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Citrullinemia Type I

[*Argininosuccinic Acid Synthetase Deficiency; CTLN1; Citrullinemia, Classic; ASS Deficiency; Argininosuccinate Synthetase Deficiency*]

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Summary

Disease characteristics. Citrullinemia type I (CTLN1) presents as a clinical spectrum that includes an acute neonatal form (the "classic" form), a milder late-onset form, a form without symptoms and/or hyperammonemia, and a form in which women have onset of severe symptoms during pregnancy or postpartum. Distinction between the clinical forms is based on clinical findings and is not clear-cut. Infants with the acute neonatal form appear normal at birth. Shortly thereafter, they develop hyperammonemia and become progressively lethargic, feed poorly, often vomit, and may develop signs of increased intracranial pressure (ICP). Without prompt intervention, hyperammonemia and the accummulation of other toxic metabolites (e.g., glutamine) result in ICP, increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death. Children with the severe form who are treated promptly may survive for an indeterminate period of time, but usually with significant neurologic deficits. The late-onset form may be milder than that seen in the acute neonatal form, for unknown reasons. The episodes of hyperammonemia are similar to those seen in the acute neonatal form, but the initial neurologic findings may be more subtle because of the older age of the affected individuals.

Diagnosis/testing. Citrullinemia type I results from deficiency of the enzyme argininosuccinate synthase (ASS), the third step in the urea cycle, in which citrulline is condensed with aspartate to form argininosuccinic acid. Untreated individuals with the severe form of citrullinemia type I have hyperammonemia (plasma ammonia concentration 1000-3000 µmol/L). Plasma quantitative amino acid analysis shows absence of argininosuccinic acid and concentration of citrulline usually greater than 1000 µmol/L (normal: <50 µmol/L). Argininosuccinate synthase enzyme activity, measured in fibroblasts, liver, and in all tissues in which ASS is expressed, is decreased. *ASS* is the only gene known to be associated with citrullinemia type I. Sequence analysis, deletion/duplication analysis, and linkage analysis are clinically available.

Management. *Treatment of manifestations:* control of hyperammonemia using the Ucyclyd protocol of alternative means of waste nitrogen disposition (sodium benzoate and phenylacetate) or, if that protocol fails after two doses of medications, emergency use of hemodialysis; concomitant appropriate protein and calorie nutrition to prevent a catabolic state; steps to prevent increased intracranial pressure. *Prevention of primary manifestations:* when solid foods are tolerated, oral administration of sodium phenylbutyrate and lifelong dietary management to maintain plasma ammonia concentration lower than 100 µmol/L and near-normal plasma glutamine concentration; L-carnitine to prevent systemic hypocarnitinemia.

Liver transplantation has been reported. *Prevention of secondary complications:* medical attention during intercurrent infections to prevent hyperammonemia. *Surveillance:* routine follow-up in a metabolic clinic; monitoring for hyperammonemia and secondary deficiency of essential amino acids; monitoring older individuals for signs of impending hyperammonia (i.e., mood changes, headache, lethargy, nausea, vomiting, refusal to feed, ankle clonus) and elevated plasma glutamine concentration. *Circumstances to avoid:* excess protein intake; exposure to communicable diseases.

Genetic counseling. Citrullinemia type I is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Sibs should be evaluated immediately after birth and placed on a protein-restricted diet until the diagnostic evaluation is complete. Prenatal diagnosis for pregnancies at 25% risk is available by enzyme analysis and linkage analysis if the family is informative for linked markers.

Diagnosis

Clinical Diagnosis

Citrullinemia type I results from deficiency of the enzyme argininosuccinate synthase, the third step in the urea cycle, in which citrulline is condensed with aspartate to form arginosuccinic acid (see Figure 1, Urea Cycle Disorders Overview: Definition).

Classic neonatal-onset citrullinemia type I is suspected in infants who have been on a full protein diet and who present in the first week of life with:

- Hyperammonemia resulting in increasing lethargy, somnolence, refusal to feed, vomiting, and tachypnea or stroke;
- Increased intracranial pressure (secondary to hyperammonemia) resulting in increased neuromuscular tone, spasticity, and ankle clonus.

Milder, adult-onset citrullinemia type I is suspected in individuals with recurrent lethargy, somnolence, mental retardation, and chronic or recurrent hyperammonemia.

Testing

Newborn screening. Expanded newborn screening, now used in most states in the United States and elsewhere in the world, may include screening for CTLN1. True positives have been reported from programs in Korea, where two in 44,300 newborns with CTLN1 were detected [Yoon et al 2003] and New England, where the detection rate was one in 200,000 [Marsden 2003].

Plasma ammonia concentration

- In the severe form, the initial plasma ammonia concentration may be 1000-3000 µmol/L.
- In the milder neonatal and adult forms, a lower plasma concentration may be seen (adult upper limit of normal: <35 µmol/L).

Plasma quantitative amino acid analysis

- Citrulline: usually greater than 1000 µmol/L (normal: <50 µmol/L)
- Argininosuccinic acid: absent

- Arginine and ornithine: low to normal range (See Urea Cycle Disorders Overview: Evaluation Strategy, Figure 3.)
- Lysine, glutamine, and alanine: increased (These are surrogate markers of hyperammonemia.)

Urinary organic acids. Normal, except orotic acid may be detected as part of urinary organic acid analysis by gas chromatography/mass spectrometry; however, the sensitivity depends upon the extraction method.

Argininosuccinate synthase (ASS) enzyme activity. Incorporation of radiolabeled citrulline into argininosuccinic acid is measured in cultured fibroblasts. ASS activity is also determined by a method based on the conversion of radiolabeled (^{14}C)-aspartate to (^{14}C)-argininosuccinate [Gao et al 2003].

- The normal enzyme activity in fibroblasts is 0.8-3.8 nmol/min/mg protein, but this is specific to tissue, method, and laboratory.
- Cultured chorionic villus cells or cultured amniocytes from the fetus may be used for prenatal diagnosis.

For laboratories offering biochemical testing see Testing.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *ASS1* is the only gene known to be associated with citrullinemia type I.

Clinical uses

- Carrier detection
- Prenatal diagnosis. Although prenatal diagnosis is performed primarily by analysis of enzyme activity, the results can be confirmed by linkage analysis in informative families.
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis.** Sequencing of genomic DNA from a variety of cells or cDNA from cultured fibroblasts detected 154 of 160 (96%) of abnormal alleles [J Häberle, personal communication]. In Japan, a small number of mutations account for the majority of cases of CTLN1 [Kakinoki et al 1997]; however, a large number of mutations are found in individuals of Caucasian origin.
- **Deletion/duplication analysis.** No deletions or duplications have been reported involving *ASS1* as causative of citrullinemia type I. However, with newly available deletion/duplication testing, the mutation detection frequency may be assumed to increase, defining mutations in patients in whom prior sequence testing was negative.
- **Linkage analysis.** An intragenic dinucleotide repeat is informative in 60%-70% of families.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Citrullinemia Type I

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*ASS1* sequence alterations	96% [1]	Clinical Testing
Deletion/duplication analysis [2]	Partial or whole-gene deletions	Unknown	
Linkage analysis	Intragenic dinucleotide repeat	Informative in 60%-70%	

1. In 80 individuals evaluated, both abnormal alleles were identified in 75 (94%), one abnormal allele in four (5%), and no abnormal alleles in one (1%).
2. By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Measurement of plasma ammonia concentration and plasma citrulline concentration establishes the diagnosis.

Enzyme assay and linkage analysis are not widely used because of the classic clinical presentation and relatively specific pattern of metabolites found in affected individuals.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *ASS1*.

Clinical Description

Natural History

Citrullinemia type I (CTLN1) presents as a spectrum that includes a neonatal acute form (the "classic" form), a milder late-onset form, a form in which women have onset of symptoms at pregnancy or postpartum, and a form without symptoms or hyperammonemia.

In the acute neonatal form, the infant appears normal at birth. After an interval of one to a few days, the infant becomes progressively lethargic, feeds poorly, may vomit, and may develop signs of increased intracranial pressure [Brusilow & Horowitz 2001]. Fifty-six percent of infants with classic citrullinemia type I are symptomatic by age four days and 67% by age one week [Bachmann 2003a].

Recently, two infants with classic CTLN1 with ammonia concentrations in the range of 400-500 µmol/L presented at age two and three months with cerebral infarcts [Choi et al 2006].

Children diagnosed and referred for appropriate treatment (see Management) survive for an indeterminate period of time, usually with significant neurologic deficits. All children with a peak plasma ammonia concentration greater than 480 µmol/L or an initial plasma ammonia concentration greater than 300 µmol/L have cognitive impairment [Bachmann 2003b]. The longest survival of an untreated infant with classic citrullinemia type I is 17 days [Thoene et al 1977].

In the late-onset form, the clinical course may be similar to or milder than that seen in the acute neonatal form, but for unknown reasons commences later in life. When episodes of hyperammonemia occur, they are similar to those seen in the acute neonatal form, but the

neurologic findings may be more subtle because of the older age of the affected individuals. These can include intense headache, scotomas, migraine-like episodes, ataxia, slurred speech, lethargy, and somnolence. Individuals with hyperammonemia also display respiratory alkalosis and tachypnea [Brusilow & Horowitz 2001]. Without prompt intervention, increased intracranial pressure occurs, with increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death.

Women with onset of severe symptoms during pregnancy or in the postpartum period have been reported [Gao et al 2003, Ruitenbeek et al 2003]. A healthy woman with untreated CTLN1 underwent two successful pregnancies [Potter et al 2004].

Individuals remaining asymptomatic up to at least age ten years have been reported; it seems possible that they may remain asymptomatic lifelong [Häberle et al 2002, Häberle et al 2003].

Neuroimaging. CT scan of infants with citrullinemia type I demonstrates cerebral atrophy, particularly in the cingulate gyrus, the insula, and the temporal lobes, as well as general cortical hypo-attenuation (i.e., the cortex appears darker than in unaffected individuals) [Albayram et al 2002].

Genotype-Phenotype Correlations

Classic citrullinemia type I typically results from the mutations p.R304W, p.G390R, p.R108L, and IVS13+5G>A [Gao et al 2003].

Late-onset citrullinemia type I is associated with the mutations p.W179R, 1085G>T (p.G362V), p.R265H, and p.R86H [Gao et al 2003].

Nomenclature

The preferred terms for argininosuccinic acid synthetase deficiency are "citrullinemia type I," or "classic citrullinemia," which are used to avoid confusion with the genetically distinct disease, citrullinemia type II, or citrin deficiency.

Prevalence

Citrullinemia type I occurs in 1:57,000 births and represented 74 of 545 (13.6%) individuals with urea cycle disorders referred to the Johns Hopkins Hospital from 1974 to 1994 [Brusilow & Horowitz 2001].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Citrullinemia type II (CTLN2) is caused by citrin deficiency resulting from mutations in *SLC25A13* on chromosome 7q21.3, which encodes the mitochondrial solute carrier protein, citrin. Citrin deficiency leads to failure to shuttle aspartate and glutamate from and to the mitochondrion, leading to a mild hyperammonemia and citrullinemia. Mutation in the same gene leads to intrahepatic cholestasis in the neonate [Saheki & Kobayashi 2002]. The clinical course in adults with citrullinemia type II is milder, possibly distinguishing it from milder late-onset citrullinemia type I. It is not known why CTLN2 is milder and later in onset than CTLN1; distinguishing between the two disorders is difficult. The prevalence of citrullinemia type II has not been reported.

It is critical to distinguish hyperammonemia caused by a defect in the urea cycle from the secondary hyperammonemia caused by an organic acidemia (see Organic Acidemia Overview), which may cause inhibition of N-acetylglutamate synthase (see Urea Cycle Disorders Overview: Definition, Figure 2).

Classic citrullinemia type I shares the phenotype of the typical acute neonatal hyperammonemia displayed by other defects in the first four steps in the urea cycle pathway. The mild phenotype shares a later onset with other disorders such as late-onset ornithine transcarbamylase (OTC) deficiency. See Figure 3, Urea Cycle Disorders Overview: Evaluation Strategy, showing a diagnostic strategy to identify which steps in the urea cycle is defective in an individual with hyperammonemia.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Measurement of: concentration of plasma ammonia, amino acids, and electrolytes; blood gases; urinary organic acids; and urinary orotic acid
- Assessment of intracranial pressure and overall neurologic status

Treatment of Manifestations

Acute management of individuals with citrullinemia depends upon early diagnosis, control of hyperammonemia, and control of intracranial pressure. Regular attendance at a metabolic clinic with access to a trained metabolic nutritionist is essential to proper patient management.

Ucyclyd protocol. The protocol designed by Brusilow and colleagues (Ucyclyd Pharma®) should be followed. This protocol uses alternative means of waste nitrogen disposition (sodium benzoate and phenylacetate). Buphenyl (Ammonaps) (oral form of sodium phenylbutyrate) is approved by the FDA. Sodium phenylacetate/sodium benzoate, 10% intravenous solution, received FDA approval as Ammonul in February 2005.

Hemodialysis. Failure to control hyperammonia with the Ucyclyd protocol after two doses of medications described above requires emergency use of hemodialysis to reduce the plasma ammonia concentration to an acceptable level, following which institution of the sustaining infusion may be attempted, supplemented with additional doses over one hour as in the initial bolus infusion as needed to control plasma ammonia concentration [Lo et al 2003].

Diet. Concomitant with the Ucyclyd protocol, appropriate protein and calorie nutrition must be provided so that the affected individual does not become catabolic. In small infants, the 40 cal/100 mL given as D10W can be significant in averting catabolism. As soon as possible, osmolar load permitting, the individual should receive total parenteral nutrition (TPN) providing 0.25 g/kg/day of protein and 50 cal/kg/day, advancing (as plasma ammonia concentration allows) to 1.0-1.5 g/kg/day of protein and 100-120 cal/kg/day. Standard TPN solutions of dextrose, Aminosol, and intralipid are used.

Prevention of increased intracranial pressure. It is critical to monitor fluid balance, intake, and output and body weight, and to maintain the individual on the dry side of fluid balance: about 85 mL/kg of body weight per day in infants; appropriate corresponding fluid restriction in children and adults. Increased intracranial pressure is manifested by tension in the fontanel, acute enlargement of the liver, edema, and worsening neurologic signs including fisting, scissoring, ankle clonus, and coma. Cerebral edema and ischemia may be documented by MRI.

Prevention of Primary Manifestations

Medication. When the affected individual is able to tolerate solid food, the oral medication sodium phenylbutyrate (Buphenyl, Ammonaps), at a dose of 450-600 mg/kg/day divided into three doses, and arginine-free base of 400 and 700 mg/kg/day are begun. Success of therapy is defined by a plasma ammonia concentration lower than 100 µmol/L and near-normal plasma glutamine concentration. Plasma arginine concentration may be up to 250% above upper normal limit for age.

As children grow, the dose changes to 9.9-13 g/m^2/day of sodium phenylbutyrate and 8.8-15.4 g/m^2/day of arginine. For details of management, the reader is referred to Brusilow & Horowitz (2001).

Treatment with L-carnitine has been advocated as auxiliary treatment to prevent systemic hypocarnitinemia, which may result from therapy with acylating agents [Sanjujo et al 1991].

Diet. Lifelong dietary management is necessary and requires the services of a metabolic nutritionist.

Liver transplantation. Liver transplantation for treatment of urea cycle disorders has been reported by several groups. Of sixteen individuals undergoing liver transplantation, 14 lived 11 months to six years post transplantation; their neurologic outcomes correlated closely with their pre-transplantation neurologic status. Few problems with long-term health were related to the liver transplantation itself and the quality of life was much improved [Whitington et al 1998].

A successful living related-donor liver transplantation (240 g) from mother to six-year-old daughter has been reported. The allopurinol challenge test was normalized in this child, who previously had very brittle control with 4-6 hyperammonemic episodes per year [Ito et al 2003].

A larger series of successful auxiliary partial liver transplants has been reported in CTLN type II [Yazaki et al 2004].

Prevention of Secondary Complications

Intercurrent infections — particularly some viral exanthems — may induce a catabolic state. Patients must be observed carefully during such episodes and medical attention sought to prevent hyperammonemia.

Surveillance

Appropriate monitoring of concentration of plasma amino acids to identify deficiency of essential amino acids as well as impending hyperammonemia is indicated.

Routine follow-up in a metabolic clinic with a qualified metabolic nutritionist and clinical biochemical geneticist is required.

Monitoring for early warning signs of impending hyperammonic episodes in older individuals include mood changes, headache, lethargy, nausea, vomiting, refusal to feed, ankle clonus, and elevated plasma concentration of glutamine and other surrogate markers. Plasma glutamine concentration may rise 48 hours in advance of increases in plasma ammonia concentration in such individuals [Brusilow & Horowitz 2001].

Agents/Circumstances to Avoid

- Excess protein intake
- Obvious exposure to communicable diseases

Testing of Relatives at Risk

Because the long-term outlook for individuals with citrullinemia type I depends on initial and peak plasma ammonia concentration, it is important that at-risk sibs are identified as soon as possible. Current practice dictates either in utero diagnosis, which permits appropriate oral therapy beginning with first feeds, or measurement of plasma concentrations of ammonia and citrulline on day one of life. Elevation of either above acceptable levels (ammonia >100 µmol/L or plasma citrulline > ~100 µmol/L) is sufficient evidence to treat.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies under Investigation

Although gene therapy has been suggested, success has not been achieved to date.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Ketoacids of essential amino acids were an early form of auxiliary waste nitrogen disposal enhancement, now replaced by the agents described in Treatment of Manifestations [Thoene et al 1977].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Citrullinemia type I (CTNL1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) have no symptoms of the urea cycle defect phenotype. One case of a heterozygote who developed cirrhosis has been reported [Gucer et al 2004].
- Sibs should be evaluated immediately after birth and placed on a protein-restricted diet until the diagnostic evaluation is complete (see Management).

Offspring of a proband. The offspring of an individual with citrullinemia type I are obligate heterozygotes (carriers) for a disease-causing mutation in the *ASS1* gene.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing is not available by biochemical methods. It is available by molecular genetic test methods if both disease-causing mutations have been identified in an affected family member.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at 25% risk is possible. Methods of prenatal diagnosis:

Measurement of argininosuccinate synthase enzyme activity in uncultured fetal tissue obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or cultured amniocytes obtained by amniocentesis usually performed at about 15-18 weeks' gestation.

Note: (1) Improvement in diagnostic accuracy using the ratio of citrulline to ornithine and arginine concentrations in amniotic fluid has been reported [Chadefaux-Vekemans et al 2002]. (2) Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Molecular genetic testing is available for families in which both mutations have been identified in an affected individual [Kakinoki et al 1997, Hong et al 2000, Hayakawa et al 2003].

Note: Linkage analysis is used to improve prenatal testing accuracy if only one or neither mutation has been identified in an affected family member. Linkage must be established in the family before prenatal testing can be performed.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Citrullinemia Type I

Gene Symbol	Chromosomal Locus	Protein Name
ASS1	9q34.1	Argininosuccinate synthase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Citrullinemia Type I

215700	CITRULLINEMIA, CLASSIC
603470	ARGININOSUCCINATE SYNTHETASE; ASS

Table C. Genomic Databases for Citrullinemia Type I

Gene Symbol	Entrez Gene	HGMD
ASS1	445 (MIM No. 603470)	ASS

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *ASS1* gene contains 16 exons; the primary transcript is 1236 bp. Transcription starts at the 5' end of exon 3. In the homozygous state, mutations 535T>C, 1186G>A and 1085G>T are associated with mild or no clinical symptoms, as is heterozygosity for 323G>T/IVS13+5G>A [Häberle et al 2002]. At least 14 *ASS1* pseudogenes are known.

Pathologic allelic variants: Fifty mutations have been found, occurring in most exons and in several intervening sequences, leading to abnormal messenger RNA splicing. Three mutations account for the majority of the cases of citrullinemia type I (p.R304W, IVS6-2A>G, and p.G390R) [Gao et al 2003]. See Genomic Databases Table above.

Normal gene product: The translational product, argininosuccinate synthase, is a homotetramer of 186 kd. It catalyzes an essential reaction in the biosynthesis of urea, causing the condensation of citrulline and aspartate to argininosuccinic acid in the cytosol, and requiring 1 mol of ATP.

Abnormal gene product: The argininosuccinate synthase enzyme is inactive or absent. Mutant ASS with abnormal K_M (Michaelis constant) or very low ASS protein detected by ELISA using anti-ASS antibody (low CRIM: cross-reacting immunologic materials) has been found.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Library of Medicine Genetics Home Reference
Citrullinemia

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: 0800 652 3181 (toll free)
Email: info.svcs@climb.org.uk
www.climb.org.uk

National Urea Cycle Disorders Foundation
4841 Hill Street
La Canada CA 91011
Phone: 800-38NUCDF (800-386-8233)
Fax: 818-790-2460
Email: info@nucdf.org
www.nucdf.org

Save Babies Through Screening Foundation, Inc
4 Manor View Circle
Malvern PA 19355-1622
Phone: 888-454-3383
Fax: 610-647-5757
Email: email@savebabies.org
www.savebabies.org/index.htm

Urea Cycle Disorders Consortium Registry
Yale University School of Medicine
Phone: 203-737-2585
Email: susan.dunigan@yale.edu
UCDC Registry

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 22 April 2008 (cd) Revision: deletion/duplication analysis available clinically
- 22 December 2006 (me) Comprehensive update posted to live Web site
- 7 July 2004 (me) Review posted to live Web site
- 9 February 2004 (jt) Original submission