: Venous blood gas results, lactate concentration and interventions throughout hospitalization of a 5-month old male Chihuahua suspected with succinic semialdehyde dehydrogenase (SSADH) deficiency.

Day	1	2 (AM)	2 (PM)	3	4	5	6	9	Reference interval
Serum lactate (mmol/L)	18.27	12.23	3.9	8.13	13.21	16.03	10.30	4.29	1.5 ± 0.5
pH	6.938	7.123	7.407	7.383	7.362	7.173	7.255	7.355	7.35-7.45
P_vCO_2 (mmHg)	30.1	31.8	31.7	27.1	24.5	26.2	23.1	27.6	35-45
HCO_3- (mmol/L)	6.4	10.4	20	16.1	13.9	9.6	10.2	15.4	22 ± 2
P_vO_2 (mmHg)	70	146	N/A	51	105	54	55	75	30 -40
BE (mmol/L)	- 26	- 19	- 5	- 9	- 12	- 19	- 17	- 10	-4 to 4
Treatment	IV fluids HCO_3-, Dextrose Vit B complex Vitamin B_{12}	IV fluids HCO_3- Dextrose Carnitine	IV fluids, HCO_3- Dextrose Carnitine	Carnitine	Carnitine DCA	Carnitine DCA	IV fluids HCO_3- Dextrose Carnitine DCA	IV fluids, HCO_3- Dextrose Carnitine DCA	

amount of free abdominal gas. The dog deteriorated clinically, and was euthanized at his owners' request, and sent for necropsy.

Post-mortem examination revealed leakage from the gastrostomy site with mild, acute peritonitis and pancreatitis. Histopathological examination of the brain revealed cerebrocortical spongiform changes with astrocyte hypertrophy. The muscle biopsies were microscopically unremarkable. Skin biopsy fibroblasts failed to grow in culture, for an unknown reason, as no contamination was detected in the culture media. This precluded some of the further investigations of the metabolic derangement.

Increase of urinary 4-hydroxybutyric acid (GHB) has been associated with deficiencies of enzymes involved in metabolism of the inhibitory neurotransmitter gamma-hydroxybutyric acid (GABA) (1). Activity levels of several enzymes involved in this pathway were measured. Hydroxy acid-oxoacid transhydrogenase (HOT) is an enzyme converting GHB to succinic semialdehyde (SSA) with stoichiometric conversion of α-ketoglutarate and D-2-hydroxyglutarate (1). Since the oxidation of GHB to SSA is the rate limiting step in the overall catabolic pathway, factors which regulate the rate of either or both these enzymes will, in turn, influence endogenous GHB tissue levels (2). Liver tissue HOT activity of this dog and of four healthy controls were measured as previously described (3). HOT activity in the reported dog was 40 ηmol/mg protein/hour, which was similar to the range of the HOT activities measured in the four control liver biopsies (20-44 ηmol/mg protein/hour), ruling out HOT deficiency.

Subsequently, the activity of succinic semialdehyde dehydrogenase (SSADH) was measured in cultured lymphoblasts from the dog. In humans, SSADH deficiency is a rare inborn error of metabolism, inherited as an autosomal recessive trait (1, 4). In individuals with SSADH deficiency, metabolism of GABA is disrupted, leading to abnormal SSA accumulation in addition to GHB (1, 4). The hallmark laboratory finding associated with SSADH deficiency is increased urinary, plasma and cerebrospinal fluid (CSF) GHB concentration (1, 4). In the dog reported herein, serum SSADH activity was measured using a fluorometic assay as previously described (29) and activity level was 30% of its activity recorded in 3 healthy controls. This, along with the markedly increased urine GHB concentration, suggested that this dog had congenital SSADH deficiency.

DISCUSSION

Inborn errors of metabolism are being increasingly reported in several dog breeds, as well as in cats, including, among others, malonic aciduria in Maltese puppies (5) pyruvate dehydrogenase (PDH) deficiency in Clumber and Sussex spaniels (6, 7), L-2 hydroxglutaric aciduria in Staffordshire bull terriers and Yorkshire terriers (8-10) and inherited cobalamin absorption deficiency in cats and in a family of giant Schnauzers (11-13). To the best of our knowledge, severe hyperlactatemia associated with SSADH deficiency has never been reported in animals.

Hyperlactatemia is divided into two types. Type-A hyperlactatemia is the most common cause of lactic acidosis, occurring in presence of tissue hypoxia, associated with con-

ditions causing poor tissue perfusion, such as hypovolemic or septic shock (14). Although arterial blood gas analysis was not performed in this case to rule out hypoxemia, the chronic history, physical examination findings and normal systolic blood pressure and oxygen saturation at presentation likely exclude tissue hypoperfusion and hypoxia, thereby ruling out a type-A hyperlactatemia.

Type-B hyperlactatemia refers to any cause of increased lactate concentration in which tissue hypoxia is unapparent, and is divided into three subcategories (15). Type-B_1 hyperlactatemia is caused by diseases such as diabetes mellitus, severe liver disease, malignancy, pheochromocytoma, as well as severe sepsis, as lactate clearance may decrease by 50% in septic patients (15). Type-B_2 hyperlactatemia is caused by various toxins and drugs that impair cellular oxygen utilization, including cyanide, acetaminophen, ethylene-glycol, catecholamines, terbutaline, salicylates and morphine (14). Type-B_3 hyperlactatemia is caused by inborn errors of metabolism involving mitochondrial dysfunction. It is the latter that is suspected in the present case.

In humans, following exclusion to type-A hyperlactatemia, disorders involving impaired lactate metabolism are divided into primary and secondary (16). Primary lactate metabolism disorders include Kreb's cycle deficiencies, disorders of gluconeogenesis and glycogen metabolism, respiratory chain defects and lactate-pyruvate oxidation defects (16). In many other inborn errors of metabolism, hyperlactatemias occur due to co-enzyme A (Co-A) metabolism disruption, and are termed secondary type-B_3 hyperlactatemias (16, 17). These include organic acidurias, urea cycle defects and fatty-acid oxidation defects (16). Secondary hyperlactatemia may be differentiated from primary hyperlactatemia based on an abnormal urine organic acids profile and serum lactate to pyruvate (L:P) ratio assessment. In humans, a normal L:P ratio (≤25), along with a normal organic acid profile, suggest PDH or gluconeogenesis defects, while an increased L:P ratio (>25) suggests a deficiency in pyruvate carboxylase, a respiratory chain defect, or a mitochondrial myopathy (16, 18). In the present dog, we can only speculate that urine L:P ratio, as calculated in table 1, was less than 25; however the normal ratio for dogs in unknown.

With exclusion of urine lactate and pyruvate, which were extremely elevated, other measured urine organic acids (i.e., GHB and its metabolites), were increased. As primary hyperlactatemias do not tend to alter the urine organic acid profile, we suspected a secondary type-B_3 hyperlactatemia. We first elected to investigate GHB. It is unclear whether the increased urine concentrations of GHB and its associated organic acids represent a "spill-over" effect of a primary PDH deficiency, or alternatively, the severe lactic acidosis herein might merely represent a negative energy balance, with excess lactate production due to an increased glycolysis. Substantial elevations in lactate are mostly absent in SSADH-deficient children, but were found in an infant with SSADH deficiency and multiple organ failure (19). In addition, the high urine GHB and acetoacetate concentrations might represent a state of negative energy balance rather than a primary GHB metabolism defect. Measurement the PDH enzyme complex activity requires fibroblast culture or tissue samples frozen in liquid nitrogen and stored at -70º C (17). As our fibroblast culturing herein failed, and the dog was euthanized, further investigation of these enzymes was impossible, precluding conclusions regarding these speculations.

GABA is the major brain inhibitory neurotransmitter, and is synthesized primarily from glutamate, the major excitatory neurotransmitter (Figure 1) (4, 20). The first enzymatic degradation step of GABA involves the enzyme GABA-transaminase, which utilizes α-ketoglutarate from the tricarboxylic acid (Kreb's) cycle to regenerate a molecule of glutamate for every catabolized GABA molecule. Hence, the vital neurotransmitter pools of GABA and glutamate are constantly replenished and tightly regulated (1). The product of the GABA-transaminase reaction is succinic semialdehyde, which is normally converted to succinic acid by SSADH. Succinic acid thereby enters the tricarboxylic acid cycle, where α-ketoglutarate is formed. The ongoing conversion of glutamate to GABA and back to glutamate is known as the GABA shunt (21).

SSADH deficiency in humans leads to various neurological and neuromuscular symptoms, although the clinical phenotype is extremely nonspecific and variable, even among affected members of the same family (17, 24). However, most individuals with SSADH deficiency are affected by mild to severe mental retardation, psychomotor retardation, and delays in language and speech development (22). In addition, in some cases, initial findings might include hypotonia, ataxia or seizures. Additional possible abnormalities include hyporeflexia, nystagmus, hyperkinesis and behavioral abnormalities (21-24). The neurological signs in SSADH deficiency are thought to reflect the effects of elevated brain GHB and

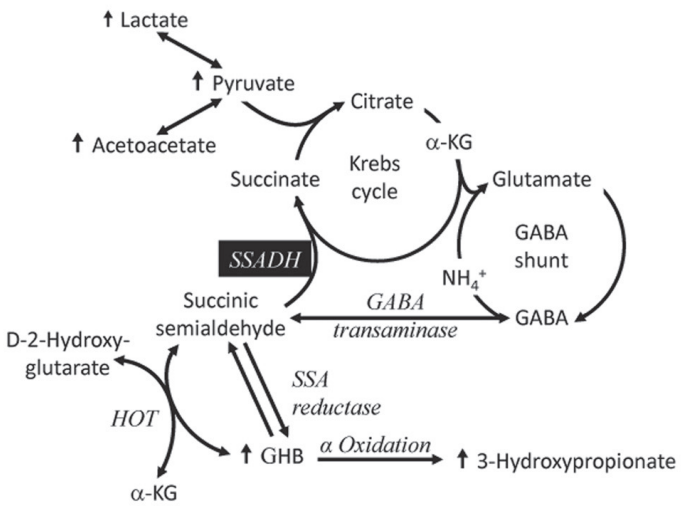

Figure 1: Pathways in γ-hydroxybutyric acid (GHB) metabolism. Metabolism of γ-butyric acid (GABA) by GABA transaminase produces succinic semialdehyde (SSA), which is converted by succinic semialdehyde dehydrogenase (SSADH) to succinate. Succinate can enter the Krebs' (TCA) cycle, to be converted to α-ketoglutarate (α-KG), to complete the cycle back to the GABA shunt. Deficiency of SSADH leads to GHB accumulation. The enzyme hydroxyacid-oxoacid transhydrogenase (HOT) can convert GHB to D-2-hydroxyglutarate. GHB α-oxidation produces the increase in 3-hydoxyproprionate. Increases in lactate, pyruvate, and acetoacetate are secondary to effects on the TCA cycle.

elevated GABA concentrations (1). In the present dog, SSADH activity was 30% its normal activity. While this is an abnormally low level, human beings with SSADH deficiency typically show more severe decrease, up to absence of SSADH activity (0-5%) (24). Parents of such children might have mid-range SSADH activity, representing a heterozygous state (20, 24). In addition, humans with SSADH deficiency might suffer from mild to moderate lactic acidosis, however, in some, hyperlactatemia is absent (20,24).

Dichloroacetate (DCA) has been used anecdotally and tested clinically as a lactate-lowering drug in humans with congenital lactic acidosis, indirectly stimulating mitochondrial PDH multi-enzyme complex activity by inhibiting PDH kinase activity, which reversibly phosphorylates and inhibits PDH (25). As a consequence of stimulating the PDH multi-enzyme complex activity, DCA accelerates the irreversible lactate oxidation (via pyruvate), which generates acetyl-CoA for the tricarboxylic acid cycle (20, 24). In this case, lactate concentration seemed to be more influenced by use of IV fluids, dextrose and bicarbonate than by DCA, which initiated on day 4 (Table 2).

Ultimately, the decision for euthanasia in this case was related to clinical deterioration due to peritonitis, secondary to leakage from the gastrostomy site. Complications associated with PEG tube placement in dogs and cats are reported to range between 42 and 57%, with septic peritonitis accounting for 0 to 10% of cases (27, 28). We can only speculate that the dog herein might have been more prone to feeding tube complications due to lack of appropriate tissue response and wound healing.

In conclusion, this report describes a young dog with progressive encephalopathy and hyperlactatemia associated with a suspected SSADH deficiency. This report reiterates that inborn errors of metabolism are likely under-diagnosed in veterinary medicine, and reinforces the fact that blood gas analysis and urine organic acid analysis should be performed in young animals with progressive encephalopathy, when other causes are ruled out. In addition, to the best of our knowledge, this is the first reported case of severe, likely non-hypoxic lactic acidosis with suspected SSADH deficiency in a dog.

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