The term “organic acidemia” or “aciduria” refers to a diverse group of disorders characterized by the excretion of non-amino organic acids in urine. Most organic acidurias result from a deficiency of a specific enzyme in the metabolic pathways of amino acids and fatty acids resulting in accumulation of organic acids. Although any organ may be affected, commonly involved organs are brain, liver, heart and kidney. While individually rare with an incidence ranging from $1/10^4$ to $1/10^6$, as a group the combined incidence of these metabolic diseases is ~ 1/2000. Common clinical findings include metabolic acidosis, hyperammonemia, hypoglycemia, ketosis, recurrent vomiting, hypotonia and altered mental status. These findings are non-specific and are frequently seen in critically ill patients. A number of these critically ill patients show very abnormal organic acidurias which mimic inherited organic acidurias and make interpretation difficult.

In the clinical laboratory, using gas-chromatography mass-spectrometry (GC-MS), we identified several (7 out of approximately 600) extremely abnormal samples for organic acids from children with acute life threatening events such as respiratory or cardiac arrest. Repeat testing or additional testing ruled out the organic acidurias.

Significant metabolic abnormalities included: severe lactic aciduria (>4000-550,000 mmol/mol creatinine) in all seven patients and severe ketosis (acetoacetic acid >1000 mmol/mol creatinine) in four children. Such high levels of lactic acid are seen in deficiency of pyruvate dehydrogenase, pyruvate carboxylase and E3 deficiency. Since severe lactic acidemia/aciduria in hypoxic-ischemic injury, such as in these patients, is a known phenomenon, these findings were attributed to these acquired conditions rather than inherited metabolic cause.

Significant elevation of 2-keto and 2-hydroxy-branched chain ketoacids, metabolites of branched chain amino acids, mimicking the profile of Maple Syrup Urine Disease (MSUD) were also seen. In two patients, 2-ketoglutarate was also significantly elevated (>2500 mmol/mol creatinine) mimicking lipoamide dehydrogenase (E3) deficiency. Normal branched chain amino acids and absence of allo-isoleucine ruled out MSUD and E3 deficiency. Acyl-carnitine profiles were also normal. The mechanism of increased 2-ketoglutarate and branched chain organic acids is not clear. As pyruvate, 2-ketoglutarate and branched-chain-2-ketoacid dehydrogenases share a common E3 subunit, it is possible that severe lactic acidosis indirectly affected 2-ketoglutarate and branched-chain-2-ketoacid dehydrogenases.

In conclusion, in critically ill patients, urine organic acids may mimic the organic acids profiles of known inherited metabolic disorders, such as lactic acidosis, MSUD and fatty acids disorders, making interpretation of organic acids profiles difficult. In such cases repeat testing and additional testing such as plasma amino acids and acylcarnitine profile should be ordered to rule out inherited metabolic disorders.

CME Series
Sponsored by Department of Pathology & Laboratory Medicine

Date: Tuesday, September 21, 2004
Time: Noon – 13:00
Location: Conference Room 2206.10 WT
Speaker: Ralph Kaufman, MD & William Caskey, PhD
Topic: Update on Intramural and Extramural Research Grant Opportunities and Application Processes
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