

## **Methylmalonic CoA Mutase Deficiency aka MUT- and MUT° Methylmalonic Acidemia (MMA)**

### **Description:**

Methylmalonic Acidemia is an autosomal recessive disorder. The incidence of both benign and severe forms is each about 1 in 50,000. MMA is caused by a deficiency of methylmalonyl-CoA mutase (MCM), a vitamin B12-dependent enzyme. The deficiency of MCM leads to accumulation of methylmalonyl-CoA, resulting in greatly increased amounts of methylmalonic acid in plasma and urine.

### **Incidence in General Population:**

MUT- & MUT°—1:75,000 live births

### **Symptoms:**

Dehydration and failure to thrive are generally the first signs of MMA. Symptoms usually begin in the first few months of life and include lethargy, vomiting, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays.

Methylmalonic acidemia can be expressed differently depending on the following:

- Absence of enzyme activity even when hydroxycobalamin is provided in excess (**mut°**).
- Reduction in enzyme activity but activity detectable when stimulated by a high concentration of hydroxycobalamin (**mut<sup>-</sup>**).

Vitamin B12-responsive MMA patients can have a milder disease and a better clinical outcome. Conversely, Vitamin B12-unresponsive MMA patients have severe disease and many encephalopathic episodes. The early onset patients have the poorest survival rate. Survivors of both the early- and late-onset forms may have poor growth and neurologic sequelae with developmental delay and neurological impairment, and many older patients present can have chronic renal failure.

### **Diagnosis:**

Newborn screening abnormality—Tandem mass spectrometry: C3—elevated  
C4 DC—elevated

A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

### **Situations That Risk Metabolic Decompensation:**

Protein catabolism can be caused by intercurrent infections, immunizations, trauma, anesthesia and surgery, fasting, dehydration, and dietary indiscretion. In cases of clinical deterioration with anorexia and/or gastric intolerance or if the child is obviously ill, the patient must be hospitalized to evaluate the clinical status and metabolic imbalance, to search for and treat intercurrent disease, and to halt protein catabolism. Emergency therapy depends on the presence of dehydration, acidosis, ketosis, and hyperammonemia.

**Monitoring:**

Clinical observation is the most important tool for monitoring patients with MMA. It is important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

**Treatment:**

Long-term dietary treatment is aimed at reducing accumulated toxic metabolites while at the same time maintaining normal development and nutritional status and preventing catabolism. Some patients tolerate normal foods; others need only minimal restriction or can even regulate the diet themselves. However, many need very specific food allowances, implying stringent dietary restrictions that will likely be a life-long necessity.

- Precise prescriptions for the daily intake of amino acids, protein, and energy will be determined by the Metabolic Treatment Center.
- Frequent monitoring of clinical and metabolic status will be done.
- Enough water must be added to prevent dehydration of these patients who may have a low renal concentrating capacity and may not tolerate hyperosmolar formulas.
- Cobalamin and carnitine supplementation are suggested.
- Short-term treatment with oral metronidazole may improve alertness and appetite, while longer treatment periods have resulted in a decrease in the number and severity of acidotic episodes, increase in appetite, decreased vomiting, growth acceleration, and improved behavior.
- Infants and children with MMA should have regularly scheduled visits at the Metabolic Treatment Center.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

**Illness:**

- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of illness.

**Immunization:**

Immunizations must be kept current. Influenza vaccinations are also recommended.

**Surgical/Surgical Procedures:**

- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

**Growth and Development:**

- It is crucial to closely monitor all growth, development, and biochemical parameters with a monthly evaluation on length, weight, and head circumference.
- The child should be referred to an early intervention program, and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
- Regular assessment of developmental progress provides the opportunity for psychological support, as social and emotional needs are major elements of the overall therapy of the affected child and of the well being of the family.



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