CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Management Principles for Acute Illness in Patients With Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

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Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) is a fatty acid oxidation disorder in which the patient is unable to break down fats to produce energy. This disorder places children at risk for metabolic decompensation during periods of stress, such as routine childhood illnesses. The intent of this clinical report is to provide pediatricians with additional information regarding the acute clinical care of patients with MCADD. Although each patient with MCADD will still be expected to have a primary metabolic physician, the involvement of the primary care provider is crucial as well. Appropriate treatment of children with MCADD can lead to avoidance of morbidity and mortality.

DISEASE DESCRIPTION

Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) is a fatty acid oxidation disorder in which the patient is unable to break down fats to produce energy.[1,2] MCADD is inherited as an autosomal recessive disorder resulting from homozygous or compound heterozygous mutations in the *ACADM* gene.[3] The incidence of MCADD in the United States is between 1:13 000 and 1:19 000.[4,5] Screening for MCADD is now included in all US newborn screening programs.[6] Medium-chain acyl-coenzyme A dehydrogenase is 1 of 4 mitochondrial enzymes that perform the initial steps in fatty acid β-oxidation, resulting in the generation of ketone bodies. Ketone bodies provide a crucial source of energy, particularly for the brain, once hepatic glycogen stores are depleted. During periods of routine childhood illness, when a child develops a negative caloric balance because of a combination of inadequate intake and increased metabolic demand, a biochemically unaffected child will first use stored hepatic glycogen then switch to fatty acid oxidation for

abstract

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production of ketones as a source of energy. Children with MCADD cannot make this switch when they have exhausted their glucose and glycogen stores. Many of the presenting symptoms of MCADD, such as vomiting, irritability, lethargy, and seizures, are attributable to the ensuing hypoketotic hypoglycemia. If not treated properly and promptly, symptoms can progress relatively rapidly to coma and death.

Children with MCADD may appear normal at birth and classically present with symptoms between 2 months and 2 years of age. However, severe presentations in neonates during the first week of life and at older ages have also been seen.[7–9] The classic presentation of MCADD usually occurs during a routine childhood illness, particularly gastroenteritis. The associated feeding intolerance, secondary to decreased desire for oral intake, paired with emesis can lead to the critical risk factor of prolonged fasting. Some children also present during weaning from nighttime feedings because they are unable to tolerate the longer periods of fasting between feedings. Before inclusion of MCADD in newborn screening panels, up to 18% of patients could have a fatal outcome after the disease is revealed with their first routine childhood illness.[7,10] MCADD is now included in the newborn screening panels in all states.[6] By testing for MCADD in newborn screening programs, providers can institute appropriate avoidance of fasting in affected patients so that catastrophic outcomes can be avoided. Further guidance regarding the evaluation of abnormal newborn screen results can be found on the American College of Medical Genetics and Genomics Web site (https://www.acmg.net).

ACUTE MANAGEMENT

At-home Care

Many children with MCADD have a metabolic specialist primarily responsible for the care of their condition. Parents are instructed to monitor the child carefully, especially during periods of illness. Symptoms that should prompt concern include decreased oral intake, increased sleepiness, decreased activity, and vomiting. Some metabolic specialists institute a home glucose monitoring plan that includes checking glucose concentrations during periods of illness and whenever hypoglycemic symptoms are suspected. Other specialists prefer that patients present for evaluation when there are illnesses or circumstances that may prompt hypoglycemia. At-home care for a patient with MCADD may be possible as long as the child can tolerate adequate oral intake to prevent hypoglycemia, but caregivers should only attempt to do so in consultation with the patient's metabolic specialist. Rehydration solutions intended to replace fluid and electrolytes during periods of diarrhea and vomiting do not contain enough sugar to maintain blood glucose concentrations in a patient with MCADD; better choices for children no longer consuming infant formula or human milk are drinks that contain higher concentrations of sugar, such as juice or sports drinks.

For some patients, the metabolic specialist will prescribe bedtime doses of raw cornstarch, a complex carbohydrate that breaks down slowly, releasing glucose for an extended period of time. However, in the face of an illness that increases metabolic demand, cornstarch alone may not be sufficient to prevent overnight hypoglycemia. Pediatric health care providers and parents should be cautious and conservative when assessing a patient with MCADD. The pediatric health care provider should pay particular attention to the parent or caregiver's assessment of mental status in a child of any age. A mild decrease in activity level or attentiveness or a behavior unusual to the caregiver may be an early signal of an MCADD exacerbation, which can progress rapidly to seizures, coma, or death.

Emergency Care

It is recommended that a child with a known diagnosis of MCADD be brought to the emergency department (ED) for supplemental glucose administration early in the course of an illness to prevent development or progression of an MCADD exacerbation. This is particularly important when regular oral intake cannot be guaranteed or when parents or caregivers are unsure of the severity of symptoms. Patients and their families are typically given a sick letter or emergency letter written by the child's metabolic specialist to present at the time of arrival in the ED. Patients may also wear a medical alert bracelet or necklace to notify medical personnel of their condition. Patients and parents or caregivers are advised to carry a copy of the emergency letter with them for unexpected illnesses while away from home and are also advised to share it with the child's primary care provider. This letter usually also contains useful information for any health care provider who is planning an elective procedure. At a minimum, this letter provides direct care instructions for the ED and contact information for the metabolic specialist or provider. The metabolic specialist should be notified promptly about a patient's visit to the ED, even if the result of the ED evaluation is negative and the patient appears well and suitable for discharge from the hospital.

It cannot be stressed enough that at the time of arrival to the ED, patients with MCADD require immediate triage and medical attention. If required to wait their turn, the illness may progress to life-threatening stages in the interim, even with a brief wait. The patient should be evaluated rapidly for signs and

symptoms of hypoglycemia, including mental status changes. Patients with hypoglycemia on presentation should be treated on the basis of the severity of hypoglycemia. The most critical aspect of management of patients with MCADD is the provision of glucose, either orally or intravenously, as soon as possible, especially if there are any concerns about mental status changes. If the glucose concentrations are at or just above the normal range, the patient is not symptomatic, and the patient can tolerate sustained oral intake, then the provision of simple carbohydrates by mouth may be enough to maintain a normal blood glucose concentration. If the determination is made to discharge such a patient from the hospital rather than admit, the health care provider needs to educate the patient and/or caregivers of the signs or symptoms that should prompt a return visit to the ED. These signs include decreased mental status, decreased oral intake due to refusal or emesis, dehydration, prolonged illness, signs or symptoms of hypoglycemia, and increased caregiver concern. Follow-up arrangements with the patient's primary metabolic specialist should be made before discharge from the ED.

Many providers recommend placement of an intravenous (IV) catheter for administration of dextrose fluids at presentation to the ED, even before the examination or laboratory evaluation. If a patient with MCADD presents with a blood glucose concentration below normal range or has symptoms of hypoglycemia, then it is critical than an IV catheter be placed immediately for the administration of dextrose-containing fluids, regardless of the patient's tolerance for oral intake. A symptomatic patient with MCADD should have acute hypoglycemia treated with a bolus of 0.25 mg/kg dextrose, up to 25 g. Once euglycemia is restored, then continuous infusion of fluids containing glucose should be established. Dextrose 10% in water without any added salts is too hypotonic for continuous infusion. For children who are younger than 12 months, dextrose 10% in one-quarter–normal saline is recommended. For children who are older, dextrose 10% in half-normal saline may be administered. The rate of delivery should be at least 1.5 times that of maintenance fluids, as calculated by weight or body surface area, to accomplish a glucose infusion rate (GIR) of 10 mg/kg per minute, which is achieved by delivering dextrose 10% at this rate.[11] If the patient is experiencing rhabdomyolysis, then IV fluids with at least a 10% dextrose solution should be administered at 2 times the maintenance rate. Dextrose 5% fluids should not be used routinely in patients with MCADD, but if IV fluids with at least a 10% dextrose solution are not immediately available, dextrose 5% in half-normal saline, infused at 2 times the maintenance rate, can be used to bridge for a brief period of time until the appropriate IV fluids with a higher dextrose solution are available from the pharmacy. Once available, the patient should immediately be changed to the higher dextrose concentration to provide the desired GIR.

A thorough physical examination and clinical evaluation should be conducted to identify the source of the precipitating illness. Uncomplicated infections typical of childhood, such as otitis media, pharyngitis, or gastroenteritis, may trigger a metabolic exacerbation. If an etiology is identified, it should be appropriately treated to decrease the intensity or duration of the underlying illness. In addition to an immediate bedside glucose check, patients with MCADD may need additional laboratory evaluation in the ED. Severity of MCADD exacerbation can be assessed with a blood glucose and blood gas analysis. Additional laboratory assessments that may elucidate the triggering illness include a complete blood cell count with differential, serum chemistries, liver enzyme tests, blood cultures, and a urinalysis. Alcohol consumption may be a factor in adolescents because alcohol intoxication, particularly binge drinking, has been reported to trigger metabolic exacerbations in patients with MCADD.[12]

While the patient is maintained on IV fluids with at least a 10% dextrose solution and a GIR of at least 10 mg/kg per minute,[11] bedside glucose checks are unnecessary because this level of dextrose infusion is sufficient to prevent hypoglycemia in the absence of additional risk factors or interrupted administration. Patients who are prescribed uncooked cornstarch therapy at bedtime on a routine basis do not need cornstarch administration continued while receiving fluids with a GIR of at least 10 mg/kg per minute. A continuous infusion at this GIR will prevent overnight hypoglycemia. New treatment with uncooked cornstarch should be initiated by a metabolic health care provider and dietitian.

If a patient with MCADD also has signs and symptoms of dehydration at presentation, the delivery of dextrose-containing fluids should not be delayed to administer a normal saline bolus. If the IV catheter is of sufficient caliber, the fluid bolus can either be administered concurrently in the same IV line as the dextrose-containing fluids or through a separate IV line. If IV access cannot be initiated promptly and the child has appropriate mental status for enteral intake, then oral intake can be encouraged with carbohydrate-containing beverages, such as sports drinks, fruit juice, or nondiet sodas for older children and formula or human milk for infants. Antiemetics should be considered for those with persistent emesis to allow for increased enteral intake. It should be noted that children with MCADD should never be given formulas

enriched with medium-chain triglyceride oil, such as those often used in patients with abnormal bile secretion, pancreatic failure, or prematurity, because of their inability to process these fatty acids. If the child refuses oral intake or has recurrent emesis and IV access still cannot be established, then placement of a nasogastric or nasojejunal tube can be considered for continuous infusion of carbohydrate-rich fluids.

During the acute phase of an MCADD exacerbation, reliable parenteral access is indicated. If a patient with MCADD who has been receiving IV fluids with at least a 10% dextrose solution loses IV access, the IV should be replaced, unless the patient is ready for discharge. The approach of decreasing the IV infusion rate and monitoring for adequate intake should be avoided unless the child has already demonstrated substantial improvement. Likewise, avoid reducing the GIR by reducing the rate of fluid infusion in an attempt to encourage oral intake, especially in young children who do not understand the intent or the consequences if adequate oral intake does not follow. When a child has reached approximately three-quarters of their typical home intake without recurrent emesis, then the rate of the IV infusion can be decreased.

The use of L-carnitine therapy during acute and chronic management of MCADD remains controversial. The logic behind the use of L-carnitine supplementation is that excess acylcarnitines generated as a result of MCADD may bind free carnitine and be excreted by kidneys, leading to secondary carnitine deficiency. Given carnitine's role in the transfer of long-chain fatty acids across the inner mitochondrial membrane for subsequent β-oxidation, a deficiency in carnitine could lead to abnormalities in fatty acid oxidation.[13,14] Some authors recommend oral supplementation with 100 mg/kg per day of carnitine to correct the potential of secondary carnitine deficiency and to enhance the elimination of toxic metabolites.[15] Others recommend monitoring carnitine levels and only supplementing when they are low. Studies evaluating exercise intolerance and response to fasting challenges have been contradictory.[16–18] Importantly, carnitine supplementation is associated with significant long-term cost and mild side effects (nausea, diarrhea, abdominal pain, and a fishy odor).[17] If patients with MCADD present for care of an acute episode, the guidance provided in their sick letter or emergency letter should be followed (ie, if patients are on a long-term carnitine regimen, then they should continue on carnitine in the ED). If a letter is not available, the pediatrician should ask the parents if their child is on routine carnitine supplementation. If possible, the child's metabolic specialist should also be contacted for further instruction regarding L-carnitine therapy during the acute MCADD exacerbation.

Perioperative Management of a Patient With MCADD

Patients with MCADD are at risk for hypoglycemia if oral intake is withheld for a prolonged period before or after surgery. For elective surgical procedures, patients should be able to tolerate oral intake of clear glucose-containing fluids up to 4 hours before surgery. In a patient with MCADD, IV administration of fluids with at least a 10% dextrose solution should be started when oral intake is discontinued. Similar to an episode of acute metabolic exacerbation, IV fluids with at least a 10% dextrose solution should be infused at a rate at least 1.5 times that of maintenance to provide a GIR of 10 mg/kg per minute. Metabolic support with IV fluids with at least a 10% dextrose solution should continue through the surgery and during the recovery phase until the patient can consume an adequate oral intake. For otherwise routine procedures, such as a tonsillectomy and adenoidectomy, this may require an overnight admission if the child is unable or unwilling to eat and drink because of postoperative pain.

Trauma Management of a Patient With MCADD

A patient with MCADD with injury requires careful management to prevent acute metabolic decompensation. Injury can increase metabolic demands while also resulting in decreased oral intake because of altered mental status or pain. IV fluids with at least a 10% dextrose solution should be started if there are any signs or symptoms of hypoglycemia. Additionally, if the patient cannot immediately resume a regular diet because of mental status, assessments, or procedures, then IV fluids with at least a 10% dextrose solution will be required at 1.5 times the maintenance rate until typical oral intake is resumed.

CONCLUSIONS

Patients with MCADD who have not suffered any sequelae from their disease may present with acute illnesses or injuries similar to other patients. However, because of their interrupted metabolic pathway, they are at risk for acute metabolic decompensation during times of increased metabolic demand or decreased caloric intake. Supporting these patients with IV fluids with at least a 10% dextrose solution at 1.5 times the maintenance rate can avert the risk of hypoglycemia and prevent catastrophic outcomes.

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ABBREVIATIONS

ED: emergency department
GIR: glucose infusion rate
IV: intravenous
MCADD: medium-chain acyl-coenzyme A dehydrogenase deficiency

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