Inborn Error of Metabolism is a Disease of any Age; Carnitining Palmitoyltransferase II Deficiency and Its Manifestations

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Introduction:
- Carnitine palmitoyltransferase II (CPT II) deficiency is a disorder of long-chain fatty-acid oxidation. The three clinical presentations are: lethal neonatal form, severe infantile hepatocardiomyoskeletal form, and myopathic form.

Chief Complaint: “Pain in my thighs”.

Case:
- 30 years old female with PMH of migraine and seizures, presented with severe pain in her thighs. According to the patient, she went to the gym 2 days prior to admission, to do her usual workout, which consists of an hour of running or aerobic exercise. However, a personal trainer offered her a tense 15-minutes workout that consisted of significant amounts of squats.
- Later that day, she noticed tightness, and muscle stiffness in her thighs, which became progressively worse to the point she could not stand or walk. She also noticed that her urine was getting dark red/black in color.

Going Back Into Her History:
- Per patient, she would wake every morning as a child with numbness in her legs, which would resolve eventually with standing. By the time she was 17, she began having episodic associated with muscle pain, weakness, and fatigue with exercise. If her muscles’ pain is severe enough, she would develop a seizure like activity, followed by a transient loss of consciousness. There is no postictal state.
- Less severe more frequent pain during her daily activity without definite exercise.

Past Medical History: Questionable seizures; her EEG was abnormal but nonspecific. Migraine, polycystic ovarian disease and fibromyalgia.

Medications: Topamax, Adductone, OCP.

Family History: Brother has myalgia and darkening of urine after exercise but it was never worked up. Sister had 2 episodes of passing out, but no workup was done. Cousin had episodes associated with muscle pain, weakness, and fatigue with exercise. If her muscles’ pain is severe enough, she would develop a seizure like activity, followed by a transient loss of consciousness. There is no postictal state.

Labs and Imaging:
- UA was positive for blood, but rare RBC on HPF, moblobin test was positive. EKG - normal sinus rhythm.
- Carnitine palmitoyltransferase II (CPT II) deficiency is an enzyme located in the inner aspect of the inner mitochondrial membrane, that cleaves the long chain acylcarnitine complex. Subsequently, long chain fatty acid could be used in beta oxidation, and production of energy in the liver, cardiac muscle and skeletal muscle.
- During periods of fasting, or long exercise; if fatty acid oxidation is defective, fat can’t be utilized, and glucose is consumed without regeneration via gluconeogenesis. Eventually hypoglycemia occurs leading to brain function impairment, seizures and loss of consciousness.
- Moreover, fat will accumulate in the liver causing steatosis, heart causing cardiomyopathy and arrhythmias, and skeletal muscle causing myopathy.

Carnitine Palmitoyltransferase II Deficiency:
- It has an autosomal recessive pattern of inheritance.
- A majority of affected individuals are homozygous or compound heterozygotes for mutations in the CPT II gene.
- The two most common gene defects, S113L and R503C may cause disease in heterozygotes.
- The three clinical presentations are: lethal neonatal form, severe infantile hepatocardiomyoskeletal form, and myopathic form. The former 2 presentations are fatal at young age.

The Myopathic Form of CPT II:
- The myopathic form of CPT II deficiency is the most common disorder of lipid metabolism affecting skeletal muscle, and the most frequent cause of hereditary myoglobinuria.
- Signs/Symptoms
  - Usually noted during first or second decade of life, but can appear as late as the fifth decade.
  - Characterized by attacks of myalgia, muscle stiffness or tenderness, weakness, and fatigue, with or without myoglobinuria. Lethargy and seizures can happen.
  - When rhabdomyolysis occurs, it may lead to acute renal failure, electrolytes abnormality causing cardiac arrhythmias, and respiratory insufficiency requiring mechanical ventilation.

Diagnosis:
- Determination of free and acylcarnitine levels in serum, urine and tissues.
- Confirmation by direct enzymatic assay or DNA analysis.
- Treatments; no specific treatment exists. Preventive measures include:
  - Diet modification; high carbohydrate, low (medium-chain) fat and low protein diet. Frequent meals. Extra carbohydrate intake before sustained exercise appears to improve exercise intolerance.
  - Triheptanoin diet appears promising. Larger studies are needed to confirm.
  - Refrain from prolonged aerobic exercise, fasting and cold exposure.
- Pharmacologic treatment with bezafibrate may be beneficial for mild CPT II deficiency. Larger studies are needed to confirm.

Teaching Point:
- Interns need to be aware of the manifestations of inborn error of muscle metabolism which can also present in adults. This case was diagnosed 14 years after her initial presentation and after been evaluated by 22 specialists.

References: