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

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Inborn Error of Metabolism is a Disease of any Age; Carniting 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 hepatocardiomuscular 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 amount 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 awake 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 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.
- 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, Aldactone, 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 with epilepsy.

Vitals: Temp = 97.9, HR = 85, Bp = 117/74, RR = 20, and SpO2 = 93% on RA.

General: AAOx3, no apparent distress.

Physical Examination: Physical examin is pertinent for; bilateral lower extremities were extremely painful and tender on palpation. Tense bilateral thighs and quadriceps. Pain on pasive motion with rigidity of b/l knees. Sensory exam was intact to pinprick throughout with subjective decrease in the left medial calf region. The rest of the physican exam was negative.

Labs and Imaging: CBC, Hgb of 14.9, Hematocrit 44.8, WBC 14 and platelets 311. BMP was within normal range. Ca 9.1, AST 1529, ALT 452, CK is 108,864. Acetaminophen is <10. UA was positive for blood, but rare RBC on HPF, moblobin test was positive. EKG - normal sinus rhythm.

Hospital Course: Patient was started on aggressive fluid resuscitation for rhabdomyolysis. Orthopedics were consulted for possible compartment syndrome. Thighs' anterior compartment pressure was measured, and it was found to be 55-60 on the right and 90 on the left. Patient was taken for stat fasciotomy. During which, all her muscles appeared healthy, clean, viable and contractile. Also Rheumatology was consulted and recommendation was to do muscle biopsy during fasciotomy. Muscle biopsy was done on closure of the fasciotomy and was sent for pathology. Pathology reading, necrotizing myopathy with excessive lipis storage.

Diagnosis: Deficiency of Carnitine palmitoyltransferase II.

Carnitine Palmitoyltransferase II:

- Carnitine palmitoyl transferase II (CPT II), 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 prolong 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.

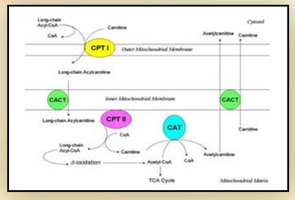

Figure 1. The Mitochondrial Carnitine System. Linus Palding Institute at Oregon State University. http://lpi.oregonstate.edu/infocenter/othernuts/carnitine/transport.html. Accessed April 24, 2014.

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 hepatocardiomuscular form, and myopathic form. The former 2 presentations are fatal at young age.

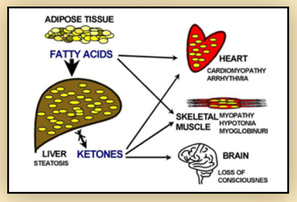

Figure 2. CPT II Deficiency.The carnitine cycle in fatty acid oxidation. In: Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. American Journal Of Medical Genetics. Part C, Seminars In Medical Genetics. May 15, 2006;142C(2):77-85.

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.
- Triggers:
  - Prolonged exercise
  - Cold exposure
  - Fever
  - Stress or infection
  - Medications that may lower carnitine levels, like pentobarbital, phenytoin, carbamazepine, depakote, sulfadiazine, pyrimethamine, cefditoren, ipecac, and zidovudine.
- 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 protien 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:

- Internists 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:

1. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Med Genet C Semin med Genet. 2006 May 2006 15;142C (2): 77-85.
2. Monograph. L-carnitine.Altern Med Rev. 2005 Mar;10(1):42-50. (seizure).
3. Corti S et al. (2008). Clinical features and new molecular findings in Carnitine Palmitoyltransferase II (CPT II) deficiency. J Neurol Sci, 266(1-2): 97-103. (autosome inheriance).
4. Tanphaichitr V, Leelahagul P. Carnitine metabolism and human carnitine deficiency. Nutrition. 1993 May-Jun;9(3):246-54. (diagnosis).
5. Bonnefont JP, et al. Bezafibrate for an inborn mitochondrial beta-oxidation defect. N Engl J Med. 2009 Feb 19;360(8):838-40.
6. Kilfoyle D, Hutchinson D, Potter H, George P. Recurrent myoglobinuria due to carnitine palmitoyltransferase II deficiency: clinical, biochemical, and genetic features of adult-onset cases. N Z med J 2005; 118:U1320.
7. Orngreen MC, Eistrup R, Vissing J. Effect of diet on exercise tolerance in carnitine palmitoyltransferase II deficiency. Neurology 2003; 61:559.
8. Roe CR, Yang BZ, Brunengraber H, et al. Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy. Neurology 2008; 71:260.
9. The Mitochondrial Carnitine System. Linus Palding Institute at Oregon State University. http://lpi.oregonstate.edu/infocenter/othernuts/carnitine/transport.html. Accessed April 25, 2014.