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Citrullinemia Type I

Synonyms: Argininosuccinate Synthetase Deficiency, Argininosuccinic Acid Synthetase Deficiency, ASS Deficiency, Classic Citrullinemia, CTLN1

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Summary

Clinical characteristics

Citrullinemia type I (CTLN1) presents as a spectrum that includes a neonatal acute form (the "classic" form), a milder late-onset form (the "non-classic" form), a form in which women have onset of symptoms at pregnancy or post partum, and a form without symptoms or hyperammonemia. Distinction between the forms is based primarily on clinical findings, although emerging evidence suggests that measurement of residual argininosuccinate synthase enzyme activity may help to predict those who are likely to have a severe phenotype and those who are likely to have an attenuated phenotype.

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 accumulation of other toxic metabolites (e.g., glutamine) result in increased 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. Even with chronic protein restriction and scavenger therapy, long-term complications such as liver failure and other (rarely reported) organ system manifestations are possible.

The late-onset form may be milder than that seen in the acute neonatal form, but commences later in life for reasons that are not completely understood. 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. Women with onset of severe symptoms including acute hepatic decompensation during pregnancy or in the postpartum period have been reported. Furthermore, previously asymptomatic and non-pregnant individuals have been described who remained asymptomatic up to at least age ten years, with the possibility that they could remain asymptomatic lifelong.

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Diagnosis/testing

The diagnosis of CTLN1 is established in a proband with elevated plasma ammonia concentration (>150 µmol/L; may range to ≥2000-3000 µmol/L), elevated plasma citrulline concentration (usually >500 µmol/L), and absent argininosuccinate and/or by identification of biallelic pathogenic variants in *ASS1* on molecular genetic testing.

Management

Treatment of manifestations: Liver transplantation is the only known curative therapy and eliminates the need for dietary restriction. Transplantation is ideally performed in affected individuals who are younger than age one year (prior to the development of any neurocognitive impairment) but older than age three months and/or above 5 kg body weight.

- Daily routine treatment in those who have not undergone a liver transplantation includes lifelong protein restriction in conjunction with a metabolic nutritionist; nitrogen scavenger medications; arginine supplementation; consideration of carnitine supplementation in those with secondary carnitine deficiency; addressing increased energy/caloric demands through tube feedings (as needed); and routine treatment of developmental delay / intellectual disability.
- Acute inpatient treatment of a metabolic crisis includes addressing hyperammonemia through withholding of all protein intake for a maximum of 24 to 28 hours; pharmacologic nitrogen scavenger therapy; and consideration of dialysis (the most effective means of reducing plasma ammonia concentration rapidly). To address increased catabolism, administration of high-energy fluids (and insulin, as needed) and intravenous intralipids is typically required. However, care must be taken to avoid electrolyte imbalance and fluid overload, which can contribute to the development of increased intracranial pressure. The patient should be maintained on the dry side of fluid balance (approximately 85 mL/kg of body weight per day in infants and appropriate corresponding fluid restriction in children and adults).

Prevention of secondary complications: Education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors; written protocols for maintenance and emergency treatment should be provided to parents and primary care providers / pediatricians, and to teachers and school staff. For those affected individuals requiring any sedated procedure where a person cannot eat for an extended period of time, drug treatment should be switched to IV and nutrition with 10% glucose with age-appropriate electrolytes should be administered via IV to promote anabolism starting as soon as the patient is NPO.

Surveillance: Follow up in a metabolic clinic with a qualified metabolic nutritionist and clinical biochemical geneticist is required. Measurement of growth parameters; evaluation of nutrition status and safety of oral intake; assessment for early warning signs of impending hyperammonemic episodes (mood changes, headache, lethargy, nausea, refusal to eat); review of dietary assessment; monitoring of developmental progress/educational needs; assessment of mobility and self-help skills; and measurement of carnitine levels (for those on sodium benzoate) at each visit. Plasma amino acid analysis at least every three months during the first year of life and every six to 12 months in the teenage/adult years (depending on clinical stability).

Agents/circumstances to avoid: Excessive protein intake, prolonged fasting, and obvious exposure to communicable diseases.

Evaluation of relatives at risk: It is important that at-risk sibs be identified as soon as possible, either through molecular genetic testing (if the pathogenic variants in the family are known) or measurement of plasma concentrations of ammonia and citrulline on the first day of life. Elevation of either above acceptable levels

(ammonia >100 µmol/L or plasma citrulline >~100 µmol/L) is sufficient evidence to initiate treatment in a newborn.

Pregnancy management: Because women with onset of severe symptoms during pregnancy or in the postpartum period have been reported, scrupulous attention needs to be paid to diet and medication during these periods.

Genetic counseling

CTLN1 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family are known.

Diagnosis

Citrullinemia type I (CTLN1) 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 Urea Cycle Disorders Overview Figure 1).

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for CTLN1 is primarily based on quantification of the analyte citrulline on dried blood spots.

Citrulline values above the cutoff reported by the screening laboratory are considered positive and require follow-up biochemical testing, which usually demonstrates the following:

- **Plasma ammonia concentration** is >150 µmol/L, and typically >400-500 µmol/L (although it can be as high as 2000-3000 µmol/L) (normal newborn: 40-150 µmol/L depending on the laboratory's reference range) in the severe form but often lower in the classic form (adult upper limit of normal: <60 µmol/L).
- **Plasma quantitative amino acid analysis** usually shows the following pattern:
  - **Citrulline** concentration is usually >500 µmol/L but often >1000 (normal: <50 µmol/L).
  - **Argininosuccinic acid** is absent.
  - **Arginine and ornithine** concentrations are in the low-to-normal range (see Urea Cycle Disorders Overview Figure 3).
  - **Lysine, glutamine, and alanine** concentrations are increased; these are surrogate markers of hyperammonemia.
- **Urinary organic acid analysis** may be normal, although orotic acid may be detected as part of urinary organic acid analysis by gas chromatography/mass spectrometry, especially during metabolic crises. This is thought to be due to a secondary impairment of ornithine transcarbamylase due to poor bioavailability of ornithine. However, the sensitivity depends on the extraction method.

The following medical interventions need to begin immediately on receipt of an abnormal NBS result while additional testing is performed to determine whether this a true positive NBS result and to establish a definitive diagnosis of CTLN:

- Inform the family of the NBS result.
- Evaluate the neonate for evidence of gastrointestinal involvement (poor feeding, vomiting, signs of liver disease), respiratory distress, and neurologic involvement (hypotonia, lethargy, seizures).
- Initiate confirmatory testing.
- In consultation with a metabolic specialist, initiate management, including protein restriction, nitrogen scavengers, and arginine supplementation.

Scenario 2: Symptomatic Individual

A symptomatic individual may have either atypical findings associated with later-onset CTLN1 or untreated infantile-onset CTLN1 resulting from any of the following: NBS not performed, false negative NBS result, caregivers not adherent to recommended treatment following a positive NBS result.

Supportive – but nonspecific – clinical, preliminary laboratory, and family history findings can include the following.

Clinical Features

Neonatal presentation. Signs and symptoms classically occur within the first week of life while on a full-protein diet:

- Increasing lethargy
- Somnolence
- Refusal to feed
- Vomiting
- Tachypnea
- Hypotonia
- Stroke
- Seizures
- Increased intracranial pressure (secondary to hyperammonemia) resulting in increased neuromuscular tone, spasticity, and ankle clonus

Non-classic presentation. Signs and symptoms may occur at any age and may not present as acutely as in the neonate:

- Recurrent lethargy and somnolence
- Intense headache
- Scotomas
- Migraine-like episodes
- Ataxia and slurred speech
- Intellectual disability

Supportive Laboratory Findings

Supportive laboratory findings include the following:

- Hyperammonemia
- Plasma amino acids analysis demonstrating elevated citrulline, absent argininosuccinate, with low-to-normal arginine and ornithine levels
- Possibly normal urine organic analysis, although orotic acid may be detected as part of urinary organic acid analysis by gas chromatography/mass spectrometry, especially during metabolic crises.

Note: Though individuals with this presentation are most likely to have CTLN1, other conditions including pyruvate carboxylase deficiency and dihydrolipoamide dehydrogenase deficiency (see Differential Diagnosis) can present with elevated citrulline levels. Given this, molecular confirmation is often performed even after the biochemical diagnosis is made (see Establishing the Diagnosis).

Family History

History is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of CTLN1 **is established** in a proband with elevated plasma ammonia concentration (>150 µmol/L; may range to ≥2000-3000 µmol/L), elevated plasma citrulline concentration (usually >500 µmol/L), and absent argininosuccinate and/or by the identification of biallelic pathogenic (or likely pathogenic) variants in *ASS1* on molecular genetic testing (see Table 1).

Note: (1) Measurement of argininosuccinate synthase (ASS) enzyme activity is not currently widely used because the clinical presentation and relatively specific pattern of metabolites found in affected individuals are sufficient to establish the diagnosis. (2) Historically, determining the prognosis prospectively was difficult in some individuals who fit the biochemical phenotype but may or may not have had serious clinical illness. Newer data suggest that individuals with ≥8% residual ASS enzymatic activity have less frequent and less severe hyperammonemic events, and better cognition. A cutoff value of 8% residual enzymatic activity has been proposed as a threshold for discrimination between severe (≤8% activity) and mild-to-moderate (>8% activity) disease [Zielonka et al 2019] (see ASS Enzyme Activity). (3) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants.

Molecular Genetic Testing Approaches

Scenario 1: Abnormal newborn screening (NBS) result. When NBS results and other laboratory findings suggest the diagnosis of CTLN1, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ASS1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A urea cycle disorders / hyperammonemia multigene panel** that includes *ASS1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Scenario 2: Symptomatic individual. When the diagnosis of CTLN1 has not been considered – for example, when a symptomatic individual has atypical findings associated with later-onset CTLN1 or untreated infantile-onset CTLN1 (resulting from NBS not performed or false negative NBS result) – **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Citrullinemia Type I

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ASS1	Sequence analysis [3]	96% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	See footnote 7.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene. The mutation detection rate is generally estimated to be >90%.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here. Clinical testing currently mainly covers coding regions and exon/intron boundaries, and are estimated to miss variants affecting regulatory regions or splicing variants.
4. Of 80 individuals evaluated, both abnormal alleles were identified in 75 (94%), one abnormal allele in four (5%), and no abnormal alleles in one (1%).
5. Sequencing of genomic DNA from a variety of cells or cDNA from cultured fibroblasts detected 154 of 160 (96%) abnormal alleles [Häberle, personal communication].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Exon and multiexon deletions have been reported [Kobayashi et al 1991, Engel et al 2009]. Imagawa et al [2020] reported a deletion encompassing the entire non-coding exon 1 and its flanking intronic sequence.

ASS Enzyme Activity

As ASS protein is predominantly expressed in the liver (and to a lesser extent the kidney), it is difficult to test reduction in protein expression unless using liver tissue. Incorporation of radiolabeled citrulline into argininosuccinic acid has been measured in cultured fibroblasts (see also Prenatal Testing and Preimplantation Genetic Testing). ASS activity can also be 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.
- Enzyme assay is not currently widely used because the clinical presentation and relatively specific pattern of metabolites found in affected individuals are sufficient to establish the diagnosis; however, a newly established mammalian biallelic expression system has been successful in determining residual enzymatic activity of ASS. This assay has proposed specific residual enzymatic activity as correlating with severe (≤8% activity) vs mild-to-moderate (>8% activity) disease [Zielonka et al 2019].

Clinical Characteristics

Clinical Description

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

It has been proposed that measurement of residual enzyme activity can be used to classify individuals as "predicted severe" (≤8% activity) and "predicted attenuated" (>8% activity) [Zielonka et al 2019]. Using this model, individuals with cytosolic urea cycle disorders (inclusive of CTLN1 and argininosuccinic aciduria [ASA]) were overrepresented in a group diagnosed via newborn screening (NBS), while those with a predicted severe phenotype were initially diagnosed after onset of symptoms.

- Severity-adjusted analysis determined that individuals identified by NBS had a lower peak ammonia level than those diagnosed by symptoms. This effect was greater in individuals with residual enzyme activity >8% (initial mean ammonia within normal range) versus those with residual enzyme activity ≤8% (initial mean ammonia 318 µmol/L).
- Early diagnosis by NBS (vs diagnosis after symptom onset) for individuals with CTLN1 and ASA was associated with improved cognitive outcomes [Posset et al 2019].
- However, early diagnosis via NBS was not associated with lower frequency of hyperammonemic events, despite appropriate early treatment [Posset et al 2020].

Neonatal ("Classic") Form

The infant appears normal at birth. After an interval of one to a few days, the infant becomes progressively more lethargic, feeds poorly, may vomit, and may develop signs of liver failure as well as cerebral edema as hyperammonemia progresses [Häberle & Rubio 2016]. Fifty-six percent of infants with unrecognized/untreated classic CTLN1 are symptomatic by age four days and 67% by age one week [Bachmann 2003]. The longest survival of an untreated infant with classic CTLN1 is 17 days.

Neonates and children diagnosed and referred for appropriate treatment (see Management) survive for an indeterminate period of time, usually with significant neurologic deficits in a manner corresponding with prior number and degree of exposures to elevated ammonia levels. The relationship between peak blood ammonia during the first hyperammonemic episode appears to be linear: 64% of individuals with initial plasma ammonia level <180 µmol/L experience typical neurodevelopment versus only 8% with an initial plasma ammonia level >360 µmol/L, despite receiving prompt treatment [Kido et al 2012, Unsinn et al 2016]. The risk for neurodevelopmental impairment can be determined using a combination of peak ammonia concentration and duration of hyperammonemic encephalopathic episode. Predictive models have been created to help providers caring for neonates with hyperammonemia assess the likelihood of survival of a hyperammonemic event [Ames et al 2022].

In those individuals with neuropsychologic deficits:

- Gross motor skills tend to be less well developed than expressive language skills, with individuals exhibiting strengths in reasoning abilities and weaknesses in visual-spatial comprehension and fine motor skills.
- Thirty percent were described as hyperactive with attention deficits.
- Cognitive impairment scores were variable by age, with 17% of school-aged children, and 50% of adults, reported to have IQ scores in the cognitive impairment range [Waisbren et al 2016].
- In a study of children undergoing liver transplantation for urea cycle disorders (of which CTLN1 was the second-highest encountered diagnosis), nearly 40% of children had definitive cognitive delay post transplant, related to hyperammonemic events prior to transplant. Transplant ultimately prevented further hyperammonemic episodes [Ziogas et al 2021].

Possible other long-term complications. An individual with classic citrullinemia treated with chronic protein restriction and scavenger therapy (see Treatment of Manifestations) developed progressive hypertrophic cardiomyopathy (diagnosed at age 23 years) and bilateral cataracts (diagnosed at age 27 years) [Brunetti-Pierri et al 2012]. No additional individuals with classic CTLN1 and similar findings have been identified. As such, the necessity for cardiac and ophthalmologic surveillance remains controversial until more affected individuals have been studied.

Neuroimaging. Neonatal-onset hyperammonemia leads to brain edema/injury that correlates to severity and duration of hyperammonemia. As severity increases, so too does location, progressing from focal to diffuse. The following pattern is seen: peri-insular, frontal, parietal, temporal, then occipital [Gunz et al 2013, Sen et al 2021].

Multicystic encephalomalacia and cerebral atrophy have been seen as early as age three to four months in an individual with classic CTLN1 who presented with neonatal hyperammonemia [Lee et al 2013].

- **Brain MRI** findings in classic citrullinemia include restricted diffusion and T_2-weighted signal hyperintensities in the basal ganglia, thalami, and subcortical white matter of the bilateral temporal, parietal, and occipital cortex [Majoie et al 2004, Bireley et al 2012].
- **CT scan** of hyperammonemic infants with CTLN1 demonstrates cerebral atrophy, particularly in the cingulate gyrus, the insula, and the temporal lobes, as well as general cortical hypoattenuation (i.e., the cortex appears darker than in unaffected individuals) [Albayram et al 2002].
- More rare neuroimaging findings include bilateral insular cortex and basifrontal involvement, suggesting herpes encephalitis [Kadwa et al 2019].

Non-Classic Form

The clinical course may be similar to or milder than that seen in the acute neonatal form, but commences later in life for reasons that are not completely understood. However, specific *ASS1* pathogenic variants may be associated with the non-classic form (see Genotype-Phenotype Correlations and Molecular Genetics). 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
- Somnolence

Individuals with hyperammonemia also display respiratory alkalosis and tachypnea [Brusilow & Horwich 2001]. Without prompt intervention, increased intracranial pressure occurs, with increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death.

Liver failure is now recognized as a primary presentation of CTLN1, contradicting the established dogma of central nervous system symptoms as the primary finding [Salek et al 2010, Faghfoury et al 2011, Lee et al 2013, Rüegger et al 2014]. When present, hepatic dysfunction is frequently noted at the time of the initial hyperammonemic episode but has also developed in an affected individual who was not experiencing significant hyperammonemia (>250 µmol/L) at the time [Lee et al 2013].

Late-onset urea cycle disorder can be associated with high mortality: neonatal plus late-onset mortality has been reported in 7% of individuals with CTLN1 [Batshaw et al 2014].

Onset of symptoms at pregnancy or post partum. Women with onset of severe symptoms including acute hepatic decompensation during pregnancy or in the postpartum period have been reported [Gao et al 2003, Ruitenbeek et al 2003, Sinclair et al 2014, Wykowski et al 2022].

- Three women not known to have citrullinemia presented in hyperammonemic coma shortly after delivery; one died and two survived without neurologic sequelae [Häberle et al 2009].
- Another previously undiagnosed woman presented at 14-18 weeks' gestation with hyperemesis gravidarum progressing to acute hepatic failure; once appropriate treatment was implemented she went on to deliver a healthy neonate [Sinclair et al 2014].
- CTLN1 has been implicated in postpartum psychosis [Enns et al 2005, Häberle et al 2010].
- In contrast, a healthy woman with untreated CTLN1 underwent two successful pregnancies [Potter et al 2004].

Asymptomatic individuals. Previously asymptomatic and non-pregnant individuals who have not been treated have been described who remained asymptomatic up to at least age ten years; it appears that they could remain asymptomatic lifelong [Häberle et al 2002, Häberle et al 2003].

Genotype-Phenotype Correlations

While certain *ASS1* pathogenic variants are identified with particular phenotypes, the phenotype cannot be predicted in all instances [Engel et al 2009].

- Severe, classic (neonatal-onset) CTLN1 typically results from 22 defined pathogenic variants [Engel et al 2009]. The pathogenic variant in exon 15, p.Gly390Arg, remains the most prevalent associated with the classic phenotype. Other variants in this category include p.Gly14Ser, p.Arg157His, p.Glu191Lys, p.Gly324Ser, and p.Arg363Trp [Engel et al 2009, Laróvere et al 2009, Diez-Fernandez et al 2017].
- Mild (i.e., late-onset) CTLN1 is associated with 12 pathogenic variants, including p.Trp179Arg, p.Tyr190Asp, p.Ala202Glu, p.Val263Met, and p.Val269Met [Engel et al 2009, Diez-Fernandez et al 2017].

Nomenclature

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

Prevalence

CTLN1 is the second-most frequent urea cycle disorder, and has been estimated to occur in 1:220,000 births [Posset et al 2020].

Newborn screening programs found CTLN1 in the following:

- In Korea: two in 44,300 newborns [Yoon et al 2003]
- In New England: one in 200,000 newborns [Marsden 2003]
- In Taiwan: five (2 severe and 3 mild) in a pilot program of 592,717 newborns; overall incidence one in 118,543 [Niu et al 2010]
- In Austria: one in 77,811 among 622,489 newborns [Kasper et al 2010]
- In Texas, New York, Michigan, California, Massachusetts, North Carolina, and Wisconsin, estimated combined prevalence of CTLN1 and argininosuccinate lyase deficiency: one in 117,000 [Summar et al 2013]

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ASS1*.

Differential Diagnosis

Neonatal ("Classic") Presentation

Elevated citrulline on newborn screening (NBS). Conditions that may result in elevated citrulline on NBS are citrullinemia type II (citrin deficiency), argininosuccinate lyase deficiency (argininosuccinic aciduria), and pyruvate carboxylase deficiency.

Hyperammonemia. It is critical to distinguish hyperammonemia caused by a defect in the urea cycle from the secondary hyperammonemia caused by an organic acidemia, which may cause inhibition of N-acetylglutamate

synthase (see Urea Cycle Disorders Overview Figure 2). Urea Cycle Disorders Overview Figure 3 shows a diagnostic strategy to identify which steps in the urea cycle are defective in an individual with hyperammonemia.

Classic citrullinemia type I (a defect in step 3 of the urea cycle) shares the phenotype of the typical acute neonatal hyperammonemia displayed by other defects in the first four steps in the urea cycle pathway: carbamoylphosphate synthetase I deficiency (step 1), ornithine transcarbamylase deficiency (step 2), and argininosuccinate lyase deficiency (step 4).

Table 2. Selected Disorders in the Differential Diagnosis of Acute Neonatal ("Classic") Citrullinemia Type I

Gene	Disorder	MOI	Laboratory Findings / Clinical Characteristics
ASL	Argininosuccinate lyase (ASL) deficiency	AR	↑ citrulline on NBS. Severe neonatal-onset ASL deficiency is assoc w/ hyperammonemia w/in 1st few days after birth that can manifest as ↑ lethargy, somnolence, refusal to feed, vomiting, tachypnea, & respiratory alkalosis.
CPS1	Carbamoyl phosphate synthase (CPS1) deficiency (See Urea Cycle Disorders Overview.)	AR	Most severe of urea cycle disorders. Persons w/complete CPS1 deficiency rapidly develop hyperammonemia in newborn period.
DLD	Dihydrolipoamide dehydrogenase (DLD) deficiency	AR	↑ citrulline on NBS. ↑ ammonia & glutamine. [1] Early-onset DLD deficiency typically manifests in infancy as hypotonia w/lactic acidosis. Affected infants frequently do not survive their initial metabolic decompensation, or die w/in 1st few yrs of life during a recurrent metabolic decompensation.
OTC	Ornithine transcarbamylase (OTC) deficiency	XL	Males w/severe neonatal-onset OTC deficiency are asymptomatic at birth but become symptomatic from hyperammonemia in 1st week of life, most often on day 2 to 3 of life, & are usually catastrophically ill when they come to medical attention.
PC	Pyruvate carboxylase deficiency	AR	↑ citrulline on NBS. Type A (infantile form): most affected children die in infancy or early childhood. Type B (severe neonatal form): biochemical abnormalities, hypoglycemia, hyperammonemia, hypernatremia, anorexia, hepatomegaly, convulsions, stupor, hypotonia, pyramidal tract signs, abnormal movements (incl high-amplitude tremor & dyskinesia), & abnormal ocular behavior.
SLC25A13	Neonatal-onset citrullinemia type II (See Citrin Deficiency.)	AR	↑ citrulline on NBS. Mild hyperammonemia & citrullinemia. Transient intrahepatic cholestasis. Other findings: diffuse fatty liver w/hepatomegaly & parenchymal cellular infiltration assoc w/hepatic fibrosis, history of low birth weight, growth restriction, hypoproteinemia, ↓ coagulation factors, hemolytic anemia, variable (mainly mild) liver dysfunction, &/or hypoglycemia.

AR = autosomal recessive; MOI = mode of inheritance; NBS = newborn screening; XL = X-linked
1. Haviv et al [2014]

Milder Late-Onset Presentation

The milder late-onset citrullinemia type I phenotype shares a later onset with other disorders such as late-onset ornithine transcarbamylase deficiency. Urea Cycle Disorders Overview Figure 3 shows a diagnostic strategy to identify which steps in the urea cycle are defective in an individual with hyperammonemia.

Citrullinemia type II (CTLN2; citrin deficiency). The clinical course in adults with CTLN2 is milder than that of CTLN1, 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.

Management

Clinical practice guidelines for citrullinemia type I (CTLN1) have been published. See Batshaw et al [2001], Summar [2001], UCD [2001], Häberle et al [2012], Häberle et al [2019] (full text).

When CTLN1 is suspected during the diagnostic evaluation due to elevated citrulline on newborn screening, metabolic treatment should be initiated immediately.

Development and evaluation of treatment plans, training and education of affected individuals and their families, and avoidance of side effects of dietary treatment (i.e., malnutrition, growth failure) require a multidisciplinary approach including multiple subspecialists, with oversight and expertise from a specialized metabolic center.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CTLN1, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of Citrullinemia Type I

Evaluation	Comment
Consultation w/metabolic physician / biochemical geneticist & specialist metabolic dietitian [1]	• Transfer to specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended). • Consider short hospitalization at center of expertise for inherited metabolic conditions to provide caregivers w/detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute encephalopathic crises).
Metabolic control	Consider measurement of following, based on clinical status, to aid in nutritional mgmt: • Plasma ammonia level • Blood gases • Electrolytes • Plasma amino acids
Consultation w/neurologist	• For eval of overall neurologic status • Assessment of intracranial pressure in those who are acutely ill • Consider brain MRI in those w/neurologic features &/or seizures.
Developmental assessment	Consider referral to developmental pediatrician.
Consultation w/psychologist &/or social worker	To ensure understanding of diagnosis & assess parental / affected person's coping skills & resources
Consultation w/PT, OT, & speech therapist	
Genetic counseling by genetics professionals 2	To inform affected persons & their families re nature, MOI, & implications of CTLN1 to facilitate medical & personal decision making

MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist
1. After a new diagnosis of CTLN1 in a child, the closest hospital and local pediatrician should also be informed.
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

See also ACMG ACT Sheet (pdf), ACMG Algorithm (pdf).

Table 4. Definitive Treatment in Individuals with Citrullinemia Type I

Treatment	Comment	Consideration/Other
Liver transplantation, incl living related-donor transplantation [1, 2]	This is the only known curative therapy & eliminates need for dietary restriction. It does not reverse any neurologic sequelae that affected persons may have at time of transplantation, but may allow for developmental progression afterward. [2, 3]	• Liver transplantation should ideally be performed in affected persons before age 1 yr (prior to development of any neurocognitive impairment) but after age 3 mos &/or when body weight is >5 kg to ↓ complications & ↑ survival rates. [4] • Although liver transplantation cures ASS enzyme deficiency, arginine is extrahepatically synthesized & remains low post transplant, requiring ongoing supplementation.

1. Liver transplantation of nine individuals with CTLN1 between ages four and 86 months showed better developmental outcomes when the transplant was performed at earlier ages [Kim et al 2013, Liu et al 2021].
2. Ando et al [2003], Ito et al [2003], Liu et al [2021]
3. A living related-donor liver transplantation from mother to son resulted in continued elevation in plasma concentration of citrulline (200-400 µmol/L). The mother, a heterozygote, had 28% residual ASS1 enzyme activity [Ando et al 2003].
4. Survival rates in those who underwent liver transplantation prior to age two years was between 90% and 95% five years post transplant [Bourdeaux et al 2007, Perito et al 2014].

Table 5. Routine Daily Treatment in Individuals with Citrullinemia Type I

Principle/Manifestation	Treatment	Considerations/Other
Protein restriction	In conjunction w/metabolic nutritionist, lifelong protein restriction is required & varies based on age of affected person.	• Adequate protein intake can be based on FAO/WHO/UNU 2007 "safe levels of protein intake." [1] • If EAA supplements are needed, it is reasonable to provide 20%-30% total protein intake in this form.
Natural protein intake in infants	• The protein source for infants should be breastmilk or standard infant formula. • Dietary therapy should be done in conjunction w/metabolic nutritionist.	• Exclusive on-demand breastfeeding is possible but requires close analytic monitoring & may require supplementation w/protein-free infant formula. • In bottle-fed infants, total daily protein amounts are divided evenly between daily feeds, & can be supplemented w/protein-free formula to round out caloric intake, &/or to appetite, w/goal for total amount to supply all required nutrients.
Nitrogen scavenger medications [2]	Oral sodium phenylbutyrate (Buphenyl®, Ammonaps®)	• In persons weighing <20 kg: up to 250 mg/kg [3] • In persons weighing >20 kg: 5 g/m^2/d, max 12 g/d [3]
	Glycerol phenylbutyrate (Ravicti®) [4]	• Initial dose for phenylbutyrate-naïve persons: 4.5-11.2 mL/m^2/d (5-12.4 g/m^2/d), max 17.5 mL/d • Dose for those transitioning from sodium phenylbutyrate: daily dose of glycerol phenylbutyrate (mL) = daily dose of sodium phenylbutyrate (g) x 0.86
	Sodium benzoate	Up to 250 mg/kg/d, max 12 g/d
Arginine supplementation [5]	• In persons weighing <20 kg: 100-300 mg/kg/d or 0.5-1.5 mmol/kg/d • In persons weighing >20 kg: 2.5-6 g/m^2/d, max 8 g/d	
Secondary carnitine deficiency	Initial oral dosage of 100 mg L-carnitine/kg/d divided into 3 or 4 doses is commonly used.	Dose is adjusted on individual basis to maintain plasma-free L-carnitine concentration w/in normal age-appropriate reference range.

Table 5. continued from previous page.

Principle/Manifestation	Treatment	Considerations/Other
Addressing ↑ energy/ caloric demands	Fundoplication, gastrostomy, or jejunostomy to address feeding issues	Adequate provision of info & education to parents, affected persons, & caregivers
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

/d = per day; EAA = essential amino acid; FAO = Food and Agriculture Organization of the United States; WHO = World Health Organization; UNU = United Nations University

1. Joint WHO/FAO/UNU Expert Consultation [2007]

2. Success of therapy is defined by a plasma ammonia concentration lower than100 µmol/L and near-normal plasma glutamine concentration.

3. Häberle et al [2019]. Higher doses are needed in some; the US FDA considers doses up to 450-600 mg/kg/d in individuals weighing <20 kg and 9.9-13.0 g/m^2/d in individuals weighing >20 kg.

4. This nitrogen scavenging medication may be more palatable.

5. Plasma arginine concentration may be up to 250% above upper normal limit for age.

Table 6. Emergency Outpatient Treatment in Individuals with Citrullinemia Type I

Manifestation	Treatment	Consideration/Other
Mildly increased catabolism [1]	• Carbohydrate supplementation orally or via tube feed [2] • ↓ natural protein intake [3] • ↑ carnitine supplementation [4]	Trial of outpatient treatment at home for up to 12 hrs; reassessment (~every 2 hrs) for clinical changes [5]
Fever	Administration of antipyretics (acetaminophen, ibuprofen) if temperature >38.5°C	
Occasional vomiting	Antiemetics [6]	

1. Fever <38.5°C (101°F); enteral or gastrostomy tube feeding tolerated without recurrent vomiting or diarrhea; absence of neurologic symptoms (altered consciousness, irritability, hypotonia, dystonia)

2. Stringent guidelines to quantify carbohydrate/caloric requirements are available to guide nutritional arrangements in the outpatient setting, with some centers recommending frequent provision of carbohydrate-rich, protein-free beverages every two hours, with frequent reassessment.

3. Some centers advocate additional steps such as reducing natural protein intake to zero or to 50% of the normal prescribed regimen for short periods (<24 hours) in the outpatient setting during intercurrent illness.

4. Temporarily increasing L-carnitine doses (e.g., to 200 mg/kg/d in infants) may be considered [Boy et al 2017].

5. Alterations in mentation/alertness, fever, and enteral feeding tolerance, with any new or evolving clinical features discussed with the designated center of expertise for inherited metabolic diseases

6. Some classes of antiemetics can be used safely on an occasional basis to temporarily improve enteral tolerance of food and beverages at home or during transfer to hospital.

Table 7. Acute Inpatient Treatment in Individuals with Citrullinemia Type I

Manifestation	Treatment [1]	Consideration/Other
Hyperammonemia	Withhold all protein intake for max 24-48 hrs.	This time frame allows for plasma ammonia concentration to be ↓ & EAA deficiency that would promote a catabolic state

Table 7. continued from previous page.

Manifestation	Treatment [1]	Consideration/Other
	Pharmacologic nitrogen scavenger therapy [2]	**Priming/bolus infusion** (given continuously over 90 mins, dissolved in D10W [25-35 mL/kg if <20 kg, in 1 L if >20 kg]): • Sodium benzoate: <20 kg: 250 mg/kg; >20 kg: 5.5 g/m^2 • Sodium phenylacetate: <20 kg: 250 mg/kg; >20 kg: 5.5 g/m^2 • 10% arginine HCl: <20 kg: 600 mg/kg; >20 kg: 600 mg/kg
		Sustaining/maintenance infusion (given continuously over 24 hrs, dissolved in D10W [25-35 mL/kg if <20 kg, in 1 L if >20 kg]): • Sodium benzoate: <20 kg: 250 mg/kg; >20 kg: 5.5 g/m^2 • Sodium phenylacetate: <20 kg: 250 mg/kg; >20 kg: 5.5 g/m^2 • 10% arginine HCl: <20 kg: 600 mg/kg; >20 kg: 600 mg/kg
	Dialysis is most effective means of ↓ plasma ammonia rapidly. [3]	• Failure to control ammonia w/scavenger therapy requires emergency use of dialysis. • Hemodialysis is preferred method of dialysis & exceeds both peritoneal dialysis & hemofiltration in rate of ammonia clearance. • Continue scavenger therapy while dialysis is being performed.
↑ catabolism due to fever, perioperative/ peri-interventional fasting periods, rptd vomiting/ diarrhea)	• Administer high-energy fluids & (if needed) insulin. [4, 5, 6] • IV interlipids • Consider L-carnitine supplementation, esp if deficient. [7] • Address electrolytes & pH imbalances w/IV fluid mgmt.	• Blood glucose, electrolyte concentrations, blood gases, plasma amino acids, plasma carnitine profiling, & urine pH/ketone screening may all be useful in guiding mgmt. • Ongoing assessment of hemodynamic status & for new neurologic signs is critical. • Inadequate or delayed start of emergency treatment → high risk of neurologic injury w/consequent long-term neurodisability.
	As soon as possible, osmolar load / hyperammonemia permitting, affected person should receive TPN or enteral feeds.	• To provide 0.25 g/kg/d of protein & 50 kcal/kg/d, advancing (as plasma ammonia concentration allows) to 1.0-1.5 g/kg/d of protein & 100-120 kcal/kg/d • Standard TPN solutions of dextrose, aminosol, & intralipid are used.

Table 7. continued from previous page.

Manifestation	Treatment [1]	Consideration/Other
Control of intracranial pressure	Affected person should be maintained on dry side of fluid balance: ~85 mL/kg of body weight per day in infants & appropriate corresponding fluid restriction in children & adults.	• It is critical to monitor fluid balance, intake & output, & body weight. • ↑ intracranial pressure is manifested by tension in fontanelle, acute enlargement of liver, edema, & worsening neurologic signs incl fisting, scissoring, ankle clonus, & coma. • Cerebral edema & ischemia may be documented by brain MRI.

/d = per day; EAA = essential amino acid; IV = intravenous; TPN = total parenteral nutrition
1. Inpatient emergency treatment should: (1) take place at the closest medical facility, (2) be started without delay, and (3) be supervised by physicians and specialist dieticians at the responsible metabolic center, who should be contacted without delay.
2. Repeat boluses are not recommended unless the individual is receiving dialysis.
3. Exchange transfusions have no place in hyperammonemic treatment.
4. IV glucose solutions should provide 12-15 g/kg/d glucose for infants and 10-12 g/kg/d for children age 12 months to 6 years.
5. In small infants, 40 kcal/100 mL given as D10W can be significant in averting catabolism.
6. Use of insulin if hyperglycemia emerges; IV insulin given at a starting dose of 0.025 IU/kg/hour in the event of persistent hyperglycemia (>150-180 mg/dL in plasma, or glucosuria)
7. L-carnitine (with options to increase the dose) can be given intravenously, which enhances bioavailability.

Transitional care from pediatric to adult-centered multidisciplinary care settings. As CTLN1 is a lifelong disorder with varying implications according to age, smooth transition of care from the pediatric setting is essential for long-term management and should be organized as a well-planned, continuous, multidisciplinary process integrating resources of all relevant subspecialties. Standardized procedures for transitional care do not exist for CTLN1 due to the absence of multidisciplinary outpatient departments.

- Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with CTLN1 together with pediatric metabolic experts, dietitians, psychologists, and social workers.
- As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-

generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Prevention of Primary Manifestations

Prevention of hyperammonemia is achieved through lifelong protein restriction, nitrogen scavenger therapy, and possible liver transplantation based on metabolic control (see Treatment of Manifestations).

Prevention of Secondary Complications

One of the most important components of management (as it relates to prevention of secondary complications) is education of parents and caregivers such that diligent observation and management can be administered expediently in the setting of intercurrent illness or other catabolic stressors (see Table 8; see also Tables 6 and 7).

Table 8. Prevention of Secondary Manifestations in Individuals with Citrullinemia Type I

Manifestation/ Situation	Prevention	Considerations/Other
Acute encephalopathic crisis	• Intense & ongoing education of affected persons & caregivers re natural history, maintenance & emergency treatment, prognosis, & risks of acute encephalopathic crises • Treatment protocols & provision of emergency letters or cards to incl guidance for care in event of illness while away from home • MedicAlert® bracelets/pendants, or car seat stickers • Adequate supplies of specialized dietary products (carbohydrate-only formulas or other caloric sources) • Medication required for maintenance & emergency treatment (antipyretics) should always be maintained at home.	• Provide written protocols for maintenance & emergency treatment to parents & primary care providers / pediatricians & to teachers & school staff. [1, 2] • Emergency letters/cards should be provided summarizing key info & principles of emergency treatment for CTLN1 & containing contact info for primary treating metabolic center. • For any planned travel or vacations, consider contacting center of expertise near destination prior to travel dates.
Surgery or procedure (incl dental procedures)	• Notify designated metabolic center in advance of procedure to discuss perioperative mgmt w/surgeons & anesthesiologists. [3] • Emergency surgeries/procedures require planning input from physicians w/expertise in inherited metabolic diseases (w/respect to perioperative fluid & nutritional mgmt). • The night before surgery, & esp once patient is made NPO, drug treatment should be switched to IV & nutrition w/10% glucose w/age-appropriate electrolytes should be administered via IV to promote anabolism.	Consider placing "flag" in affected person's medical record so that all care providers are aware of diagnosis & need to solicit opinions & guidance from designated metabolic specialists in setting of certain procedures.

IV = intravenous; NPO = nil per os ("nothing by mouth")

1. Essential information including written treatment protocols should be in place in anticipation of possible future need for inpatient emergency treatment.

2. Parents or local hospitals should immediately inform the designated metabolic center if: (1) temperature rises >38.5°C; (2) vomiting/ diarrhea or other symptoms of intercurrent illness develop; or (3) new neurologic symptoms occur.

3. Perioperative/perianesthetic management precautions may include visitations at specialist anesthetic clinics for persons deemed to be at high risk for perioperative complications.

Surveillance

Follow up in a metabolic clinic with a qualified metabolic nutritionist and clinical biochemical geneticist is required (see Table 9).

Table 9. Recommended Surveillance for Individuals with Citrullinemia Type I

Manifestation/Concern	Evaluation	Frequency
Poor growth	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Early warning signs of impending hyperammonemic episodes	Monitor for mood changes, headache, lethargy, nausea, vomiting, refusal to eat, hyperreflexia, & ankle clonus. [1]	
Nutrition review	Dietary assessment (whether by diary or recall) to review adequate/complete nutrition is being received	
Nutritional status monitoring	Carnitine levels to monitor for secondary carnitine deficiency in patients on sodium benzoate	
	Plasma amino acids analysis to identify deficiency of EAA, & monitor arginine, citrulline, & EAA supplementation	• During 1st yr of life: at least every 3 mos • In teen/adult yrs: every 6-12 mos, depending on clinical stability
Development	Monitor developmental progress & educational needs.	At each visit
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

EEA = essential amino acids; OT = occupational therapy; PT = physical therapy

1. This should prompt assessment of (at a minimum) plasma ammonia level, plasma amino acid analysis, and other metabolic labs (electrolytes, glucose level, liver function tests, and complete blood count). Plasma glutamate concentration may rise 48 hours in advance of plasma ammonia concentration.

Agents/Circumstances to Avoid

Avoid the following:

- Excess protein intake
- Prolonged fasting
- Obvious exposure to communicable diseases

Evaluation of Relatives at Risk

For early diagnosis and treatment. Because the long-term prognosis for individuals with CTLN1 depends on initial and peak plasma ammonia concentration, it is important that at-risk sibs be identified as soon as possible. Evaluations can include the following:

- Molecular genetic testing if the pathogenic variants in the family are known, In utero diagnosis (which permits appropriate oral therapy beginning with first feeds), if possible, is preferred.
- 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 initiate treatment.
- Newborn full sibs of individuals who had early-onset presentation and in whom prenatal genetic testing has not been performed should be started on a protein-restricted diet with consideration of immediately starting an IV with provision of (1) age-appropriate glucose infusion rates and appropriate electrolytes and (2) protein-free infant formula, pending completion of the diagnostic evaluation.

For liver donation. Relatives who are potential liver donors should undergo molecular genetic testing to clarify their genetic status so that only those who do not have biallelic *ASS1* pathogenic variants are evaluated further. In living related-donor transplants for individuals with urea cycle disorders, heterozygosity does not appear to be problematic if the donor is asymptomatic; symptomatic heterozygous donor candidates should not be considered [Häberle et al 2019].

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

Pregnancy Management

Because women with onset of severe symptoms during pregnancy or in the postpartum period have been reported, scrupulous attention needs to be paid to diet and medication during these periods.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Gene therapy has been suggested; success has not been achieved to date.

Phase I and Phase II clinical trials to assess the safety and efficacy of human hepatocyte transplantation as either an alternative to liver transplantation or a temporizing measure for individuals with CTLN1 awaiting transplantation have completed.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Citrullinemia type I (CTLN1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ASS1* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ASS1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent

[Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same 2 pathogenic variants), additional possibilities to consider include:
    - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
    - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) have no symptoms of the urea cycle defect phenotype.

Sibs of a proband

- If both parents are known to be heterozygous for an *ASS1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Sibs should be evaluated immediately after birth and placed on a protein-restricted diet until the diagnostic evaluation is complete (see Management, Evaluation of Relatives at Risk).
- Heterozygotes (carriers) have no symptoms of the urea cycle defect phenotype.

Offspring of a proband. The offspring of an individual with CTLN1 are obligate heterozygotes (carriers) for a pathogenic variant in *ASS1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ASS1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *ASS1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *ASS1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Argininosuccinate synthase enzyme activity can be measured in uncultured fetal tissue obtained by chorionic villus sampling or cultured amniocytes obtained by amniocentesis if the familial pathogenic *ASS1* variants have not been identified. However, variability has been observed in citrulline incorporation assay results on normal specimens, which may be explained in part by biologic variation, limiting utility in prenatal diagnosis.

Note: Improvement in diagnostic accuracy using the ratio of citrulline-to-ornithine concentrations in amniotic fluid has been reported, with proposed approach of combining *ASS1* sequencing and amniotic fluid citrulline-to-ornithine leading to the highest diagnostic yield [Miller et al 2014].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Citrullinemia
- **National Urea Cycle Disorders Foundation**
  Phone: 626-578-0833
  nucdf.org
- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  Citrullinaemia
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state
- **Urea Cycle Disorders Consortium**
  Phone: 202-306-6489
  Email: jseminar@childrensnational.org
  ucdc.rarediseasesnetwork.org
- **European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)**
  www.e-imd.org/en/index.phtml
- **Urea Cycle Disorders Consortium Registry**
  Children's National Medical Center
  RDCRN Contact Registry
- **Urea Cycle Disorders International Patient Registry**
  Phone: 626-578-0833
  Fax: 626-578-0823
  Email: coordinator@ucdparegistry.org
  www.ucdregistry.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Citrullinemia Type I: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ASS1	9q34.11	Argininosuccinate synthase	ASS1 @ LOVD	ASS1	ASS1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Citrullinemia Type I (View All in OMIM)

215700	CITRULLINEMIA, CLASSIC
603470	ARGININOSUCCINATE SYNTHETASE 1; ASS1

Molecular Pathogenesis

The translational product argininosuccinate synthase is a homotetramer of 186 kilodaltons. Each monomer consists of a nucleotide-binding domain, a synthetase domain, and a C-terminal helix. 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.

Failure of the urea cycle at this step leads to accumulation of citrulline, glutamine, and ammonia in plasma, and increased orotic acid production and excretion in the urine. Subsequently there are low plasma levels of argininosuccinate and arginine. High citrulline levels differentiate cytosolic from mitochondrial urea cycle disorders. Citrulline includes in its molecular structure one molecule of ornithine and one atom of waste nitrogen, as opposed to argininosuccinate, which carries two atoms of waste nitrogen, making citrulline a poorer waste nitrogen carrier. Urinary excretion of citrulline helps to remove waste nitrogen, though at the expense of two molecules of ornithine per urea equivalent. Hyperammonemic episodes are more frequent in individuals with citrullinemia type I compared to argininosuccinate lyase deficiency, as secondary impairment of ornithine transcarbamylas occurs in part due to poor bioavailability of ornithine [Häberle & Rubio 2016].

Mechanism of disease causation. Loss of function

***ASS1*-specific laboratory technical considerations.** Transcription starts near the 5' end of exon 3. At least 14 *ASS1* pseudogenes are known. For a detailed summary of gene and protein information, see Table A, **Gene**.

Table 10. Notable *ASS1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_054012.4 NP_446464.1	c.257G>A	p.Arg86His	Assoc w/late-onset CTLN1; mild or no clinical symptoms when homozygous [2, 3]
	c.535T>C	p.Trp179Arg [1]	Mild or no clinical symptoms when homozygous [2, 3]
	c.787G>A	p.Val263Met [1]	
	c.794G>A	p.Arg265His	Assoc w/late-onset CTLN1; mild or no clinical symptoms when homozygous [2, 3]
	c.851C>T	p.Thr284Ile	Mild or no clinical symptoms when homozygous [2, 3]
	c.1085G>T	p.Gly362Val [1]	
NM_054012.4	c.[323G>T];[970+5G>A]	--	Mild or no clinical symptoms when heterozygous for these two variants [2, 3]
	c.773+49C>T	--	Mild or no clinical symptoms when homozygous [2, 3]

CTLN1 = citrullinemia type I
Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Fifty percent of individuals with non-classic presentations were found to be homozygous for one of the following three missense variants: p.Trp179Arg, p.Val263Met, or p.Gly362Val [Rüegger et al 2014].
2. Häberle et al [2002]
3. Engel et al [2009]

Chapter Notes

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Revision History

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