February 2018 Critical Care Case of the Month

Robert A. Raschke, MD

University of Arizona College of Medicine-Phoenix
Phoenix, AZ

History of Present Illness

A 25-year-old was admitted to an outside hospital with an acute episode of nausea and vomiting and *chronic* progressive weakness. He smoked 2 cigarettes per day and drank a 12-pack of beer per month. He had a history of undefined chronic liver disease.

Physician Examination

Physical examination was reported as showing a chronically ill appearing man who was “weak” using crutches to ambulate.

The patient was made NPO and was rehydrated with intravenous normal saline.

Which of the following are **indicated at this time?**

1. Creatinine phosphokinase (CPK)
2. Serum potassium
3. Thyroid studies
4. 1 and 3
5. All of the above

Correct!
5. All of the above

Weakness is a nonspecific complaint which can be caused by a variety of neurological, muscular and metabolic diseases in addition to heart and/or lung diseases.

His admission laboratories were relatively unremarkable on admission but CPK, LETs and ammonia rose over 6 days to-

- Ammonia 129 mcg/dL (normal 15-45 in adults)
- CPK 6500 mcg/L (normal 10-120)
- Aspartate aminotransferase 1800 U/L (AST, normal 10-40)

Other abnormal laboratory values included-

- Creatinine 4.0 mg/dL (normal 0.6-1.2)
- Total bilirubin 4.0 mg/dL (normal 0.1 to 1.2)
- Lactate 2.3 mmol/L (normal 0.5-1.0)

He experienced episodes of hypoglycemia. His mental status declined and he developed hypercarbic respiratory failure (pCO₂ 240 mm Hg) requiring intubation.

He was transferred to Banner University Medical Center-Phoenix for further evaluation.

PMH, SH and FH

- At the age of 9 he was diagnosed with Reye's syndrome and was reported to have an elevated ammonia of 150 mcg/dL (normal 40-80 in children).
- A muscle biopsy was performed at the age of 13 which showed type 1 fiber atrophy.
- He had five previous episodes over the past three years, triggered by physical exertion (or EtOH ingestion) in which he experienced nausea, vomiting, altered mental status, sometimes associated with hypoglycemia
- He had been diagnosed with myasthenia gravis one year prior to admission, but did not respond to corticosteroid administration.

Physical Examination

- Vitals signs: BP 133/82 mm Hg, pulse 91 beats/min, respirations 14 breaths/min while receiving mechanical ventilation, SpO₂ 99%.
- HEENT: temporal muscle wasting.
- Lungs: clear.
- Heart: regular rhythm without murmur.
- Abdomen: marked firm hepatomegaly
- Neurologic: He was awake and alert. Cranial nerves appeared intact. Deep tendon reflexes were 1+ bilaterally. His muscle tone was flaccid and he could not lift his heels or head off the bed.

Laboratory Evaluation

- CPK 1692 mcg/L
- Ammonia 90 mcg/dL (normal 9.5-49 in adults)
- Lactic dehydrogenase 2796 (LDH, normal 140-280 U/L)
- Prothrombin time 13.9 secs (normal 11-13.5)

A CT scan of the abdomen was performed which showed hepatosplenomegaly with the liver infiltrated with fat (Figure 1).

Figure 1. Representative image from the abdominal CT scan. The liver is infiltrated with fat.

Which of the following is **are indicated at this time?**

1. Plasma carnitine level
2. Serum ketones
3. Urine glutaric acid
4. Urine myoglobin
5. All of the above

Correct!
5. All of the above

The constellation of weakness, fatty liver, hypoglycemia and hyperammonemia suggest a problem with fatty acid metabolism: either carnitine deficiency, deficiencies of carnitine palmitoyltransferase deficiency (which transport FA into the mitochondria), defects of acyl dehydrogenases that participate in beta-oxidation of fatty acids, or a defect of electron transport flavoprotein (which resides in the electron transport chain and is the entry point for FADH₂ that delivers the high-energy chemical bonds from FA metabolism into the electron transport chain) (1).

Disorders of fatty acid metabolism can cause metabolic myopathy. They are sometimes misdiagnosed as muscular dystrophies, inflammatory myopathies or Reye's syndrome when the serum ammonia is elevated. Classification is by the primary energy source affected-glycogen storage, purine metabolism, lipid storage or abnormalities of the electron transport chain.

Electron transfer flavoprotein (ETF) and ETF-ubiquinone oxidoreductase (ETF-QO) are nuclear encoded proteins through which electrons from flavoprotein acyl CoA dehydrogenases, dimethylglycine dehydrogenase, and sarcosine dehydrogenase enter ubiquinone in the respiratory chain. Inherited defects of either protein cause glutaric acidemia type II. Glutaric acidemia type II is characterized clinically by hypoketotic hypoglycemia and metabolic acidosis; pathologically by fatty infiltration of the liver, heart, and kidneys; and biochemically by a diagnostic organic aciduria.

Primary defects of ETF-QO and those of either ETF subunit are inherited as autosomal recessive traits. Several pathogenic mutations have been identified in the genes for ETF-QO and the α -ETF subunit. No single ETF-QO mutation is common, but of six that have been identified in the α -ETF gene, α T266M may account for about 40 percent of mutant alleles.

Our patient had a markedly elevated urine glutaric acid consistent with electron transport flavoprotein defect. This was confirmed by genetic analysis.

Which of the following are recommended to **treat electron transport flavoprotein defect?**

1. Avoidance of fasting
2. Avoidance of prolong exercise
3. Carbohydrate rich diet
4. Carnitine administration
5. All of the above

Correct!
5. All of the above

No specific treatment for electron transport flavoprotein defect exists (1). A defect of this molecule causes dependence on glucose metabolism. During periods of fasting, such as that imposed by NPO status after admission for nausea/vomiting, the normal “starvation” shift of metabolism to utilization of fatty acids fails. Muscle energetics fail and the fatty acid delivered to the liver accumulate causing fatty liver. Other metabolic pathways that are affected include purine metabolism (resulting in hyperammonemia) and amino acid metabolism (resulting in glutaric aciduria – the diagnostic test performed in this patient). Preventive measures, such as high-carbohydrate and low-fat diet and frequent small meals, may be helpful. Carbohydrate supplements also are advised before and during anticipated exercise. Prolonged exercise should be avoided to prevent attacks of rhabdomyolysis.

Our patient was treated with glucose-containing intravenous fluids, carnitine, riboflavin, glucose infusion, hepatic-aid and lactulose. He made a remarkable recovery. He was quickly weaned from mechanical ventilation. His hepatomegaly completely resolved over the course of 10 days and he was discharged from the hospital.

His hospital course at the referring hospital (and several of the previous episodes he described) were clues to his diagnosis. In each case, his condition worsened after he was made NPO for nausea, and was rehydrated with saline. The ensuing starvation state stressed his impaired ability to metabolize fatty acids exacerbating all the clinical manifestations of ETFD.

Reference

1. Katirji B. Metabolic myopathies. Medscape. October 19, 2016. Available at: <https://emedicine.medscape.com/article/1173338-overview#a1> (accessed 1/16/18).