

Disease Name:

CITRULLINEMIA, TYPE 2

(CITRULLINEMIA, TYPE II, ADULT-ONSET; CTLN2; CITRULLINEMIA, TYPE II, NEONATAL-ONSET; CHOLESTASIS, NEONATAL INTRAHEPATIC, CAUSED BY CITRIN DEFICIENCY)

Classification: Urea cycle defect

Genetic Information:

Inheritance: Autosomal recessive

Population Incidence: Unknown

Ethnic Incidence: Of the 150 identified cases, all but 7 have been in Japan

Gene & Location: SLC25A13 gene- 7q21.3

Common Mutation: IVS11+1G>A- accounts for 40% of mutated alleles found in Japan. Second most common is 851del4. Together they account for 70% of patients in Japan.

OMIM # #603471; #605814

Disease Information:

Symptom Onset: The neonatal intrahepatic cholestasis develops between 1-5 months of age. The adult onset 11-64 years of age.

Symptoms: Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) has been diagnosed in over 70 infants between 1-5 months of age. In addition to intrahepatic cholestasis they have jaundice and fatty liver at biopsy. Liver disease generally resolves by one year of age. Three patients developed liver failure necessitating transplants before 12 months of age.
Among patients with CTLN2 presentation may be in childhood or adulthood (11-64 years). Symptoms may be acute or develop gradually and include enuresis, delayed menarche, insomnia, nocturnal sweats and terrors, recurrent vomiting, diarrhea, tremors, confusion, lethargy, convulsions, delusions, hallucinations and episodes of coma. Hypercitrullinemia and hyperammonemia are present. Pancreatitis, hyperlipidemia or death from cerebral edema generally occurs within a few years of the diagnosis. Hepatocellular carcinoma has been reported in a few cases.

Physical Findings: No dysmorphisms. Only physical findings are related to the cholestasis or the psychological findings in adulthood.

Treatment: Treatment of choice is liver transplant in the adult form, it is not known if the neonatal form patients will go on to develop the adult form. Neonatal symptoms tend to resolve with protein restriction. Arginine may help ameliorate the symptoms.

Natural History without treatment: The neonatal form may resolve. The adult form progresses to death.

Natural History with treatment: Liver transplantation may cure the disorder.

Metabolic Information:

Missing Enzyme & Location: Citrin is a calcium dependent mitochondrial aspartate glutamate transporter that inactivates argininosuccinate synthetase activity only in the liver, presumably by disrupting mitochondrial export of aspartate and from defects in the malate aspartate shuttle.

MS/MS profile: Citrulline- elevated

Prenatal testing: Possible to do enzyme assay in at risk pregnancy with amniocytes or CVS.

Miscellaneous Information:

Prepared for the NW Regional Newborn Screening Program by Sara Copeland MD, Judith Tuerck RN MS and Lorinda Paradise at OHSU in Portland, OR.

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