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Child Neurology: Medium-chain acyl-coenzyme A dehydrogenase deficiency

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Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency (MCADD) is an autosomal recessive inherited fatty acid oxidation disorder. In MCADD, mitochondria cannot process medium-chain fatty acids via the β-oxidation pathway because of a lack of MCAD. While patients may be asymptomatic during the prenatal or immediate postnatal periods, patients will experience decompensation due to profound hypoglycemia during fasting or illness with often rapid progression to encephalopathy, seizures, coma, or death. Newborn screening tests can identify virtually all new cases of MCADD in a cost-effective manner, often with reflex follow-up targeted mutation analysis for the 2 most common alleles. With appropriate monitoring, prevention through avoidance of fasting, and intervention during an impending crisis, patients with MCADD can survive into adulthood with no neurologic sequelae.

CLINICAL CASE After an uncomplicated term pregnancy, a male child was born via spontaneous vaginal delivery, the third child of unrelated, healthy parents. Newborn screening revealed elevated acylcarnitines. The pediatrician expedited referral to a metabolic specialist. Urinary levels of dicarboxylic acids and acylglycines were elevated. Subsequent fibroblast testing showed undetectable MCAD enzymatic activity and genetic testing confirmed the patient's homozygosity for *ACADM* (c.985A>G) and parents' carrier statuses.

At 8 months, the patient had fever, vomiting, and diarrhea. In the emergency department, he was pale, was tachycardic, and had a weak cry in response to pain. Hepatosplenomegaly was absent. Intake serum studies showed a glucose level of 68 mg/dL and elevated transaminases. Urine ketones were absent. Lumbar puncture studies were unrevealing. Despite a serum glucose within a normal reference range, the on-call fellow for the patient's metabolic specialist advised immediate treatment with a bolus of IV fluids containing 10% dextrose. After dextrose in bolus and maintenance fluids, the infant's examination improved to baseline. A stool test confirmed *Rotavirus* infection.

The patient had 2 more hospitalizations before age 3 for poor oral intake during illnesses. Each time the patient responded to aggressive rehydration with 10% dextrose. Otherwise, he was healthy with normal development and high achievement in a mainstream school.

At age 15 years, during a basketball tryout, the patient ran out of sports drink and subsequently experienced an episode of syncope. He was difficult to arouse and confused when emergency medical personnel evaluated him. A medical bracelet alerted emergency room staff of his diagnosis. With prompt IV infusion of 10% dextrose, the patient had a rapid recovery to baseline.

Differential diagnosis. The differential diagnosis for a child presenting with hypoglycemia and encephalopathy is broad, including infectious and many toxic/metabolic causes. The classic presentation of hypoketotic hypoglycemia, hepatosteatosis, and dicarboxylic/acylglycine aciduria strongly suggests MCADD and other fatty acid β-oxidation disorders, especially in an infant without prenatal screening. Cardiomyopathy at presentation suggests very long-chain acyl-CoA dehydrogenase deficiency.[1] With a significant acidosis, one must consider congenital organic acidurias (e.g., glutaric aciduria type 2). A urea cycle disorder would present with an anion gap related to elevated serum ammonia, arginine, citrulline, or ornithine. Disorders of ketogenesis will clinically resemble MCADD and require amino acid and acylcarnitine profiles to diagnose. Mitochondrial respiratory chain defects present with protean manifestations, hypotonia, and lactate elevation. Carbohydrate metabolism defects (e.g., hereditary fructose intolerance, galactosemia) present with hepatosplenomegaly and jaundice following fruit or milk ingestion. Encephalopathy with hepatosteatosis in setting of a recent viral infection and use of aspirin/salicylates defines Reye syndrome.[1,2] Even with universal screening, MCADD should be considered (with other inborn metabolic errors) in an otherwise unexplained sudden infant death.[2]

DISCUSSION **Prevalence.** MCADD is the most common fatty acid oxidation disorder.[1] The prevalence of

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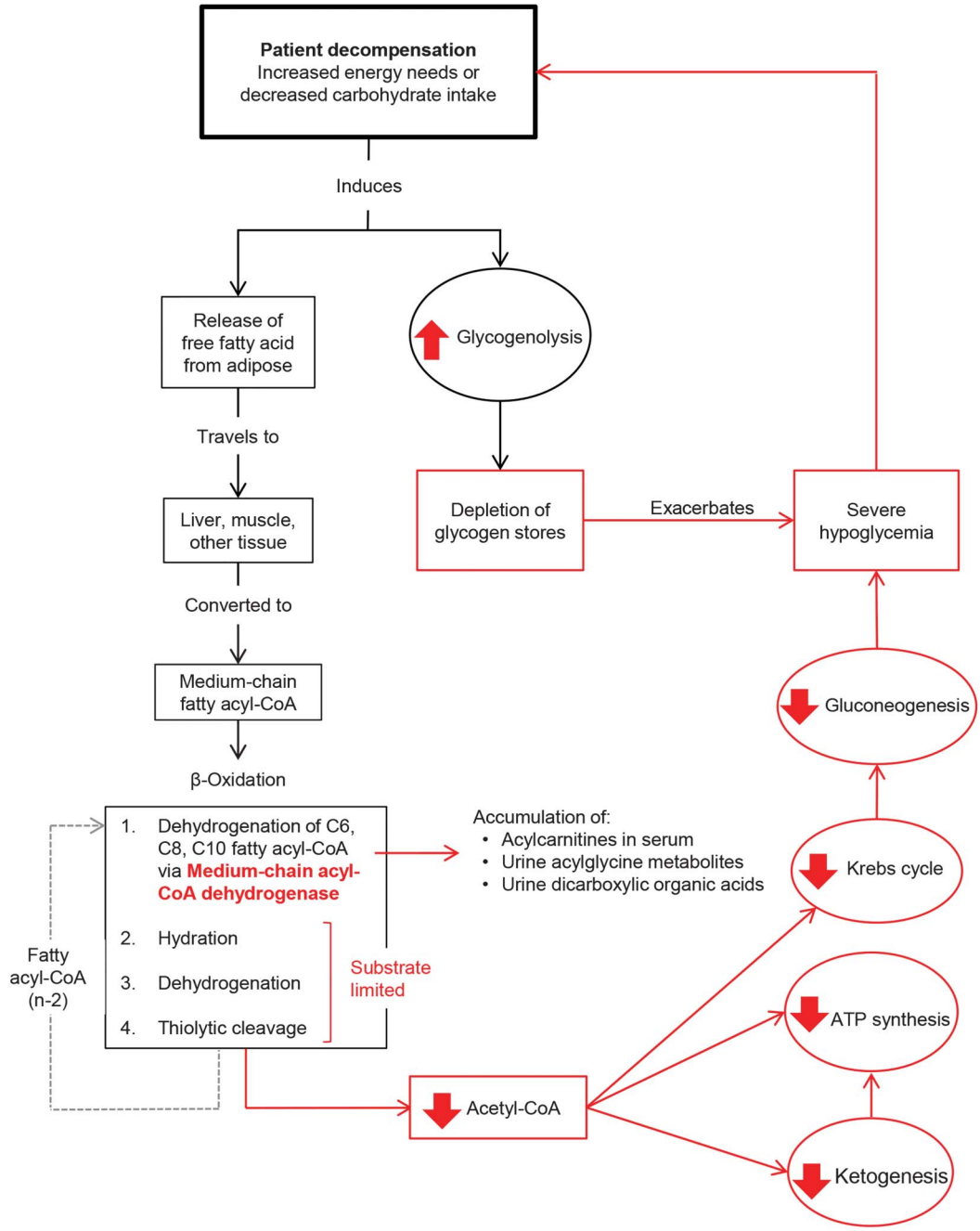
Figure Pathophysiology of patient with MCADD in crisis



In response to an increased need for energy, the body utilizes glycogen stores and releases free fatty acids for use in β-oxidation. Normal β-oxidation begins with a dehydrogenation reaction catalyzed by a length-dependent acyl-CoA dehydrogenase to produce $FADH_2$ and an enoyl derivative. Next, the β-carbon undergoes hydroxylation, which is then removed by a second dehydrogenase reaction to produce NADH and 3-ketoacyl-CoA. The final reaction is catalyzed by a second coenzyme A molecule, which attacks at the β-carbon to produce acetyl-CoA and a fatty acyl-CoA that is 2 carbons shorter and will undergo further oxidation until reduced entirely to acetyl-CoA. With the loss or insufficiency of medium-chain acyl-CoA dehydrogenase, several critical processes needed to (re)generate energy sources are severely hindered, indicated here in red. Without medium-chain acyl-coenzyme A dehydrogenase (MCAD), the oxidation of all fatty acyl-CoAs that contain more than 6 carbons is greatly reduced, leading to a significant reduction of available substrate for ketogenesis, adenosine triphosphate (ATP) synthesis, and the Krebs cycle. Downstream effects include insufficient substrate of gluconeogenesis, which acts in concert with the depletion of glycogen stores to exacerbate the patient's severe hypoglycemia. The cumulative effects result in a rapidly decompensating patient in urgent need of medical care.

MCADD in the United States is 1:15,700. Estimated prevalence varies by population (1:4,900 in Northern Germany vs 1:17,000 in Taiwan).[2]

Clinical characteristics. Children with MCADD have no predictable physical stigmata except hepatomegaly and steatosis,[1] which may be present initially or

only transiently during crises.[1,3] MCADD can present any time, but typically appears between 3 months (overnight sleeping) and 2 years of age with a mean of 12 months.[3,4] Initial presentation in adulthood is rare.[4] Symptomatic patients can have hypoglycemia (often with hypoketosis), hyperammonemia, transaminitis, and other evidence of hepatic dysfunction.[2–4] Untreated, MCADD crisis causes rapid decompensation with encephalopathy, seizures, coma, and death.[2–4]

Genetics. MCADD is an autosomal recessive inherited disorder caused by mutations in the *ACADM* gene coding for the primary enzyme that catabolizes medium chain fatty acids (MCAD).[2,5] The most commonly identified disease-causing alteration in 80% of symptomatic homozygous patients is a missense mutation in *ACADM* (c.985A>G) resulting in lysine being exchanged for glutamic acid at position 304 in the protein (p.Lys304Glu).[2,6] This mutation results in protein misfolding and loss of function.[7] Other less frequently seen mutations are mainly missense mutations with the next most common being the point mutation Tyr42His (199C>T) at an allelic frequency of 6%.[2,5] Null mutations have been observed and can result in the most severe forms of the disease.[2,5,6] In the few cases that present with adolescent or adult onset, most are homozygous or heterozygous for the c.985A>G mutation and have a mild phenotype, suggesting that other factors contribute to the age and severity of presentation.[4]

Pathogenesis. Patients with MCADD normally compensate for underproduction of energy from β-oxidation through the expenditure of glycogen stores; during times of fasting or illness, glycogen stores are rapidly exhausted. In MCADD, mitochondria have reduced MCAD function and cannot convert medium-chain fatty acids (those with 6–10 carbons) into acetyl-CoA, which may interfere with other critical metabolic processes (figure). The depletion of glycogen coupled with an inability to utilize fatty acids for energy (and potentially for gluconeogenesis) results in progression to hypoglycemia and decompensation.[2,6,8]

Diagnosis. All US states use tandem mass spectrometry of dried blood spots to identify elevated octanoylcarnitine (C8) or milder elevations in 6- and 10-carbon (C6 and C10) acylcarnitines, findings that are highly sensitive and specific for MCADD.[2,6,9] A positive (or missed) newborn screen should be followed by a metabolic workup including a serum acylcarnitine profile (to confirm the newborn screen findings) and urine organic acids (which may show a medium chain dicarboxylic aciduria with C6>C8>C10).[2] In asymptomatic individuals, these studies may be normal; a urine acylglycine assay is needed to show diagnostic elevations of n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine.[9]

Definitive testing requires sequencing of both *ACADM* genes (prenatal screening reflex testing includes the 2 common mutations) or measuring <10% normal MCAD activity in patient tissue (i.e., fibroblasts, liver, heart, skeletal muscle). Prenatal evaluation of amniocyte enzyme activity or gene sequencing is possible.

When a new case is identified within a family with no prior known affected members, genetic testing is recommended for first-degree relatives.[2]

Treatment. There is no definitive treatment for MCADD; enzyme replacement therapy is not available. Patients must have an updated emergency letter with them at all times. The letter should contain the names and contact information for the patient's metabolic specialists and explicit instructions regarding treatment of exacerbations.

The major strategy to prevent exacerbations is prevention of hypoglycemia during times of high energy demand and avoidance of prolonged fasting through frequent small meals. The recommended maximum fasting times vary by age, with no more than 8 hours of fasting for ages 6–12 months, no more than 10 hours between age 1 and 2 years, and no more than 12 hours after age 2 years.[10] Toddlers can receive complex carbohydrate supplementation (e.g., cornstarch, 2 g/kg).[2] Infants with MCADD cannot imbibe supplements with medium chain fatty acids as the primary energy source. Current recommendations endorse carnitine supplementation only for patients with MCADD with low serum carnitine levels.[2]

When patients are febrile, appear ill, or experience prolonged fasting, caregivers should provide immediate supplementation with glucose sources like nondiet beverages, orange juice, or rapidly dissolving oral glucose tablets. Caregivers must appreciate the danger of sudden death in MCADD and supplement even during mild illnesses. In emergencies, IV fluids with high percentage dextrose should be used until the patient returns to baseline with appropriate oral intake. Interventions should begin as soon as a patient is symptomatic because capillary (i.e., fingerstick glucometer readings) and serum glucose measurements are poor indicators of status in patients with MCADD who have no reserve energy sources (figure). Ketones will be low or normal and have no role in triage.

Prognosis. With identification in the newborn period and appropriate prevention of MCADD crises, the prognosis for most patients is a normal lifespan without significant disability. The estimated mortality rate from MCADD is ~20%, but this figure originates

from retrospectively identified cases in an unscreened population.[1] However, if patients have repeated nonfatal MCADD decompensations without prompt intervention with carbohydrate-enriched fluid, there are often sequelae such as intellectual disability, developmental delay, severe behavioral problems, hypotonia, and spasticity.[3,10]

Studies suggest that patients with MCADD are at high risk of obesity, and so emphasizing a healthy diet and active lifestyle are of primary importance.[10] Since patients with MCADD lack the enzyme that processes medium chain fatty acids, it might seem beneficial to eliminate the intake of all fats. However, restricting dietary fat intake below usual dietary recommendations is controversial in MCADD, because while the consequences of untreated crises are obvious, there is no evidence that the accumulation of dietary medium chain fatty acids itself is toxic.[2]

As the clinical case demonstrated, MCADD is not limited to infancy. Adolescent and adult patients with MCADD remain at risk of exacerbations. Athletes of any age need to ensure adequate carbohydrate intake during participation in sports. Patients should avoid binge consumption of alcohol and use of illicit substances as periods of drug-induced stupor, hangover, vomiting, and drug-induced hypothermia could precipitate a metabolic crisis with disastrous consequences.[4] Pregnancy and delivery, surgery, and weight loss efforts also require special attention to prevent complications.[4] Aside from continued surveillance, MCADD in adulthood is relatively benign. A study of MCADD in adult patients noted high levels of self-reported myalgias and exercise intolerance that was not significantly limiting, and neurocognitive testing confirmed normal range results.[10]

AUTHOR CONTRIBUTIONS

V. Gartner conceptualized, drafted, and revised the manuscript. Dr. McGuire provided significant revisions to the manuscript. Dr. Lee conceptualized, drafted, and revised the manuscript.

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DISCLOSURE

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