Genetics Newborn Screening Program
Health Professional Fact Sheet

Ethylmalonic Aciduria (EDA)

Introduction

Ethylmalonic Aciduria Encephalopathy is a rare disorder characterized by damage to the central nervous system resulting in developmental delay, weak arms and legs and involuntary muscle spasms. EDA is a common finding in patients with inborn errors of short chain fatty acid beta-oxidation. There are also several large masses of grey matter embedded in the brains white matter (basal ganglia). This disorder is thought to be caused by mutations in the ETHE1 gene which has been located on the short arm of chromosome 19. Four unrelated Italian patients were identified with encephalopathy and a pattern of metabolite excretions including ethylmalonic acid and branched chain acylglycines and acylcarnitines suggestive of a deficiency of short-methylbranched chain acyl-CoA Dehydrogenase in the catabolic pathways of both valine and isoleucine.

Clinical Features

Patients may present with neonatal hypotonia followed by severe progressive pyramidal dysfunction, mental retardation, orthostatic acrocyanosis with distal swelling, chronic diarrhea, recurrent petechiae, and abnormal brain MRI. MRI shows areas of hyperintensity in the cerebellar white matter and the caudate and lenticular nuclei. Patients have had chronic lactic acidemia and repeated metabolic decompensation with metabolic acidosis but not ketosis and normal blood glucose and ammonia levels. MRI may show a large number of lesions in many areas of the brain including the basal ganglia, putamen, and caudate. Dysmorphic features, hepatomegaly, retinal lesions, and gross hematuria may also be seen.. These symptoms are similar to those seen in mitochondrial disorders, and ethylmalonic acid is common in proven mitochondrial defects.

The possibility of this disorder involving both valine and isoleucine catabolism should be considered in patients with lactic acidemia, hypotonia, spastic diplegia, orthostatic acrocyanosis with distal swelling, and diarrhea. The pattern of organic acid metabolites in urine with highly elevated ethylmalonic acid and isobutyrylglycine, together with elevation of methylsuccinic acid, butyryglycine, isovalerylglycine, and 2-methylbutyrylglycine and elevated C4 and C5 acylcarnitines in plasma and urine but without elevation of glutaric or 2-hydroxyglutaric acid appears to be diagnostic. Multiple acyl-CoA Dehydrogenase deficiency should be ruled out by fatty acid oxidation studies or assay for Electron Transfer Flavoprotein(ETF) and ETF Dehydrogenase.

Diagnosis

Newborn screening—Tandem mass spectrometry C4 and C5

Confirmation— a second sample may be requested or follow up testing will be done at the Metabolic Treatment Center at Yale or UCONN Genetics.

Treatment

An effective treatment is not known. A diet low in branched chain amino acids would theoretically be appropriate.

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