AEJ ANESTHESIA EJOURNAL
Volume 7- No. 7 2019

Carnitine Palmitoyl Transferase 1A (CPT1A) Deficiency, The Arctic Variant

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Abstract

Carnitine Palmitoyl Transferase 1A (CPT1A) is a crucial enzyme needed for mitochondrial fatty acid oxidation and is fundamental for appropriate metabolic responses to prolonged fasting. Under normal conditions, the human body guarantees a constant energy supply by metabolizing glucose for energy in the short term, and by oxidizing fatty acids into ketones during long term fasting or starvation. Fasting induces the breakdown of hepatic glycogen supply into glucose. Continued fasting eventually leads to glycogen depletion followed by a decrease in serum glucose and insulin levels. This decrease then activates hormone-sensitive lipases located in adipose tissues and causes the release of free fatty acids into the blood. Normally these free fatty acids would undergo beta-oxidation and the Krebs cycle to produce energy; however, CPT1A deficiency results in about an 80% decreased activity of the CPT1A enzyme. This decreased CPT1A activity causes an inability to utilize fatty acids as energy and leads to a significant hepatic glycogen depletion during periods of fasting.
Preoperative fasting in these patients may result in vomiting, lethargy, hypoketotic hypoglycemia, seizures, liver failure, and an increased risk for respiratory illnesses that place this population at increased perioperative risk. Interventions include, but are not limited to, parent education and prevention techniques, early recognition of symptoms, prompt treatment with glucose, and even surgery cancellation. CPT1A deficiency is found in circum-arctic populations such as Alaskan Inupiat and Yupik, Canadian and Greenland Inuit, and Siberian Yupik and is also known as the "Arctic Variant" of CPT1A. Once thought of as a rare disorder, the introduction of tandem mass spectrometry (MS/MS) to Alaska newborn screenings in 2003 revealed that the polymorphism c.1436C>T variant in the CPT1A gene has an incidence as high as 80% in specific regions of Alaska. As of 2011, an estimated 700 Alaska Native Infants born each year are homozygous for the c.1436C>T Arctic Variant. To safely care for this patient population throughout the perioperative period it is important for anesthesia professionals, in Alaska and other arctic regions, to understand what the Arctic Variant of CPT1A is, who it affects, the anesthetic implications, and the recommended interventions for treating and preventing symptoms.

Carnitine Palmitoyl Transferase, Type 1A Arctic Variant

(CPT1A Arctic Variant)

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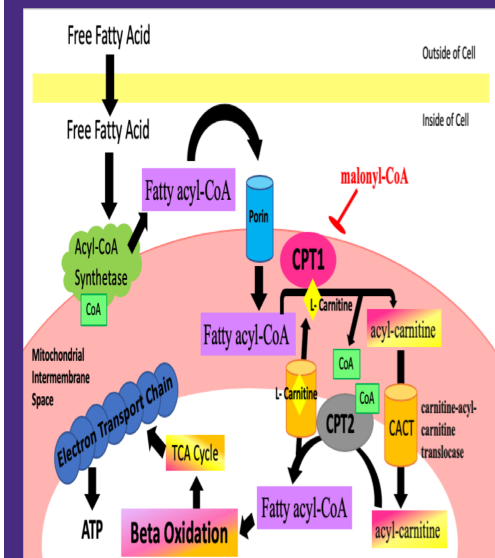
Introduction:

- CPT1 is a mitochondrial enzyme responsible for the first step in fatty acid oxidation.
- CPT1A is the isoform of CPT1 found in the liver.[1]
- CPT1A catalyzes the rate limiting step that imports long chain fatty acids into the mitochondrion, allowing for the production of ketones and subsequent ATP energy from the breakdown of fat.[2]
- CPT1A Arctic Variant is an inherited autosomal recessive variant resulting in 80% decreased activity of the CPT1A enzyme.[3]
- The c.1436C>T variant occurs in 26% - 80% of Arctic populations including Alaska, Canada, Greenland and Siberia.[4,5]

Background Physiology:

- Normally, during periods of fasting, the body initially breaks down the hepatic glycogen supply into glucose.[4] Once glycogen is depleted, the decrease in serum glucose and insulin levels activate hormone-sensitive lipases, located in adipose tissues, triggering the release of free fatty acids.[4]
- Free fatty acids enter cells but cannot enter the mitochondria until converted by Acyl-CoA synthetase into fatty acyl-CoA.
- Mitochondrial porins then allow fatty acyl-CoA through the outer membrane and into the intermembrane space where CPT1 catalyzes the acyl group of fatty acyl-CoA to L-carnitine, forming acyl-carnitine and recycling the CoA to be used again.[6, 7]
- The acyl-carnitine then crosses into the mitochondrial matrix via the transporter carnitine-acyl-carnitine translocase (CACT).[6, 7]
- Once in the mitochondrial matrix, CPT2, located on the inner mitochondrial membrane, will catalyze the conversion of acyl-carnitine back into a fatty acyl-CoA.[6, 7]
- The fatty acyl-CoA undergoes beta oxidation to form acetyl-CoA and enters the Citric Acid Cycle (Krebs) where electrons are removed and transported to the Electron Transport Chain in order to produce ATP.[7,8]


Free Fatty Acid
Outside of Cell
Free Fatty Acid
Inside of Cell
Fatty acyl-CoA
Porin
malonyl-CoA
Acyl-CoA Synthetase
CoA
CPT1
L-Carnitine
Fatty acyl-CoA
acyl-carnitine
CoA
Mitochondrial Intermembrane Space
L-Carnitine
CoA
CPT2
CACT
carnitine-acyl-carnitine translocase
Electron Transport Chain
TCA Cycle
ATP
Beta Oxidation
Fatty acyl-CoA
acyl-carnitine

This project did not require IRB review per 45 CFR part 46.

Consequences of the Arctic Variant

- This loss of activity may impair fasting ketogenesis and gluconeogenesis under certain conditions[1,2,4,9,10] by limiting the amount of fatty acids that can be transported into the liver's mitochondria to undergo beta oxidation.
- Symptoms are often triggered by fasting, especially if an illness or extreme stress is co-existing. Symptoms may include: vomiting,[1] lethargy,[3] hypoketotic hypoglycemia,[3,11] seizures,[11] jitteriness, and poor feedings.[3]
- In 2003, tandem mass spectrometry (MS/MS) was utilized to identify the c.1436C>T variant on newborn screening.[9] However, due to only a 10% detection with MS/MS, all newborns in Alaska now undergo universal DNA testing for the Arctic Variant.[2,10]

Who it affects?

- The Arctic Variant is the most common allele of *CPT1A* among Yupik and Inupiat Alaska Native people, Canadian and Greenland Inuit, and indigenous people of Eastern Siberia.[10]
- Evidence suggest that the Arctic Variant underwent positive selection among circum-arctic populations.[5,10]
- The Arctic Variant is thought to be mostly a concern in newborns, infants, young children and the elderly, as they potentially are unable to tolerate fasting in the presence of an illness or extreme stress.

Prevalence in Alaska Natives

- Data is from newborn screenings from July 2016 to present
- All babies from Alaska: 26% homozygous and 35% heterozygous[2, 3]
- Northern (Inupiat) and Western (Yupik) Alaska: 51% homozygous and 47% heterozygous[2, 3]
- Allele frequency: 0.7[2,3]
- Approximately 51% of Alaska Native infants born in Western and Northern Alaska are homozygous for the *CPT1A* Arctic Variant, this equals around 700 babies every year.[10]
- Some regions were found to have an incidence as high as 80% of Native individuals being homozygous for the Arctic variant.[4]

Care of children with CPT1A Arctic Variant:

Avoid prolonged periods without food[12]

- Recommended no more than 6-8 hours without eating[12]
- A baby/infant may need to be woken up to nurse/eat[12]

If the child is sick:

•Children with CPT1A arctic variant who are sick need to drink fluids with glucose, even if they do not feel hungry:[12]

- Juice
- Sports drinks such as Gatorade
- Oral electrolyte solution such as Pedialyte

Parents/guardians should call a health care provider if:

- their child is sick and unable to eat or drink glucose-containing fluids for greater than 6-8 hours[12,13]
- their baby/child seems sleepier than normal harder to wake up, seems confused, or is excessively irritable[12]
- The child has any of these symptoms:[12]
  - poor appetite
  - low energy or excessive sleepiness
  - vomiting
  - diarrhea
  - an infection
  - a fever

•The child may require intravenous (IV) infusion, or nasogastric (NG) administration of a glucose containing solution.[13]

Case Description:

- A 5-year-old, 19.5 kg, 105 cm, male was scheduled for dental restoration
- PMH: Negative, except a diagnosis of CPT1A Arctic Variant
- No known drug allergies
- PSH: Circumcision without complications
- Vital signs were unremarkable
- No pre-operative labs were ordered
- Anesthesia Plan: 10 mg of oral midazolam (versed) and 250mg of oral acetaminophen (Tylenol) followed by 30-60 mLs of apple juice, general endotracheal anesthesia

Anesthetic Management

- On arrival to the operating room (OR), the staff utilized storytelling and distraction techniques to place monitors
- Inhaled induction with nitrous oxide 1.5 L/min with oxygen 3.5 L/min and sevoflurane 8% at a flow rate of 10 L/min. A 22-gauge peripheral intravenous catheter was placed
- General anesthesia was induced with fentanyl 10 mcg, propofol 50 mg, and dexmedetomidine 2 mcg
- Oxymetazoline and water-based lubricant applied to both nares, #4.5 nasal RAE cuffed endotracheal tube was placed easily in the patients right nare
- Maintained using sevoflurane 2% end-tidal concentration in a mixture of nitrous oxide 1.5 L/min with oxygen 3.5 L/min
- Spontaneous respirations returned quickly and placed on pressure support ventilation
- Dexamethasone 4 mg was administered
- Blood glucose level checked and resulted: 112 mg/dL
- Dexmedetomidine 2 mcg IV administered three additional times during anesthesia maintenance for a case total dose of 8 mcg
- Ondansetron 2 mg was administered intravenously at end of case
- Extubation successful and transferred to the post anesthesia care unit (PACU)
- PACU stay uneventful, VSS, patient woke up crying, after about 20 minutes was transferred to Stage 2 recovery area to be with parents
- Parents educated by staff about providing a source of glucose to the child after discharge, monitoring behavior for hypoglycemia, and when to bring the child back to the hospital

Anesthesia Discussion/Recommendations:

Pre-operatively:

- It is important to know when a AV-CPT1A child last ate as they have different metabolic needs. Parents should be instructed to have the child drink breastmilk or clear liquids such as apple juice about 4 to 6 hours prior to surgery.[12]
- Children may receive midazolam accompanied with juice, serving dual purpose of anxiolysis and glucose.
- Note child's mental status and behavior. If showing symptoms of hypoglycemia, check blood sugar.
- If the child is hypoglycemic, surgery may need to be cancelled. The child may need hospital admission to correct metabolic status by receiving intravenous (IV) or nasogastric (NG) administration of glucose.[13] A standard maintenance rate of dextrose containing IV fluids is usually sufficient.[13]

Intra-operatively:

- Blood glucose levels should be checked and maintained.[14]
- Inpatient AV- CPT1A children should continue glucose-containing IV fluids intra-operatively.
- Concerns of malignant hyperthermia are valid with mitochondrial enzymatic defects however, the use of volatile agents was found to be safe in this population.[14]
- Propofol provides a large lipid load and may impair mitochondrial electron transport leading to development of Propofol-infusion syndrome and severe metabolic acidosis.[14] It is prudent to limit the use of propofol and then use a volatile agent for the maintenance of anesthesia.[14]

Post-operatively:

- A dextrose infusion should be considered for deterioration in neurologic status during the postoperative period (vomiting, lethargy, or change in mental status).[14]

Theories supporting the evolutionary selective sweep of the arctic variant

- The arctic variant in CPT1A causes decreased inhibitory effect of malonyl-CoA on fatty-acid beta-oxidation, compensating for decreased ketogenesis.[5]
- Lemas et al, suggested that the Arctic Variant c.1435C>T polymorphism may exert a cardioprotective role in the Alaska Yup'ik population by increasing high-density lipoproteins (HDL) cholesterol, and reducing adiposity.[9,15]
- The large amounts of n-3 polyunsaturated fatty acids (PUFA) found in arctic populations diet, increases the activity of CPT1A.[9] Selecting for the c.1436C>T mutation and a decrease in CPT1A activity may provide protection against the overproduction of ketone bodies[4] and deadly ketoacidosis.
- Interaction between high n-3 PUFA diet and homozygosity for the arctic variant is basis for the "healthy obesity" phenotype in the Yup'ik and Inuit populations on traditional diets.[9]
  - This includes low triglyceride levels, reduced C-reactive protein, and high circulating HDL-cholesterol.[9]

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