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Argininosuccinate Lyase Deficiency

Synonyms: Argininosuccinic Acid Lyase Deficiency, Argininosuccinic Aciduria, ASLD

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Summary

Clinical characteristics

Deficiency of argininosuccinate lyase (ASL), the enzyme that cleaves argininosuccinic acid to produce arginine and fumarate in the fourth step of the urea cycle, may present as a severe neonatal-onset form or a late-onset form:

- The severe neonatal-onset form is characterized by hyperammonemia within the first few days after birth that can manifest as increasing lethargy, somnolence, refusal to feed, vomiting, tachypnea, and respiratory alkalosis. Absence of treatment leads to worsening lethargy, seizures, coma, and even death.
- In contrast, the manifestations of late-onset form range from episodic hyperammonemia triggered by acute infection or stress to cognitive impairment, behavioral abnormalities, and/or learning disabilities in the absence of any documented episodes of hyperammonemia.

Manifestations of ASL deficiency that appear to be unrelated to the severity or duration of hyperammonemic episodes:

- Neurocognitive deficiencies (attention-deficit/hyperactivity disorder, developmental delay, seizures, and learning disability)
- Liver disease (hepatitis, cirrhosis)
- Trichorrhexis nodosa (coarse brittle hair that breaks easily)
- Systemic hypertension

Diagnosis/testing

Elevated plasma ammonia concentration (>100 µmol/L), elevated plasma citrulline concentration (usually 100-300 µmol/L), and elevated argininosuccinic acid in the plasma or urine establish the diagnosis of ASL deficiency. Identification of biallelic pathogenic variants in *ASL* by molecular genetic testing or – in limited

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instances – by significantly reduced ASL enzyme activity from skin fibroblasts, red blood cells, or in a flash-frozen sample from a liver biopsy help in confirmation of the diagnosis. Note: All 50 states in the US include ASL deficiency in their newborn screening programs.

Management

Treatment of manifestations: Treatment involves rapid control of hyperammonemia during metabolic decompensations and long-term management to help prevent episodes of hyperammonemia and long-term complications. During acute hyperammonemic episodes, oral protein intake is discontinued, oral intake is supplemented with intravenous lipids and/or glucose, and intravenous nitrogen-scavenging therapy is used. If ammonia levels do not normalize, hemodialysis is the next step.

Dietary restriction of protein and dietary supplementation with arginine are the mainstays in long-term management; for those not responsive to these measures, oral nitrogen-scavenging therapy can be considered. Orthotopic liver transplantation (OLT) is considered only in patients with recurrent hyperammonemia or metabolic decompensations resistant to conventional medical therapy.

Surveillance: Monitoring the concentration of plasma amino acids to identify deficiency of essential amino acids and impending hyperammonemia at intervals depending on age and metabolic status.

Agents/circumstances to avoid: Excess protein intake; less than recommended intake of protein; prolonged fasting or starvation; obvious exposure to communicable diseases; valproic acid; intravenous steroids; hepatotoxic drugs (in those with hepatic involvement).

Evaluation of relatives at risk: Testing of at-risk sibs (either by molecular genetic testing if the family-specific pathogenic variants are known or by biochemical testing) shortly after birth can reduce morbidity by permitting early diagnosis and treatment of those who are affected.

Genetic counseling

ASL deficiency 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 family members and prenatal testing and preimplantation diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Argininosuccinate lyase (ASL) is the enzyme that catalyzes the fourth step in the urea cycle, in which argininosuccinic acid is cleaved to produce arginine and fumarate. All 50 states in the US include ASL deficiency in their newborn screening programs.

Suggestive Findings

ASL deficiency **should be suspected** in infants with a positive newborn screening result and in symptomatic individuals with supportive clinical and laboratory findings.

Positive Newborn Screening (NBS) Result

NBS for ASL deficiency 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, but elevation of citrulline can also be seen with citrullinemia type 1, citrin deficiency, and pyruvate carboxylase deficiency; hence, confirmation of the diagnosis of ASL deficiency requires follow-up testing to detect elevated plasma or

urine concentration of argininosuccinic acid or its anhydride compounds. If testing supports the likelihood of ASL deficiency, additional testing is required to establish the diagnosis (see Establishing the Diagnosis).

Clinical Findings

Individuals with ASL deficiency may present with the following nonspecific supportive clinical features and preliminary laboratory findings that vary by age.

In the neonatal period

- Hyperammonemia can manifest as increasing lethargy, somnolence, refusal to feed, vomiting, tachypnea, and respiratory alkalosis.
- The presentation is typically indistinguishable from that of other proximal urea cycle disorders (i.e., carbamoyl-phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, and citrullinemia type I).

In individuals outside the neonatal period

- Episodic hyperammonemia that is triggered by acute infection, stress, or non-compliance with dietary restrictions or medications
- Liver involvement including hepatomegaly, elevated transaminases, liver fibrosis, or cirrhosis
- Neurocognitive deficits such as ADHD, developmental delay, learning disability, and seizures that may be independent of hyperammonemia
- Trichorrhexis nodosa consisting of coarse and brittle hair that breaks easily. See images.
- Hypertension that may occur in late childhood and adolescence, in the absence of secondary causes
- Hypokalemia of unknown etiology that may be chronic and secondary to excess urinary loss of potassium

Laboratory Findings

Plasma ammonia concentration

- In the severe forms of ASL deficiency, the initial plasma ammonia concentration (before treatment) may be greater than 1,000 µmol/L, though typically elevations are in the ranges of few hundred µmol/L.
- In the milder neonatal and late-onset forms of ASL deficiency, the elevations of plasma ammonia concentration may be less pronounced but above the upper limits of normal for age (see Table 1).

Table 1. Upper Limits of Normal Plasma Ammonia Concentration by Age

Age	Upper Limits of Normal Ammonia Concentration (µmol/L) [1]
0-7 days	94
8-30 days	80
1-12 months	47
1-15 years	48
>16 years	26

1. The values depicted are only representative of the normal ranges; the normal reference ranges of individual laboratories should be used for clinical interpretation.

Plasma quantitative amino acid analysis. See Table 2.

The typical range of citrulline at presentation is 100-300 µmol/L [Brusilow & Horwich 2001]. The typical plasma levels of argininosuccinic acid are between 5 and 110 µmol/L [Ficicioglu et al 2009].

Table 2. Age-Related Plasma Amino Acid Concentrations in ASL Deficiency

Metabolite	Normal Plasma Levels Age <2 Years (µmol/L) [1]	Normal Plasma Levels Age 2-18 Years (µmol/L) [1]	In ASL Deficiency
Citrulline	2-41	6-38	Elevated
Argininosuccinic acid	0-1	0-1	Elevated [2]
Arginine	42-132	18-127	Low to normal
Glycine	104-344	92-346	Normal to high
Glutamine	238-842	266-746	Normal to high
Alanine	148-420	103-528	Normal to high

1. The values depicted are only representative of the normal ranges; the normal references of individual laboratories should be used for clinical interpretation.
2. The argininosuccinate chromatographic peak may co-elute with leucine or isoleucine, resulting in an apparent increase in one of these two amino acids. The anhydrides that elute later in the run allow for the correct identification of argininosuccinate.

Urinary analysis

- Orotic acid excretion is typically normal (0.3-2.8 mmol/mol of creatinine); however, orotic aciduria may be observed [Gerrits et al 1993, Brosnan & Brosnan 2007].
- Argininosuccinic acid is significantly elevated. Urinary concentration of argininosuccinate is typically greater than 10,000 µmol/g of creatinine on urine amino acid analysis [Ficicioglu et al 2009] (normal range 0-1 µmol/L).

Establishing the Diagnosis

The diagnosis of ASL deficiency **is established** in a proband with suggestive metabolic/biochemical findings and confirmed by the following set of specific laboratory test findings:

- Elevated plasma ammonia concentration
- Elevated plasma citrulline concentration (usually 100-300 µmol/L)
- Elevated argininosuccinic acid in the plasma or urine

Identification of biallelic pathogenic (or likely pathogenic) variants in *ASL* by molecular genetic testing (Table 3) or – in limited instances – by significantly reduced ASL enzyme activity from skin fibroblasts or red blood cells or in a flash-frozen sample from a liver biopsy help in confirmation of the diagnosis. As the laboratories that can assess enzymatic activity are limited and as molecular genetic testing has become widely available, the latter modality has become the more commonly used confirmatory test for ASL deficiency.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *ASL* variants of uncertain significance (or of one known *ASL* pathogenic variant and one *ASL* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches, which depend on the clinical findings, can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (typically exome sequencing and exome array).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Children with the distinctive laboratory findings of ASL deficiency described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas symptomatic individuals

with nonspecific supportive clinical and laboratory findings (who have not undergone NBS or who had normal NBS results in the past) in whom the diagnosis of ASL deficiency has not been considered are more likely to be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When NBS results and other laboratory findings suggest the diagnosis of ASL deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ASL* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: Single-gene testing is most appropriate when the diagnosis is made based on results of biochemical testing that show elevated levels of argininosuccinic acid in the plasma or urine.

- **A multigene panel** that includes *ASL* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  Note: A multigene panel test may be considered first when the presentation is with hyperammonemia and confirmatory biochemical diagnosis has not been performed or is unavailable.

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

Option 2

When an individual presents with hyperammonemia and confirmatory biochemical diagnosis has not been performed or is unavailable, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Table 3. Molecular Genetic Testing Used in Argininosuccinate Lyase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method [3]
ASL	Sequence analysis [4]	>90%
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Author observation
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used 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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

The clinical presentation of argininosuccinate lyase (ASL) deficiency is variable. The two most common forms are severe neonatal-onset form and late-onset form.

Severe neonatal-onset form. The clinical presentation of the severe neonatal-onset form, which is indistinguishable from that of other urea cycle disorders, is characterized by hyperammonemia within the first few days after birth. Newborns typically appear healthy for the first 24 hours but within the next few days develop vomiting, lethargy, and refusal to accept feeds [Brusilow & Horwich 2001]. Tachypnea and respiratory alkalosis are early findings. Failure to recognize and treat the defect in ureagenesis leads to worsening lethargy, seizures, coma, and even death. The findings of hepatomegaly and trichorrhexis nodosa (coarse and friable hair) at this early stage are the only clinical findings that may suggest the diagnosis of ASL deficiency [Brusilow & Horwich 2001].

Late-onset form. In contrast to the neonatal-onset form, the manifestations of the late-onset form range from episodic hyperammonemia (triggered by acute infection, stress, or non-compliance with dietary and/or medication recommendations) to cognitive impairment, behavioral abnormalities, and/or learning disabilities in the absence of any documented episodes of hyperammonemia [Brusilow & Horwich 2001].

Whereas manifestations secondary to hyperammonemia are common to all urea cycle disorders, many individuals with ASL deficiency can present with a complex clinical phenotype. The incidence of (1) neurocognitive deficiencies; (2) hepatitis, cirrhosis; (3) trichorrhexis nodosa; and (4) systemic hypertension are overrepresented in individuals with ASL deficiency [Nagamani et al 2012a, Kölker et al 2015, Kho et al 2018]. These manifestations may be unrelated to the severity or duration of hyperammonemic episodes [Saudubray et al 1999, Mori et al 2002, Ficicioglu et al 2009].

Complications of ASL Deficiency

Neurocognitive deficiencies. In a cross-sectional study of individuals with a urea cycle disorder (UCD), it was observed that persons with ASL deficiency had a higher incidence of developmental delay and neurologic abnormalities than did individuals with OTC deficiency [Tuchman et al 2008].

Individuals with ASL deficiency also had an increased incidence of attention-deficit/hyperactivity disorder (ADHD), developmental delay (intellectual disability, behavioral abnormalities, and/or learning disability), and seizures compared to persons with all other UCDs [Tuchman et al 2008]. In a recent retrospective study, developmental delay and epilepsy were observed in 92% (48/52) and 42% (22/52) of individuals, respectively [Baruteau et al 2017]. Though neurocognitive deficits are common in ASL deficiency, they are not universally present; many individuals with ASL deficiency who are treated with protein restriction and supplemental arginine have normal cognition and development [Widhalm et al 1992, Ficicioglu et al 2009].

The increasing reliance on newborn screening programs for early diagnosis of ASL deficiency allows the evaluation of early treatment on disease progression, especially in the late-onset form:

- Ficicioglu et al [2009] reported the long-term outcome of 13 infants diagnosed between age four and six weeks by newborn screening programs. All had low ASL enzyme activity; in spite of optimal therapy with protein restriction and arginine supplementation, four of 13 had learning disability, three had mild developmental delay, three had seizures, and six had an abnormal EEG including abnormal sharp irregular background activity, frequent bilateral paroxysms, and increased slow wave activity.
- In a separate cohort of 17 individuals with ASL deficiency diagnosed by newborn screening in Austria, IQ was average or above average in 11 (65%), low average in five (29%), and in the mild intellectual disability range in one (6%). Four had an abnormal EEG without evidence of clinical seizures [Mercimek-Mahmutoglu et al 2010]. The overall favorable outcomes in persons in this cohort may be attributable not only to early dietary and therapeutic interventions but also to the high proportion of persons with very mild disease.

Liver disease in individuals with ASL deficiency also appears to be independent of the defect in ureagenesis. The spectrum of hepatic involvement ranges from hepatomegaly to elevations of liver enzymes to severe liver fibrosis [Billmeier et al 1974, Mori et al 2002, Tuchman et al 2008]. Liver involvement has been noted even in individuals treated with protein restriction and arginine supplementation who had not experienced significant hyperammonemia [Mori et al 2002, Mercimek-Mahmutoglu et al 2010]. In a recent retrospective study, hepatomegaly and elevated alanine aminotransferase (ALT) were observed in nearly half of individuals with ASL deficiency [Baruteau et al 2017]. At present no biochemical or molecular features help predict liver dysfunction in people with ASL deficiency. Given the potential direct toxicity of argininosuccinate on hepatocytes, lowering of the argininosuccinate levels in plasma (a reflection of its production by the liver) may have potential benefit [Nagamani et al 2012c].

Trichorrhexis nodosa (see images) is characterized by nodular swellings of the hair shaft accompanied by frayed fibers and loss of cuticle. About half of individuals with ASL deficiency have an abnormality of the hair manifest as dull, brittle hair surrounded by areas of partial alopecia [Fichtel et al 2007]. Normal hair contains 10.5% arginine by weight; hair that is deficient in arginine as a result of ASL deficiency is weak and tends to break. Thus, this clinical feature responds to arginine treatment.

Hypertension. Whereas there have only been anecdotal reports of hypertension in ASL deficiency, preclinical data and systematic analysis of blood pressures from one controlled clinical trial have shown that ASL deficiency can directly result in endothelial dysfunction and hypertension [Kho et al 2018]. Usually no secondary causes of hypertension are detected, suggesting that this finding is related to the tissue-autonomous loss of ASL in the vascular endothelium.

Electrolyte imbalances. Some individuals develop electrolyte imbalances such as hypokalemia. The hypokalemia is observed even in individuals who are not treated with sodium phenylbutyrate. The etiology is unclear; increased renal wasting has been suggested.

Genotype-Phenotype Correlations

Data are insufficient to infer any genotype-phenotype correlations.

Prevalence

The estimated prevalence is 1:70,000 to 1:218,000 live births [Brusilow & Horwich 2001, NORD]. However, ASL deficiency is very likely underdiagnosed, making it difficult to assess the true frequency in the general population.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The severe neonatal-onset form of argininosuccinate lyase (ASL) deficiency shares the phenotype of the typical acute neonatal hyperammonemia displayed by other defects in the first four steps in the urea cycle pathway (see Urea Cycle Disorders Overview).

The late-onset form of ASL deficiency shares a later onset with other disorders such as late-onset ornithine transcarbamylase (OTC) deficiency, and late-onset citrullinemia type 1. However, the elevation of argininosuccinate is characteristic and differentiates ASL deficiency from other urea cycle disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual with argininosuccinate lyase (ASL) deficiency following diagnosis, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis of ASL Deficiency

Evaluation	Comment
Consult w/metabolic physician / biochemical geneticist & specialist metabolic dietitian 1	• Transfer to a specialist center w/experience in mgmt of inherited metabolic diseases (strongly recommended) • Consider a short hospitalization at a center of expertise for inherited metabolic conditions to provide detailed education (natural history, maintenance & emergency treatment, prognosis, & risks for acute crises) for caregivers. • Consultation w/genetic counselor to understand inheritance of ASL deficiency
Neurocognitive assessment	Consider referral to a developmental pediatrician, psychologist, &/or neurologist.
Baseline eval for evidence of hepatic involvement incl hepatomegaly, hepatitis, & signs of liver failure	• Plasma AST, ALT, bilirubin, albumin, PT, & INR • Hepatic ultrasound to monitor for hepatomegaly, fibrosis, & additional complications incl hepatocellular carcinoma • Referral to hepatologist as required
Plotting of systolic & diastolic blood pressure on centile charts based on age & stature	

Table 4. continued from previous page.

Evaluation	Comment
Consultation w/clinical geneticist &/or genetic counselor	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; PT = prothrombin time
1. After a new diagnosis of ASL deficiency in a child, the closest hospital and local pediatrician should also be informed.

Treatment of Manifestations

Treatment involves rapid control of hyperammonemia during metabolic decompensations and long-term management to help prevent episodes of hyperammonemia and long-term complications.

During acute hyperammonemic episodes severe enough to cause neurologic symptoms, the treatment includes the following [Ahrens et al 2001] (see Table 5).

Table 5. Acute Inpatient Treatment in Individuals with ASL Deficiency

Manifestation/ Concern	Treatment	Consideration/Other
Acute hyperammonemic episodes	Discontinue oral protein intake.	
	Supplement oral intake w/IV lipids, glucose, & insulin if needed (w/close monitoring of blood glucose) to promote anabolism.	
	IV nitrogen-scavenging therapy. A loading dose of 600 mg/kg L-arginine-HCL & 250 mg/kg each of sodium benzoate & sodium phenylacetate in 25-35 mL/kg of 10% dextrose solution given intravenously over a 90-min period is recommended, followed by a sustained IV infusion of 600 mg/kg L-arginine-HCL & 250 mg/kg each of sodium benzoate & sodium phenylacetate over a 24-hr period.	When available, plasma concentrations of ammonia-scavenging drugs should be monitored to avoid toxicity. In the absence of drug levels, a serum anion gap of >15 mEq/L & an anion gap that has risen >6 mEq/L could indicate drug accumulation & ↑ risk for toxicity.

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Consideration/Other
Failure to ↓ ammonia levels w/ medical therapy	Prompt institution of hemodialysis	• Continuous arteriovenous hemodialysis or continuous venovenous hemodialysis w/flow rates >40-60 mL/min is optimal. • Some centers use extracorporeal membrane oxygenation w/hemodialysis. • Although this combination of techniques provides very high flow rates (170-200 mL/min) & rapidly reduces ammonia levels, morbidity is greater due to need for surgical vascular access. • Nitrogen-scavenging therapy needs to be continued during hemodialysis. • It is the authors' policy to continue nitrogen-scavenging therapy for 12-24 hrs after patient is stabilized & able to accept enteral feeds & medications [Author, personal observation].

HCL = hydrochloride; IV = intravenous
Inpatient emergency treatment should: (a) take place at the closest medical facility equipped to treat individuals with metabolic disorders, (b) be started without delay, and (c) be supervised by physicians and specialist dieticians at the responsible metabolic center, who should be contacted without delay.

Long-term management. Dietary restriction of protein and dietary supplementation with arginine are the mainstays of long-term management as detailed in Table 6.

Table 6. Routine Daily Treatment in Individuals with ASL Deficiency

Principle/ Manifestation	Treatment	Consideration/Other
Dietary restriction of protein	Lifelong dietary management is necessary & requires the services of a metabolic nutritionist. [1]	• RDA for dietary protein is higher than minimum needed for normal growth; thus, most children w/a urea cycle disorder can receive less than the RDA of protein & still maintain adequate growth. • Dietary therapy. Maintain: ◦ Plasma concentrations of ammonia, branched-chain amino acids, & arginine w/in normal ranges; ◦ Serum plasma total protein & prealbumin levels w/in low normal ranges; ◦ Plasma glutamine concentration at ˂1,000 µmol/L if possible (normal range for persons age 2-18 yrs: 266-746 µmol/L).
Arginine base supplementation	The doses of arginine base routinely recommended are 400-700 mg/kg/day in persons weighing ˂20 kg & 8.8-15.4 g/m^2/day in those weighing >20 kg. The authors prefer to use a lower dose of arginine whenever possible, in the range of 100-250 mg/kg/day.	• Supplementation w/arginine base helps replenish this amino acid (which is deficient in persons w/ASL deficiency) & promote excretion of nitrogen through urea cycle as argininosuccinate. • Arginine base is preferred for long-term chronic treatment as the chronic use of arginine hydrochloride may → hyperchloremic acidosis.

Table 6. continued from previous page.

Principle/ Manifestation	Treatment	Consideration/Other
		• Arginine base supplementation has been shown to reverse hair changes; however, its efficacy in preventing chronic complications is not known. While evidence suggests that arginine base supplementation may prevent metabolic decompensations in those w/severe early-onset disease, long-term follow up of persons identified through newborn screening programs did not detect a difference in outcomes between those who were supplemented w/arginine base & those who were not [Batshaw et al 2001, Ficicioglu et al 2009, Mercimek-Mahmutoglu et al 2010]. • As the renal clearance of argininosuccinic acid is high, increasing its production through arginine supplementation effectively increases waste nitrogen disposal, thereby decreasing the risk of hyperammonemia. • However, because of the theoretic risk of argininosuccinic acid toxicity on hepatocytes, reducing the amount of supplemental arginine by initiating nitrogen-scavenging therapy may have merits. The authors prefer to keep the dose of arginine in the range of 100-250 mg/kg/day whenever possible.
Oral nitrogen-scavenging therapy (an alternative pathway therapy in which sodium benzoate & phenyl butyrate stimulate excretion of nitrogen as hippuric acid & phenylacety-lglutamine, respectively)	The typical dose ranges [2] for the medications: • Sodium phenylbutyrate, 400-600 mg/kg/day for persons weighing ≤20 kg; 9.9-13 g/m^2/day for those weighing >20 kg • Glycerol phenylbutyrate, 4.4-11.2 mL/m^2/day • Sodium benzoate, 250-500 mg/kg/day or 5.5 g/m^2/day	Persons who have had frequent metabolic decompensations or episodes of ↑ ammonia despite being on a protein-restricted diet & arginine base supplementation are candidates for oral nitrogen-scavenging therapy.
Orthotopic liver transplantation (OLT)	Recommended only in those w/recurrent hyperammonemia or metabolic decompensations that are resistant to conventional medical therapy, or in those who develop cirrhosis w/associated metabolic decompensations [Author, personal observations]	OLT does not correct the arginine deficiency or elevation of argininosuccinic acid at the tissue level, two abnormalities thought to account for the long-term complications of ASL deficiency.
Hypertension	• Salt restriction & use of antihypertensives indicated in those w/↑ blood pressure. • Antihypertensives may be tried; their efficacy has not been established.	
Hypokalemia	Electrolyte (potassium) supplementation is appropriate when indicated.	

Table 6. continued from previous page.

Principle/ Manifestation	Treatment	Consideration/Other
Neurocognitive delay	Special educational services & therapies as needed	

RDA = recommended daily allowance
1. Some of the correlations between compliance with the prescribed diet and outcome are contradictory. Although in some patients dietary therapy along with arginine supplementation have been shown to reverse the abnormalities of hair, to improve cognitive outcome, and to reverse abnormalities on EEG [Coryell et al 1964, Kvedar et al 1991, Ficicioglu et al 2009], in many dietary therapy has not been shown to influence the outcome of liver disease or cognitive impairment [Mori et al 2002, Mercimek-Mahmutoglu et al 2010].
2. The dose ranges depicted are those typically used in individuals with ASL deficiency. The safety and efficacy of phenylbutyrate doses >20 g/day are not known. The dose of glycerol phenylbutyrate depicted is the recommended initial dose in phenylbutyrate-naïve patients. When switching from sodium phenylbutyrate, the total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate (g) x 0.86. The maximal daily dose for benzoate is 12 grams. When prescribing doses in the upper ranges of the recommended dosing, toxicity should be monitored.

Surveillance

Table 7. Recommended Surveillance for Individuals with Argininosuccinate Lyase Deficiency

Manifestation/ Concern	Evaluation	Frequency/Comment
Management of disorder	Follow up in a metabolic clinic w/qualified metabolic dietician & clinical biochemical geneticist	Lab & clinical monitoring frequency depending on metabolic status of the patient. In general: • Neonates: every 2 wks • Infants age 2 mos-1 yr: every 1-3 mos • Children ≥2 yrs: every 3-4 mos Monitor following changes in medical or dietary prescriptions.
Abnormal amino acid levels	Analysis of plasma amino acids to identify deficiency of essential amino acids as well as impending hyperammonemia [1]	
Hypertension	Measurement of blood pressure using appropriate-sized cuff & plotting centile values for age & stature	At each clinic visit
Abnormal liver function	Liver function tests (ALT, AST)	Every 6-12 mos as required
Abnormal electrolytes	Serum electrolyte analysis	Every 1-2 yrs as required

ALT = alanine aminotransferase; AST = aspartate aminotransferase
1. Early signs of impending hyperammonemic episodes in older individuals include mood changes, headache, lethargy, nausea, vomiting, refusal to feed, ankle clonus, and elevated plasma concentrations of glutamine, alanine, and glycine. Plasma glutamine concentration may rise 48 hours in advance of increases in plasma ammonia concentration in such individuals.

Agents/Circumstances to Avoid

Avoid the following:

- Excess protein intake
- Large boluses of protein or amino acids
- Less than recommended intake of protein
- Prolonged fasting or starvation
- Obvious exposure to communicable diseases
- Valproic acid
- Intravenous steroids
- Hepatotoxic drugs in individuals with hepatic involvement

Evaluation of Relatives at Risk

Evaluation of at-risk sibs shortly after birth can reduce morbidity by permitting early diagnosis and treatment of those who are affected. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Plasma amino acids to specifically assess for argininosuccinic acid in a newborn at risk prior to molecular genetic testing or while waiting for molecular genetic testing results.

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

Therapies Under Investigation

Nitrite and nitrate supplementation is being evaluated as potential therapy for hypertension and vascular dysfunction in ASL deficiency [NCT02252770, NCT03064048, Nagamani et al 2012b].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

Argininosuccinate lyase (ASL) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *ASL* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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.
- Though the phenotypic manifestations may vary, in a family with one child with the severe neonatal-onset form subsequent children are likely to have the severe neonatal-onset form. In contrast, the phenotype of late-onset forms associated with partial ASL enzyme activity is variable.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- The offspring of an individual with ASL deficiency are obligate heterozygotes (carriers) for an *ASL* pathogenic variant.
- Unless an affected individual's reproductive partner also has ASL deficiency or is a carrier, offspring will be obligate heterozygotes (carriers) for an *ASL* pathogenic variant.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the 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, clarification of carrier status, 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 or at risk of being affected, or are carriers or 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 *ASL* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk for ASL deficiency and preimplantation genetic testing are possible.

Biochemical testing. Elevated levels of argininosuccinic acid in the amniotic fluid can reliably detect an affected fetus [Kamoun et al 1995, Kleijer et al 2006]. The concentration of argininosuccinate in the amniotic fluid can be measured between 15 and 18 weeks' gestation. Because of limited data, the sensitivity of the test is not known. However, because argininosuccinate is not detectable in amniotic fluid under normal conditions and because ASL deficiency is the only disorder that causes elevation of argininosuccinate, the finding of increased concentrations of argininosuccinate in the amniotic fluid is diagnostic of ASL deficiency. In the authors' experience there is complete concordance between the presence of argininosuccinic acid in the amniotic fluid and decreased ASL enzyme activity on cultured amniocytes [Author, personal observation].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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.

- **British Inherited Metabolic Disease Group (BIMDG)**
  TEMPLE (Tools Enabling Metabolic Parents LEarning)
  United Kingdom
  Argininosuccinic aciduria

- **MedlinePlus**
  Argininosuccinic aciduria
- **National Urea Cycle Disorders Foundation**
  Phone: 626-578-0833
  nucdf.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  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. Argininosuccinate Lyase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ASL	7q11.21	Argininosuccinate lyase	ASL @ LOVD	ASL	ASL

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 Argininosuccinate Lyase Deficiency (View All in OMIM)

207900	ARGININOSUCCINIC ACIDURIA
608310	ARGININOSUCCINATE LYASE; ASL

Molecular Pathogenesis

Arginine serves as the precursor for the synthesis of urea, nitric oxide, polyamines, proline, glutamate, creatine, and agmatine (Figure 1) and is a semi-essential amino acid. The sources of arginine are exogenous from the diet and endogenous from the breakdown of proteins and synthesis from citrulline [Wu & Morris 1998]. Healthy adults typically generate sufficient arginine through endogenous synthesis. However, in situations such as catabolic stress or dysfunction of the kidneys or small intestine, endogenous arginine production is insufficient and arginine becomes an essential amino acid (i.e., it must be provided exogenously).

ASL encodes a polypeptide that forms a homotetramer. Its main role in the urea cycle is conversion of argininosuccinate into arginine and fumarate. It is the key enzyme in the cellular production of arginine. It also participates in a complex that channels arginine from out of the cell into the cell for the purpose of nitric oxide synthesis. To do so, it maintains a complex that involves nitric oxide synthase, the arginine transporter CAT1, and HSP90. Loss of argininosuccinate lyase (ASL) leads to loss of this complex and inability to generate nitric oxide even with supplemental arginine.

The liver, the major site of arginine metabolism, rapidly converts arginine generated in the urea cycle to urea and ornithine and does not contribute to the circulating pool of arginine.

The kidney, where approximately 60% of net synthesis of arginine occurs, extracts citrulline from the blood and converts it to arginine via the enzymes argininosuccinate synthetase (ASS1) and ASL, which are localized within the proximal tubules [Windmueller & Spaeth 1981]. Other tissues and cell types also generate arginine from citrulline via this pathway [Mori & Gotoh 2004]. In ASL deficiency, arginine becomes an essential amino acid because all cells and tissues are deficient in the enzyme ASL.

Mechanism of disease causation. ASL deficiency occurs through loss of argininosuccinate lyase enzyme function. Residual enzyme activity may be present.

ASL deficiency leads to accumulation of argininosuccinate and depletion of arginine. The block in ureagenesis can cause hyperammonemia. In addition, argininosuccinate accumulates; though it has been hypothesized to be a potential toxic metabolite, the specific phenotypic features that can result from elevated argininosuccinate are not yet clearly defined. Finally, loss of ASL leads to loss of production of nitric oxide from nitric oxide synthase-dependent mechanisms.

***ASL*-specific laboratory considerations.** Analysis of *ASL* is complicated by a pseudogene, Ψ *ASL2*, located approximately three Mb upstream of *ASL*. The pseudogene includes intron 2, exon 3, and part of intron 3 of *ASL* [Trevisson et al 2007].

Yeast-based functional complementation assays have been used to assess the pathogenicity of *ASL* alleles [Trevisson et al 2009]. This model demonstrated that abnormal *ASL* alleles typically found in affected individuals with late-onset ASL deficiency had either high residual ASL enzyme activity or two mutated alleles that exhibited complementation [Yu & Howell 2000, Trevisson et al 2009].

Table 8. Notable *ASL* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001024943.1 NP_001020114.1	c.1153C>T	p.Arg385Cys	Founder variant in the Finnish population, assoc w/residual ASL enzyme activity [Kleijer et al 2002]
	c.1060C>T	p.Gln354Ter	Founder variants present in people of Arab ancestry from the Kingdom of Saudi Arabia [Al-Sayed et al 2005]
	c.346C>T	p.Gln116Ter	

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.

Chapter Notes

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- 3 February 2011 (me) Review posted live
- 31 August 2010 (ae) Original submission

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Published Guidelines / Consensus Statements

- Urea Cycle Disorders Conference Group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr. 2001;138:S1-5.

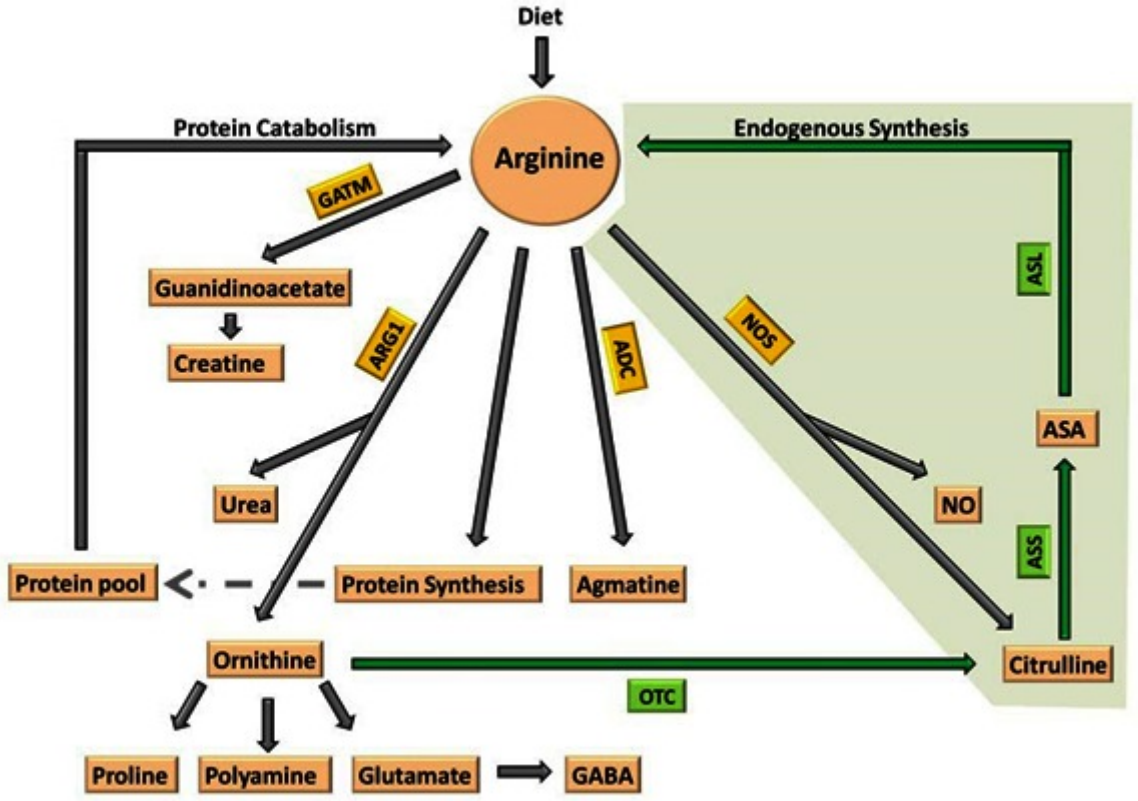

Figure 1. Metabolic fates of arginine

Arginine is derived from dietary sources, protein catabolism, or endogenous synthesis. The arginine-citrulline cycle is responsible for regeneration of arginine in various tissues. Arginine serves as the precursor for many biologically important molecules; a decrease in arginine may result in decreased production of compounds for which it serves as a precursor.

GATM = glycine amidinotransferase

Arg1 = arginase 1

ADC = arginine decarboxylase

NOS = nitric oxide synthase

NO = nitric oxide

OTC = ornithine transcarbamoylase

ASS = argininosuccinate synthase

ASA = argininosuccinic acid

ASL = argininosuccinate lyase

GABA = γ-amino butyric acid

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