Remembering MUDPILES: A Case of Unexplained Metabolic Acidosis

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CASE

A 7-year-old medically complex girl was admitted for unexplained metabolic acidosis. Her history was significant for cerebral palsy, failure to thrive, developmental delay, feeding difficulties, and microcephaly. She was adopted from Bulgaria with no known past medical or family histories. Admission laboratory studies were significant for increased anion gap metabolic acidosis with an elevated lactate and urine pH of 5.0. The patient was initially managed on maintenance intravenous fluids with 10% dextrose with 0.22% normal saline and 40 mEq/L of sodium bicarbonate. Oral food and fluids were withheld while additional laboratory testing was conducted. Through genetic testing, the patient was diagnosed with pyruvate dehydrogenase deficiency. She was started on a ketogenic diet and clinically improved. Since discharge, she has continued to follow up with a geneticist and metabolic dietitian. This case highlights the proper evaluation of a patient who presents with metabolic acidosis.

A 7-year-old girl with history of cerebral palsy, failure to thrive, developmental delay, feeding difficulties, and microcephaly was transferred to our tertiary care pediatric unit from an outside emergency department (ED) with unexplained metabolic acidosis. She presented to the ED after her father witnessed her become acutely limp with apparent right-sided neck contraction, leg twitching, increased sleepiness, and rapid breathing. Of note, teachers mentioned increasing lethargy and a decline in mental status over the day before presentation.

The patient was adopted from Bulgaria 9 months earlier without any available past medical or family history. At that time she was nonambulatory, nonverbal, underweight, and needed spoon feeding. Since adoption she had gained 5 pounds and was drinking from a cup, eating soft foods, and walking with assistance. Until starting school 2 to 3 weeks before admission, the patient was at home full time with her adoptive mother and 7 siblings. Apart from a runny nose, the patient had been in her usual state of health.

On evaluation her temperature was 37.1°C, blood pressure 119/97 mm Hg, heart rate 126 beats per minute, respiratory rate 28 breaths per minute, and oxygen saturation was 100% on room air. Weight was 17.3 kg, which was less than the first percentile on the growth curve. Physical examination was remarkable for microcephaly, decreased eye contact, intermittent dysconjugate gaze, spastic quadriparesis, mild contractures at the elbows, and decreased muscle mass. The remainder of the physical examination was normal.

Initial venous blood gas in the ED demonstrated a primary metabolic acidosis (pH 7.27, P_{CO_2} 16.8 mm Hg, bicarbonate 7.6 mmol/L), with an increased anion gap (23 mEq/L, HCO_3 8). Additional laboratory results were significant for an elevated lactate of 10.7 mmol/L and leukocytosis of 18.9 K/uL. A urine toxicology screen was negative. Urinalysis was noteworthy for a pH of 5.0.

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Question: What evaluation should be done for a patient with metabolic acidosis?

Discussion

The initial evaluation of a metabolic acidosis should determine whether it is an anion gap or non–anion gap metabolic acidosis. The anion gap is calculated as the difference of the cations and anions in the serum, based on those that are easily measured. The anion gap is calculated by subtracting the sum of the chloride and bicarbonate from sodium. The anion gap is considered elevated if it is >12 mEq/L.[1] Potassium can be included as a measured cation, which raises the normal value by 4 mEq/L.[2]
A metabolic acidosis with a normal anion gap has a variety of causes, such as gastrointestinal loss of bicarbonate, drugs, hyperalimentation, rapid intravenous (IV) hydration with normal saline, renal loss of bicarbonate, or hypoaldosteronism. The etiologies of an anion gap metabolic acidosis can be remembered by the mnemonic MUDPILES: methanol, uremia, diabetic ketoacidosis, propylene glycol, paraldehyde, iron tablets or isoniazid, lactic acidosis, ethylene glycol, salicylates, or accumulation of organic acids due to an inborn error of metabolism.[1]

If a patient has an anion gap metabolic acidosis, calculating the osmolar gap will help differentiate potential etiologies. The osmolar gap is calculated by subtracting the calculated osmolality from the measured osmolality. Calculated osmolality is as follows[2]:

$$\left[2 \times Na^+ \ (mEq/L) \right]$$
$$+ \left[\frac{serum\ urea\ nitrogen(mg/dL)}{2.8} \right]$$
$$+ \left[\frac{Glucose(mg/dL)}{18} \right]$$

A normal osmolar gap is <10. An elevated osmolar gap indicates the presence of an abnormal solute, such as ethylene glycol or methanol.[2]

CASE CONTINUATION

Our patient had an anion gap of 23 mEq/L on presentation. Her serum osmolality was 288 mOsm/kg, and her calculated osmolality was 281.8 mOsm/kg, making her osmolar gap 6.2 mOsm/kg. With a normal osmolar gap, we were able to eliminate external substances as a potential etiology of her anion gap metabolic acidosis. Initial laboratory work also eliminated diabetic ketoacidosis and uremia as potential etiologies of her anion gap metabolic acidosis. As mentioned previously, the initial lactate on presentation was elevated at 10.7 mmol/L, indicating lactic acidosis.

Question: What is the approach to lactic acidosis?

Discussion

Lactic acidosis can be broken down into type A and type B. Type A lactic acidosis is more common and is caused by marked tissue hypoperfusion. Type B lactic acidosis occurs when there is no clinical evidence of poor tissue perfusion or oxygenation. Type B lactic acidosis can occur in association with common disorders such as hepatic failure, diabetes, cancer, and renal failure or can be caused by drugs and toxins such as biguanides (eg, metformin), alcohol, iron, isoniazid, and salicylates. Lastly, type B lactic acidosis can also be caused by inborn errors of metabolism.[1]

CASE CONTINUATION

Our patient's lactic acidosis persisted despite adequate hydration status, indicating that she did not have a type A lactic acidosis. She had no other signs or symptoms of common disorders associated with type B lactic acidosis and had not been exposed to any drugs or toxins. Thus, an inborn error of metabolism was highly suspected in our patient. She also showed findings suggestive of a chronic metabolic disorder with history of failure to thrive and developmental delay.

Question: What is the initial management of a patient with a suspected inborn errors of metabolism?

Discussion

For initial management, it is important to establish a positive caloric balance with IV glucose at 8 to 10 mg/kg per minute.[3] Typically 10% dextrose is started in initial fluid management. Sodium bicarbonate administration (~2–3 mEq/kg per 6 hours) may be used to correct the acidosis.[4] The patient's fluid and electrolyte status must also be considered in choosing replacement fluid therapy. There must be close monitoring of blood gases and electrolytes during the initial phase of treatment. While awaiting laboratory testing, it is important to limit or avoid oral intake to prevent continued ingestion of a possible offending metabolite.[3] Another consideration is hemodialysis if there is difficulty in removing toxic metabolites (eg, ammonia).[3,4]

CASE CONTINUATION

Our patient was initially managed on maintenance IV fluids with 10% dextrose with 0.22% normal saline and 40 mEq/L of sodium bicarbonate. The addition of 40 mEq/L of sodium bicarbonate to 0.22% normal saline provided our patient with a similar sodium infusion rate to that of 0.45% normal saline. We frequently monitored her electrolytes and lactate. We also restricted our patient's oral intake while awaiting results of additional laboratory testing.

Question: What is the evaluation of a patient with a suspected inborn error of metabolism?

Discussion

Basic evaluation includes a comprehensive metabolic panel, complete blood cell count, arterial blood gas, ammonia, uric acid, and urinalysis. Additional tests that are helpful include a pyruvate level (with lactate level drawn at the same time), blood and urine amino acids, urine organic acids, carnitine (plasma total and free), very long-chain fatty acids, free fatty acids, acylcarnitine profile, and blood ketones (β-hydroxybutyrate).[4,5] It is also appropriate to consult a geneticist early in the evaluation to assist in determining appropriate evaluation and management. Ophthalmologic examination is also helpful because ocular manifestations occur in various metabolic disorders and can involve the cornea, lens, retina, or optic nerve.[6]

The lactate-to-pyruvate ratio is useful to distinguish possible inborn errors of

metabolism. A high lactate-to-pyruvate ratio (>30) has a differential diagnosis of pyruvate carboxylase deficiency, α-ketoglutarate dehydrogenase deficiency, and mitochondrial defect of oxidative phosphorylation. A normal or low lactate-to-pyruvate ratio (normal is <25) has a differential diagnosis of pyruvate dehydrogenase (PDH) deficiency and defect in enzyme of gluconeogenesis (eg, fructose-1,6-bisphosphatase or glucose-6-phosphatase).[5]

CASE CONTINUATION

Our patient's pyruvate level was 10.2 mg/dL, and a lactate level drawn at the same time was 10.5 mmol/L. To compare the values, we converted the pyruvate value to millimoles per liter. After the conversion, the lactate-to-pyruvate ratio was 18.5. With a low or normal lactate-to-pyruvate ratio, our differential diagnosis was limited to PDH deficiency or a defect in an enzyme of gluconeogenesis. Urine organic acid analysis revealed a mild elevation of pyruvate, lactate, and several unknown compounds that were probably exogenous. Plasma amino acid analysis revealed several deviations, including elevated alanine and proline, which may be a normal variation; however, elevated proline and alanine together may also be associated with chronic lactic acidosis. Normal studies in our patient included β-hydroxybutyrate, ammonia, acylcarnitine profile, thyroid studies, insulin-like growth factor binding protein 3, and insulin-like growth factor 1.

Results were highly suggestive of PDH deficiency. Additional diagnostic testing was pursued, and our patient was managed accordingly.

Question: How is PDH deficiency diagnosed and managed?

Discussion

The diagnosis of PDH deficiency is confirmed with genetic testing. The genetic testing used for our patient looked for mutations in 9 nuclear genes for PDH and the electron transport chain complex that are involved in PDH deficiency and lactic acidosis.

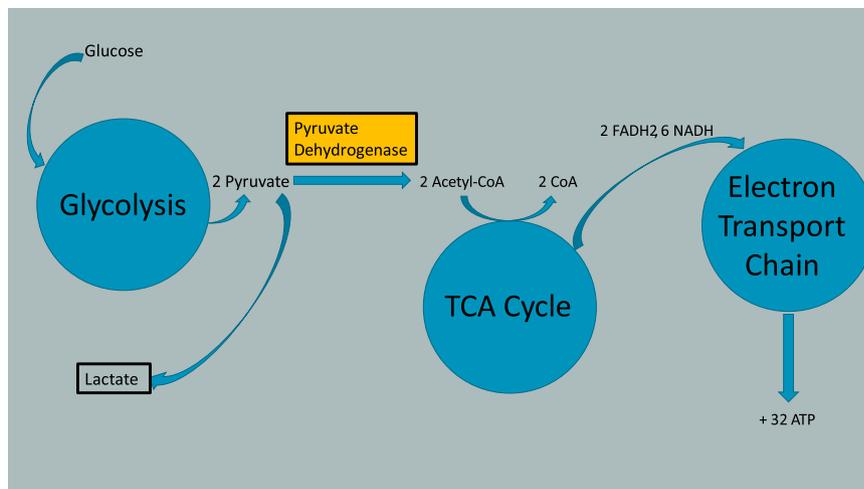The PDH complex consists of 3 catalytic subunits known as E1, E2, and E3. If 1 of the

FIGURE 1 Aerobic respiration. There are 4 major reaction pathways including glycolysis, the conversion of pyruvate to acetyl-CoA, the TCA cycle, and the electron transport chain. In glycolysis, glucose is broken down to form 2 pyruvates. Pyruvate is then oxidized to form acetyl-CoA via PDH. Acetyl-CoA then enters the TCA cycle. The TCA cycle consists of 8 separate reactions that are catalyzed by different enzymes and yield nicotinamide adenine dinucleotide (NADH), flavin adenine dinucleotide (FADH2), ATP, and CO_2. The electron transport chain breaks down NADH and FADH2 to produce ATP via 4 separate complexes in the mitochondrial membrane.

components has reduced function secondary to a mutation, the whole complex is unable to function properly. Mutations in the E1 α subunit are responsible for most PDH deficiencies.[7]

Patients with PDH deficiency lack the enzyme that converts pyruvate to acetyl coenzyme (CoA) for entry to the tricarboxylic acid (TCA) cycle and the electron transport chain. These pathways are essential generators of adenosine triphosphate (ATP), a major molecule involved in energy transport (Fig 1). Therefore, patients with PDH deficiency successfully complete glycolysis but have accumulations of pyruvate and its byproducts, including lactate.[7] Without this enzyme, they are unable to completely use the energy in glucose via the electron transport chain. This deficiency affects many organs, especially the brain, which needs large amounts of energy.[7,8]

A high-fat diet bypasses this metabolic defect by generating acetyl-CoA via β oxidation. This diet is called a ketogenic diet and aims to provide 65% to 90% of calories from fat, with the remainder of calories from protein and carbohydrates.[9,10] The intake of carbohydrates is monitored

particularly closely because carbohydrate intake can increase blood lactate levels. A ketogenic diet mimics the metabolic response during periods of starvation and results in the production of ketones as a byproduct of fat breakdown.[9] Patients should monitor urine ketones, with a goal of a high level of urine ketones.

Patients may also need oral bicarbonate to avoid acidosis. Because β oxidation uses greater amounts of carnitine to remove byproducts, blood carnitines should be checked and supplemented if necessary. For patients who can experience a metabolic crisis during illness episodes, it is standard practice to give the family an emergency protocol that educates and guides practitioners who may be called to provide care emergently.

If PDH deficiency is suspected, management should be started while genetic results are pending.

CASE CONCLUSION

Our patient was placed on a ketogenic diet, and her lactic acidosis resolved. She was discharged from the hospital on a ketogenic diet, carnitine supplementation, and oral sodium bicarbonate. Genetic testing results

returned after discharge showed a homozygous mutation in *PDHX* (gene that encodes a component of the PDH complex), which is inherited in an autosomal recessive pattern. Clinical features of this mutation include lactic acidosis, developmental delay, hypotonia, and severe psychomotor retardation, which our patient exhibited.

This case is particularly interesting because it is possible that the starvation our patient probably encountered while living in the orphanage could have resulted in a ketogenic state, which indirectly managed the enzyme defect, although we have no way to confirm this possibility.

She continues to follow up with a geneticist and metabolic dietitian. She remains on a ketogenic diet, and urine ketones are monitored weekly at home. She also takes sodium bicarbonate and L-carnitine. The family has an emergency protocol for use during illness episodes.

Question: Is our patient's adoption from Bulgaria pertinent to her case?

Discussion

Our patient has the p.R446* alteration, which is typically seen in the Roma population. Thus, her suspected ethnic background does provide a clue to diagnosis. In fact, this mutation is seen in ≤60% of Roma patients with PDH deficiency,[11] so the mutation testing in these patients could start with sequencing the *PDHX* gene. Her presentation in childhood (rather than in infancy) as a girl with severe intellectual disability, spasticity, and growth retardation is typical for this gene change.[11]

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