Inborn Errors of Metabolism with Acidosis

Organic Acidemias and Defects of Pyruvate and Ketone Body Metabolism

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KEYWORDS

• Organic acidemia • Ketone utilization • Pyruvate metabolism • Metabolic acidosis • Ketoacidosis • Inborn error of metabolism

KEY POINTS

- Early identification and treatment of inborn errors of metabolism can prevent irreversible damage.
- A normal newborn screen does not rule out an inborn error of metabolism.
- Acute treatment to reverse catabolism does not require precise diagnosis.
- Collect and freeze extra serum and urine samples during the acute presentation.

Pediatricians know that inborn errors of metabolism (IEM) require early diagnosis and early treatment to prevent permanent neurologic damage.[1] Most patients present acutely in the neonatal period with nonspecific symptoms, but they can appear later with a few common presentations, including hypoglycemia; hyperammonemia; neurologic abnormalities; and, the focus of this article, increased anion gap metabolic acidosis. This article intends to help the practicing provider use basic laboratory findings to identify those children at highest risk for an IEM and initiate life-saving and brain-sparing treatments.

Metabolic acidosis is the accumulation of excess hydrogen ions in the blood. Lower pH reflects a higher concentration of unbuffered (free) hydrogen ions. Although this is the physiologically significant issue in most cases of acidosis, accurate diagnosis and

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management is more concerned with the anions accumulating in association with the hydrogen ion and, in the IEM, these anions may cause toxicity. Metabolic acidosis can be readily demonstrated through blood gas and electrolyte measurements and is characterized by decreased blood pH, decreased bicarbonate (HCO_3^-), and decreased P_{CO_2}. Specifically, metabolic acidosis is defined as pH less than 7.30, P_{CO_2} less than 30, and serum HCO_3^- less than 15.[2] The reduced P_{CO_2} reflects the respiratory response to compensate, confirming that the acidosis is not secondary to respiratory insufficiency, thus it is a metabolic acidosis.

Basic blood chemistries measure the most common cations and anions in the serum, sodium (Na^+) being the major cation, and chloride (Cl^-) and HCO_3^- representing the major anions. Potassium does not contribute much to the total cation load in the serum because it is primarily intracellular, and it tends to vary because of physiologic variation and artifacts due to hemolysis of blood samples. For the purpose of this discussion, the anion gap (normal = 7–16) is defined as the difference between the serum Na^+ and the sum of the serum Cl^- plus HCO_3^-.

These are not all of the ions present in the serum; there is a gap between the measured cations and anions. The physiologic requirement for electroneutrality does not allow a true gap between the concentration of cations and anions in the serum, thus a difference represents the sum of all of the unmeasured ions. An increase in the anion gap can result from either a decrease in unmeasured cations (eg, hypokalemia, hypocalcemia, hypomagnesemia) or an increase in unmeasured anions (additional organic compounds circulating).[3]

Metabolic acidosis can be classified into 2 categories: high anion gap or normal anion gap acidosis. A reduction in unmeasured cations or an increase in negatively charged plasma proteins may not be associated with acidosis, thus the anion gap in the absence of acidosis reflects other types of physiologic disruption that are not discussed in this article.

Metabolic acidosis with an anion gap greater than 16, reflecting an increase in an unmeasured anion, is one of the most specific laboratory findings suggestive of an IEM causing acidosis. **Box 1** shows the commonly used mnemonic to remember the differential diagnosis of high anion gap metabolic acidosis. Initial history and laboratory results should reveal most of these etiologic factors, leaving only unexplained anions from IEM or significant poisonings in the differential.[3] In normal anion gap metabolic acidosis the decrease in serum HCO_3^- is matched by an equivalent increase in serum Cl^-, resulting from direct loss of HCO_3^- from the gastrointestinal tract

Box 1
Differential diagnosis of high anion gap metabolic acidosis

MUDPILES

Methanol

Uremia

Diabetic ketoacidosis (ketones)

Propylene glycol ingestion

IEM, infection, isoniazid intoxication, or iron intoxication

Lactic acid (ischemia or hypotension)

Ethylene glycol ingestion

Salicylates