

**Medium Chain Acyl-coa Dehydrogenase (MCAD) Deficiency;  
Suggested protocol for diagnosis and management in Iran  
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- MCAD def. is one of the most common fatty acid  $\beta$ -oxidation disorder.

**When should we suspect MCAD def?**

MCAD deficiency should be suspected in:

- 1. An infant with positive newborn screening result
- 2. A previously healthy individual who becomes symptomatic
- 3. A case of sudden and unexpected death

**1. Positive Newborn Screening (NBS) Result**

It includes elevations of C8-acylcarnitine with lesser elevations of C6-, and C10-acylcarnitine.

Ratios of C8/C2 and C8/C10 in presumptive positive cases may be used to increase NBS sensitivity.

Infants with positive NBS results should perform confirmatory biochemical tests including:

- Plasma acylcarnitine analysis
- Urine organic acid analysis
- Urine acylglycine analysis

False positive causes for elevations of C8-acylcarnitines are as below:

- term infants, appropriate for gestational age and heterozygous for the common c.985A>G pathogenic variant
- premature infants

False negative NBS results may be occurred in newborns with low free carnitine levels, such as:

- infants born to a mother with low free carnitine levels, including previously undiagnosed mothers with MCAD deficiency, maternal carnitine transporter deficiency, or nutritional carnitine deficiency

A newborn may become symptomatic before the screening results are available. Breast fed infants are at higher risk because of small supply of breast milk at this time. They may present with hypoglycemia or arrhythmia.

**2. A previously healthy individual who becomes symptomatic**

Manifestations of acute decompensation:

- Hepatomegaly

- Hypoketotic hypoglycemia,
- Increased anion gap,
- Hyperuricemia,
- Elevated liver transaminases
- Hyperammonemia

Affected individuals tend to present in response to either prolonged fasting (e.g., weaning the infant from nighttime feedings) or intercurrent and common infections (e.g., viral gastrointestinal or upper respiratory tract infections), which typically cause loss of appetite and increased energy requirements when fever is present.

The presence of low levels of ketones on urinalysis, urine organic acids, or serum beta-hydroxybutyrate should not be taken as evidence against MCAD deficiency (hypoketotic" as compared to nonketotic), as ketones may be detected during times of acute metabolic decompensation.

Acute decompensation may occur at later ages.

Several patients, were firstly diagnosed between 16 and 45 years of age with metabolic acidosis, hyperammonemia, hyper lactic acidemia, hypoglycemia, myoglobinuria and elevation of creatine kinase (CK).

Other manifestations of undiagnosed patients include:

**Neurologic** (secondary to uncontrolled metabolic decompensation):

losing developmental milestones

aphasia

attention-deficit disorder

**Muscular:**

Chronic muscle weakness (18%)

Fatigue

Poor exercise intolerance

**Cardiac** (rare):

Prolongation of the QTc interval, arrhythmia

**Renal** disease:

Risk of chronic kidney disease with increasing age

### 3. Un-explained death

The following information supports the possibility of MCAD deficiency for an un-explained death:

- Evidence of lethargy, vomiting, and/or fasting in the 48 hours prior to death
- Breast-fed infant (rather than bottle-fed)

- Adult following an episode of fasting or alcohol consumption
- A family history of sudden death or Reye syndrome in sibs.
- Findings at autopsy of cerebral edema and fatty infiltration of the liver, kidneys, and heart

### **Definite diagnosis of MCAD deficiency**

- **Plasma acylcarnitine analysis:**

prominent accumulation of C8- (octanoylcarnitine), with lesser elevations of C6-, C10-, and C10:1-acylcarnitines.

Sole reliance on plasma acylcarnitine analysis may not be sufficient.

- Urine organic acids and acylglycines (ideally collected during an acute episode of metabolic decompensation) should be analyzed too.

### **Urine organic acid analysis:**

Standard urine organic acid profiles are often uninformative in individuals with MCAD deficiency who are clinically stable and not fasting.

### **Urine acylglycine analysis:**

- Elevated n-hexanoylglycine, 3-phenylpropionylglycine, and suberylglycine are more sensitive and specific for asymptomatic individuals than organic acid analysis alone.

*Urine organic acids and acylglycines, as well as plasma acylcarnitines, could normalize when the individual is not under metabolic stress.*

### **Molecular Genetic Testing:**

- Gene-targeted testing (single-gene testing, multigene panel)
- Comprehensive genomic testing

Infants with positive NBS and confirmatory follow-up testing:

Gene-targeted testing is recommended.

Symptomatic individuals with nonspecific supportive clinical and laboratory findings:

Comprehensive genomic testing (including whole exome sequencing) is recommended.

A common mutation, c.985A>G, accounts for 70 percent of mutant alleles in individuals of Northern European ancestry. There is not enough data about common mutations in Iran.

### **Management**

**Avoidance of Fasting** is the mainstay of treatment of MCAD deficiency.

The length of time that asymptomatic individuals should be able to fast in the absence of an intercurrent infection with fever or other stressing conditions:

Up to eight hours in infants between ages six and 12 months

Up to ten hours during the second year of life

Up to 12 hours after age two years

**A general rule of thumb:**

four hours between birth and age four months,  
then add an additional hour of fasting for each month of age up to 12 months.

**Practical points to avoid excessive fasting:**

Infants require frequent feedings (every 2-3 hours), as is the practice with unaffected newborn infants.

Some physicians recommend overnight feedings, a bedtime snack, or 2 g/kg of uncooked cornstarch as a source of complex carbohydrates at bedtime to ensure sufficient glucose supply overnight. However, if an individual does not have an illness, this supplemental feeding may not be necessary.

**Diet:**

A normal, healthy diet containing no more than 30% of total energy from fat may be followed.

**Breastmilk or standard infant formulas are appropriate to meet nutritional needs during infancy, with introduction of solids per standard infant feeding guidelines.**

**Management of symptomatic individuals:**

Reversal of catabolism and prevention of hypoglycemia by providing simple carbohydrates by mouth (e.g., glucose products or sweetened non-diet beverages) or intravenous fluids as below if the individual is unable to receive sufficient oral intake to maintain anabolism.

IV administration of glucose:  
immediately with a bolus of 4 mL/kg 10% dextrose, followed by 10% dextrose with appropriate electrolytes at a rate of 1.5 times maintenance rate to achieve and maintain a blood glucose level between 120 and 170 mg/dL

L-carnitine supplementation is controversial. Low-dose L-carnitine supplementation is recommended when free carnitine levels are below the normal range.

**Surveillance:**

**first months of life:**

- Monthly visits to ensure that families understand and are comfortable with treatment while the infant is otherwise well.
- A metabolic dietician should be involved to ensure proper nutrition in terms of quality and quantity.

The frequency of routine follow-up visits is individualized based on comfort level of the affected persons, their families, and health care providers.

**follow up:**

- Weight control measures, proper nutrition, physical exercise
- Neurodevelopmental assessments and intervention

**Agents to avoid:**

Infant formulas, coconut oil, and other manufactured foods containing medium-chain triglycerides as the primary source of fat are contraindicated in MCAD deficiency.

Popular high-fat/low-carbohydrate diets are not appropriate in MCAD deficiency

Alcohol consumption, in particular acute alcohol intoxication (e.g., binge drinking), often elicits metabolic decompensation

Aspirin has been demonstrated to exacerbate MCAD deficiency by increasing mitochondrial fatty acid oxidation and long-chain fatty acid flux, and inhibiting peroxisomal fatty acid oxidation, which normally serves as a lipotoxic buffer

**Relatives at Risk**

It is appropriate to evaluate other siblings:

If the ACADM pathogenic variants in the family are known, **molecular genetic testing** can be used to clarify the genetic status of at-risk sibs and offspring of a proband.

If the ACADM pathogenic variants in the family are not known, **plasma acylcarnitine and urine acylglycine** analysis can be used.

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