

Disease Name:

3-METHYLGLUTACONIC ACIDURIA TYPE II
(X-LINKED CARIOSKELATAL MYOPATHY, NEUTROPENIA & ABNORMAL MITOCHONDRIA) (BARTH SYNDROME; MGA, TYPE II)

Classification: Organic aciduria

Genetic Information:

Inheritance: X-linked recessive

Population Incidence: Rare, less than 50 cases described (probably underdiagnosed)

Ethnic Incidence: No known population at increased risk

Gene & Location: G4.5 protein (tafazzin) gene on Xq28

Common Mutation: No known common mutations

OMIM # #302060; *300394

Disease Information:

Symptom Onset: Presents in the neonatal period

Symptoms: The initial presentation of the syndrome varies. Newborns tend to be small for gestational age. Prenatal detection of cardiac abnormalities has been found in some affected infants. Dilated cardiomyopathy, cyclic neutropenia, growth retardation, short stature, skeletal myopathy and 3-methylglutaconic aciduria (3MGA) are the most common clinical findings. 3MGAuria is variable and tends to be less severe than that seen in MGA, Type 1. Shoulder and pelvic muscles are most affected by the skeletal myopathy and is progressive, while extraocular and bulbar muscles are spared. Neutropenia has been noted on cord blood studies, tends to be congenital but varies with time. Differentiation in bone marrow becomes arrested at the myelocyte stage causing granulocytopenia. Patients die from overwhelming infection or cardiac failure- have been reports of sudden infant death, which may be related to arrhythmia. Common infections observed are bacterial skin lesions and oral aphthous lesions without severe illness. The cardiomyopathy and frequency and severity of bacterial infections decreased with age in some families. Over time the facial features become myopathic. Patients with Barth syndrome may have some specific learning problems. In one limited study problems with visual-spatial learning and visual motor scores were noted. IQ does not appear to be much different from age matched controls. However, there was a tendency toward lower math scores

Physical Findings: No dysmorphisms, as they age tend to have myopathic appearance to their faces.

Treatment: Carnitine does not appear to improve cardiac function; in one patient it caused heart failure. Some authors propose that it is contraindicated. Pantothenic acid, a precursor for coenzyme A, has been used in some with improved cardiac function. However, oral pantothenol not efficacious. Otherwise there are no specific therapies available except supportive care for cardiac problems and infection. The cardiomyopathy responds to digoxin therapy and some patients have been placed on granulocyte colony stimulating factor (GCSF) for the neutropenia.

Natural History without treatment: Without care of the neutropenia and cardiac failure patients will die.

Natural History with treatment: If care is given the patient has improved chance of survival but still at high risk for morbidity and mortality.

Metabolic Information:

Missing Enzyme & Location: The basic enzyme defect involves cardiolipin, membrane lipid with importance to stability of mitochondrial respiratory chain.

MS/MS profile: C5-OH (3-hydroxyisovaleryl carnitine) - elevated

Prenatal testing: Possible if mutation previously identified in family.

Miscellaneous Information:

In two families with documented G4.5 mutations, no 3-methylglutaconic acid has been found on analysis of urine organic acids.

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