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Serine Deficiency Disorders

Synonyms: Serine Biosynthesis Disorders, Serine Synthesis Disorders

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Summary

Clinical characteristics

Serine deficiency disorders include a spectrum of disease ranging from lethal prenatal-onset Neu-Laxova syndrome to serine deficiency with infantile, juvenile, or adult onset. Neu-Laxova syndrome is characterized by severe intrauterine growth deficiency, microcephaly, congenital bilateral cataracts, characteristic dysmorphic features, limb anomalies, and collodion-like ichthyosis. Infants are typically stillborn or die in early infancy. Infantile-onset serine deficiency is characterized by seizures, microcephaly, developmental delay, intellectual disability, and spastic quadriplegia. Individuals that present with juvenile-onset serine deficiency have seizures and many develop spastic quadriplegia. Adult-onset serine deficiency is characterized by progressive axonal polyneuropathy with ataxia and possible cognitive impairment.

Diagnosis/testing

The diagnosis of a serine deficiency disorder is established in a proband with biallelic pathogenic variants in *PHGDH*, *PSAT1*, or *PSPH* identified by molecular genetic testing.

Management

Targeted therapy: Early treatment with L-serine supplementation; glycine supplementation with L-serine has been used in some individuals.

Supportive care: L-serine therapy is more effective than anti-seizure medication for treatment of seizures; developmental and educational support; feeding therapy for persistent feeding issues; treatment of cataracts per ophthalmologist; standard treatments for spasticity and polyneuropathy; preventative dental care for those on oral L-serine powder; social work support and care coordination as needed.

Surveillance: Monitor for seizures, changes in tone, contractures, developmental and educational needs, behavior issues, growth and nutrition, constipation and feeding issues, respiratory issues, musculoskeletal manifestations,

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and family needs at each visit. Dental evaluation every six months. Assessment of care needs when transitioning from pediatric to adult care.

Agents/circumstances to avoid: Known triggers of seizure activity (e.g., infection, physical stress, emotional stress).

Evaluation of relatives at risk: It is appropriate to evaluate newborn sibs and apparently asymptomatic older and younger sibs of a proband to identify as early as possible those who would benefit from prompt initiation of L-serine treatment.

Genetic counseling

Serine deficiency disorders are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a serine deficiency-causing 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. Once the serine deficiency-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

GeneReview Scope

Serine Deficiency Disorders: Phenotypic Spectrum

Severity	Phenotype [1]
Lethal prenatal phenotype	Neu-Laxova syndrome
Nonlethal phenotypes	• Infantile-onset phenotype: severe neurodevelopmental disorder w/epilepsy & microcephaly • Juvenile-onset phenotype: developmental & behavioral issues & epilepsy • Adult-onset phenotype: progressive axonal neuropathy, variable ataxia &/or cognitive impairment

1. For other genetic causes of these phenotypes, see Differential Diagnosis.

Diagnosis

No consensus clinical diagnostic criteria for serine deficiency disorders have been published.

Suggestive Findings

A serine deficiency disorder **should be suspected** in individuals with the following clinical, imaging, and laboratory findings and family history.

Clinical and brain MRI findings can vary between phenotypes:

- **Prenatal onset (Neu-Laxova syndrome)**
  - Severe intrauterine growth deficiency
  - Microcephaly
  - Congenital bilateral cataracts
  - Dysmorphic features: sloping forehead, proptosis or short palpebral fissures with absent or abnormal eyelids, edematous and/or low-set or malformed ears, depressed nasal ridge, fixed narrow mouth with edematous lips, micrognathia, cleft palate, and short neck
  - Thin, transparent, and tight skin with collodion-like ichthyosis
  - Limb anomalies: short limbs, flexion contractures, cutaneous syndactyly, edematous hands and feet, rocker-bottom feet
  - Neural tube defects

    - Brain MRI findings: cortical dysplasia with gyral simplification (anterior more than posterior), enlarged ventricles, decreased white matter, and structural abnormalities of the cerebellum [Acuna-Hidalgo et al 2014, Shapira Zaltsberg et al 2020]
- **Infantile onset**
    - Seizures
    - Microcephaly (congenital or postnatal)
    - Developmental delay
    - Severe intellectual disability
    - Spastic quadriplegia
    - Growth deficiency (prenatal and/or postnatal)
    - Ocular manifestations: nystagmus, congenital bilateral cataracts
    - Ichthyosis
    - Brain MRI findings: severe hypomyelination, white matter attenuation and delayed myelination, nonspecific cerebellar abnormalities
- **Juvenile onset**
    - Seizures
    - Developmental delay
    - Intellectual disability
    - Behavioral disorders
    - Normal brain MRI [de Koning et al 2000b]
- **Adult onset**
    - Progressive polyneuropathy
    - Ataxia in some individuals
    - Mild cognitive impairment in some individuals
    - Normal brain MRI [de Koning et al 2000b]

Laboratory findings are consistent across all phenotypes:

- Cerebrospinal fluid (CSF) serine is very low, usually <13 umol/L, and in most individuals <10 umol/L [van der Crabben et al 2013]. CSF serine levels in individuals with infantile-onset serine deficiency do not differ significantly from individuals with juvenile- or adult-onset serine deficiency.
- Fasting plasma serine is low, but nonfasting samples can be normal.
- CSF 5-methyltetrahydrofolate is very low [de Koning et al 2000a].
- CSF glycine is low to normal; fasting plasma glycine can be low to normal.
- Urine amino acids are noninformative; results are usually normal.

Note: Use age-specific reference ranges for CSF and plasma serine; normal serine levels are significantly higher between birth and age three months [van der Crabben et al 2013].

Family 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 a serine deficiency disorder **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PHGDH*, *PSAT1*, or *PSPH* identified by molecular genetic testing (see Table 1).

Note: (1) 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. (2) Identification of biallelic *PHGDH*, *PSAT1*, or *PSPH* variants of uncertain significance (or identification of one known pathogenic variant and one variant of uncertain significance) does not establish or rule out the diagnosis (see Other Testing).

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings (e.g., prenatal-onset Neu-Laxova syndrome) are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with seizures and developmental delay are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

An intellectual disability or epilepsy multigene panel that includes some or all of the genes listed in Table 1 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.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Comprehensive genomic testing is most likely to be informative when clinicians provide detailed clinical, radiologic, and biochemical findings to accurately filter and interpret variants that are identified.

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 Serine Deficiency Disorders

Gene [1, 2]	Proportion of Serine Deficiency Disorders Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
PHGDH	69% [6]	>90% [7]	<10% [7]
PSAT1	6% [6]	100% [7]	None reported [7, 8]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Serine Deficiency Disorders Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
PSPH	25% [6]	100% [7]	None reported [7, 8]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. 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.
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. Authors, unpublished data
7. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
8. To date, large deletions/duplications in *PSAT1* or *PSPH* have not been reported in individuals with a serine deficiency disorder.

Other Testing

In those with variants of uncertain significance identified on molecular genetic testing, the diagnosis of a serine deficiency disorder can be established by identification of low D-3-phosphoglycerate dehydrogenase, phosphoserine aminotransferase, or phosphoserine phosphatase enzymatic activity. However, due to decreased availability of substrates for the enzymatic reactions, this testing is no longer routinely available.

Clinical Characteristics

Clinical Description

Serine deficiency disorders include a spectrum of disease ranging from lethal prenatal-onset Neu-Laxova syndrome to adult-onset serine deficiency characterized by progressive polyneuropathy. Several clinical phenotypes can be identified: prenatal onset, infantile onset, juvenile onset, and adult onset. To date, more than 50 individuals have been identified with biallelic pathogenic variants in *PHGDH*, *PSAT1*, or *PSPH* [Acuna-Hidalgo et al 2014, Shaheen et al 2014, Brassier et al 2016, El-Hattab et al 2016, Abdelfattah et al 2020, Debs et al 2021, Serrano Olave et al 2022, Shen et al 2022, Fu et al 2023]. The majority of individuals reported have the infantile-onset phenotype. The following description of the phenotypic features associated with this condition is based on these reports.

Neu-Laxova Syndrome (Prenatal Onset)

Neu-Laxova syndrome is characterized by severe intrauterine growth deficiency, decreased or absent fetal movements, microcephaly, congenital bilateral cataracts, and ichthyosis [Acuna-Hidalgo et al 2014]. Characteristic dysmorphic features include sloping forehead [Abdelfattah et al 2020], hypertelorism [Acuna-Hidalgo et al 2014], proptosis or short palpebral fissures with absent or abnormal eyelids, edematous and low-set or malformed ears, depressed nasal ridge or flat/abnormal nose, fixed narrow mouth with edematous lips, micrognathia, cleft palate, and short neck. Limbs are short with flexion contractures and edematous hands and feet obscuring the digits. Rocker-bottom feet have also been described [Acuna-Hidalgo et al 2014]. The skin is thin, transparent, and tight, with scaling or collodion-like ichthyosis and subcutaneous edema [Acuna-Hidalgo et al 2014]. Additional reported anomalies include neural tube defects and genitourinary anomalies. Many infants with Neu-Laxova syndrome are stillborn. The remainder succumb to the disorder shortly after birth, but survival until age two months has been described [Shaheen et al 2014, El-Hattab et al 2016].

Infantile-Onset Serine Deficiency

Seizures start in the first weeks or months of life in all individuals. In about one third of individuals, seizures start as infantile spasms syndrome (previously termed West syndrome); in the remaining infants, various types of seizures are observed (e.g., myoclonic, tonic-clonic, gelastic, tonic, atonic). In individuals presenting with infantile spasms syndrome, EEGs show hypsarrhythmia, but in others there is multifocal seizure activity evolving into Lennox-Gasteaux syndrome [van der Crabben et al 2013].

Seizures are refractory to anti-seizure medications in almost all individuals. Some individuals have up to 60-70 clinically evident tonic-clonic seizures a day. In all individuals, seizures significantly improve upon treatment with L-serine; many become seizure free, decreasing the need for chronic anti-seizure medications. Improvement in EEG abnormalities may not occur until after six months of L-serine treatment [Authors, personal observations].

Microcephaly is congenital in 68% of individuals with the infantile-onset subtype. In others, microcephaly becomes evident in the first few months of life; postnatal microcephaly is reported in 95% of individuals with infantile onset. Those with infantile spasms syndrome have arrest of head growth.

Developmental delay. Prior to the availability of L-serine treatment, most individuals with a serine deficiency disorder presented with the infantile-onset phenotype initially as a hypotonic infant in the first months of life evolving into hypertonic, irritable infants. Individuals diagnosed after the first months of life and certainly after age six months had severe developmental delay and poor developmental outcomes. Development usually plateaus in the first year, and affected children have a developmental age of approximately one year. Seizures and treatment with anti-seizure medications often result in a loss of minimally acquired developmental milestones.

Individuals treated with L-serine prenatally or immediately after birth have normal developmental outcomes [de Koning et al 2004, Hart et al 2007]. Those treated with L-serine at age four months or later have severe developmental delay, functioning at a preschool level in adulthood. Apparently, early treatment is required to prevent irreversible damage to the central nervous system.

Intellectual disability. Delayed treatment with L-serine results in severe intellectual disability. However, results of formal cognitive testing have not been reported in individuals with infantile onset.

Additional neurologic manifestations. Spastic quadriplegia is reported in 63% of individuals.

Growth deficiency. Intrauterine growth deficiency is observed in 16% of affected infants. Postnatal growth deficiency is reported in 42% of infants and is likely due to a combination of factors. Affected infants are irritable, with increased crying and vomiting, and 37% have feeding difficulties due to motor delays and seizures. Anti-seizure medications can further exacerbate feeding difficulties, and many infants require nasogastric or gastrostomy tube feeding to gain weight.

After initiation of L-serine treatment, well-being improves rapidly, with decreased irritability and improved feeding. However, infants that were symptomatic prior to L-serine treatment continue to have severe neurologic symptoms impacting feeding and weight gain.

Nystagmus is reported in 42% of children with infantile-onset serine deficiency. This ophthalmologic finding has not been investigated in detail, and the nature and origin of nystagmus is unknown.

Cataracts. Congenital cataracts are reported in 26% of individuals with infantile onset. The cataracts are bilateral and detected in the first months of life. Additional features of the cataracts have not been documented.

Ichthyosis. Therapy with high-dose oral L-serine and glycine completely resolves the ichthyosis [Shen et al 2022].

Craniofacial features identified in individuals with infantile-onset serine deficiency include elongated face, large ears (becoming apparent in older individuals), upslanted palpebral fissures, and a broad nasal tip [Authors, unpublished data].

Juvenile-Onset Serine Deficiency

Seizures. Individuals with juvenile-onset serine deficiency typically develop seizures at school age. Absence seizures started at age four to nine years in one cohort; seizures were resistant to anti-seizure medication in one individual [Tabatabaie et al 2011]. EEGs showed the typical bilateral synchronous 3-Hz spike-and-wave complexes of absence seizures, which were enhanced after hyperventilation.

Development/cognition. Motor and language skills can be mildly delayed or normal; cognitive function can range from mild intellectual disability to normal cognitive development [Tabatabaie et al 2011, Shen et al 2022].

Behavioral and psychiatric manifestations. Hyperactive behavior, behavioral issues, and mood disturbances have been reported [Tabatabaie et al 2011]. Individuals with normal behavior have also been reported [Shen et al 2022]. Young adults treated with L-serine for many years can develop psychiatric symptoms when L-serine supplements are discontinued [Authors, personal communication].

Additional manifestations. Many individuals develop spastic quadriplegia or tetraplegia and subsequent deformities of the spine and extremities.

Adult-Onset Serine Deficiency

Individuals with adult-onset serine deficiency present with progressive axonal polyneuropathy (resembling Charcot-Marie-Tooth disease type 2 on EMG).

Some adults were reported to have ataxia [Méneret et al 2012].

In adult-onset serine deficiency, individuals had normal cognitive function to mild cognitive impairment.

Individuals treated with L-serine for many years can develop psychiatric symptoms when L-serine supplements are discontinued [Author, personal communication].

One adult who presented with progressive polyneuropathy and progressive motor disability had surgical treatment for bilateral congenital cataracts at age three months [Méneret et al 2012].

Other

The following have been reported in only a limited number of affected individuals: adducted thumbs, inguinal and umbilical hernias, hypogonadism, megaloblastic anemia, and generalized ichthyosis. These features may be seen in individuals with any of the phenotypes [Authors, personal communication].

Phenotype Correlations by Gene

There is no correlation between the gene involved and the clinical phenotype. All phenotypes (lethal prenatal onset to adult onset) can be observed in individuals with pathogenic variants in *PHGDH*, *PSAT1*, or *PSPH*.

Genotype-Phenotype Correlations

No clear genotype-phenotype correlations for *PHGDH*, *PSAT1*, or *PSPH* have been identified.

Preliminary conclusions regarding possible genotype-phenotype correlations for *PHGDH* and *PSAT1* can be made, however. Neu-Laxova syndrome is predominantly associated with pathogenic variants located in the substrate-binding domain and nucleotide-binding domain (83%) [Abdelfattah et al 2020], whereas pathogenic variants in the substrate-binding domain have not been reported in individuals with infantile-, juvenile-, or

adult-onset serine deficiency. Pathogenic variants in nonlethal phenotypes were primarily located in the regulatory domain (63%). To date, the number of nonsense variants reported is very limited, even in individuals with Neu-Laxova syndrome. The authors are not aware of individuals with biallelic nonsense variants, which may lead to an early lethal phenotype.

Prevalence

The prevalence of serine deficiency disorders is not known. It is estimated that there are more than 50 affected individuals reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PHGDH*, *PSAT1*, or *PSPH*.

Differential Diagnosis

ASCT1 transporter deficiency, GOT2 deficiency, and other selected disorders with clinical and/or biochemical features that may resemble serine deficiency disorders are summarized in Table 2.

Note: Given the first step in the synthesis of L-serine is an oxidation-reduction (redox) reaction (see Figure 1), all defects that affect the redox reaction (e.g., GOT1 deficiency, mitochondrial complex I deficiency) can potentially affect the synthesis of serine and result in secondary serine deficiency.

Table 2. Genetic Disorders in the Differential Diagnosis of Serine Deficiency Disorders

Gene	Disorder	MOI	Clinical Characteristics	Laboratory Findings
SLC1A4	ASCT1 transporter deficiency (OMIM 616657)	AR	• Considerable phenotypic overlap w/serine deficiency disorders. Assoc w/DD, microcephaly, spastic tetraplegia, & variable seizures (infantile form may or may not be assoc w/seizures [1]). • Hypomyelination & thin corpus callosum on MRI	• No associated biochemical abnormalities • Note: As ASCT1 is the major transporter for L-serine in brain tissue, it is possible that a defect of ASCT1 leads to an intracellular deficiency of L-serine. [2]
GOT2	GOT2 deficiency (OMIM 618721)	AR	• Early-onset encephalopathy w/ progressive microcephaly & early-onset seizures (seizures are pyridoxine & L-serine responsive). [3] • Atrophy & white matter abnormalities w/thin corpus callosum on MRI	• Inhibited synthesis of serine results in secondary serine deficiency. • In addition, citrulline may be ↑ & ammonia & lactate are mildly ↑.

Table 2. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics	Laboratory Findings
ATP7A	Menkes disease (See *ATP7A*-Related Copper Transport Disorders.)	XL	• Infants w/classic Menkes disease appear healthy until age 1.5-3 mos, when loss of developmental milestones, hypotonia, seizures, & poor weight gain occur. Diagnosis is usually suspected when infants exhibit neurologic findings & characteristic hair changes. • Cerebral & cerebellar atrophy w/ ventriculomegaly, delayed myelination, & vascular tortuosity on brain MRI	Low plasma & CSF serine values were observed in multiple boys w/ Menkes disease-related early-onset intractable seizures & severe hypotonia (mechanism of low serine in these boys is unknown). [2]
~40 genes [4]	Mitochondrial complex I deficiency (OMIM PS252010 & 500014)	Depends on genetic etiology	Severe DD & seizures	Severe secondary serine deficiency has been observed in persons w/ mitochondrial complex 1 deficiency. [2]

AR = autosomal recessive; CSF = cerebrospinal fluid; DD = developmental delay; MOI = mode of inheritance; XL = X-linked
1. Damseh et al [2015]
2. Authors, personal observations
3. van Karnebeek at al [2019]
4. See OMIM Phenotypic Series: Mitochondrial complex I deficiency, nuclear type and OMIM 500014.

Acquired disorders. Severe viral illness / encephalitis can be associated with secondary serine deficiency [Keularts et al 2010].

Management

No clinical practice guidelines for serine deficiency disorders have been published.

Evaluations Following Initial Diagnosis

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

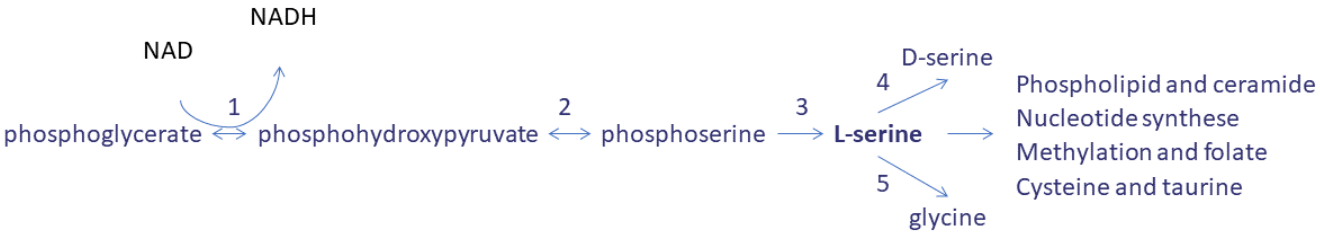

Figure 1. Serine synthesis

1 = D-3-phosphoglycerate dehydrogenase (encoded by *PHGDH*); 2 = phosphoserine aminotransferase (encoded by *PSAT1*); 3 = phosphoserine phosphatase (encoded by *PSPH*); 4 = serine racemase; 5 = serine hydroxymethyltransferase

Table 3. Serine Deficiency Disorders: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	• Neurologic eval • EEG	• To incl brain MRI
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 yrs: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic eval	To assess for nystagmus & cataracts
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of serine deficiency disorders to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	In those w/juvenile-onset serine deficiency to assess impact on family from behavioral issues

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

High doses of L-serine are needed to correct the serine deficiency and obtain serine values within the reference ranges in plasma and cerebrospinal fluid (CSF). For young individuals, L-serine doses up to 500-700 mg/kg/day are usually needed to correct the deficiency and obtain satisfactory treatment results.

- Usually, L-serine therapy is started at 200-400 mg/kg/day (given orally and divided into 4-6 doses), because in some individuals, transient acoustic startles and myoclonus were observed with larger doses.
- The L-serine dose is gradually increased to 500-700 mg/kg/day. A dose of 400 mg/kg/day was insufficient to prevent recurrence of seizures [Authors, personal observations].
- In some individuals who did not have a satisfactory response, glycine (200 mg/kg/day given orally and divided into 4-6 doses) was added to L-serine treatment.
- In adolescents and adults, lower L-serine doses can be used (100-150 mg/kg/day).

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Serine Deficiency Disorders: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	• See Targeted Therapy w/ L-serine. • Standardized treatment w/ASM by experienced neurologist	• Treatment w/ASM may not be required after adequate response to L-serine therapy. • Many ASMs may prove to be ineffective; none has been demonstrated effective specifically for this disorder, except L-serine therapy. • Education of parents/caregivers [1]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Cataracts	Treatment per ophthalmologist	
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Polyneuropathy	Eval by neurologist w/experience in neuromuscular diseases	Likely need adaptations for proper daily functioning & mgmt by physical medicine & rehab / PT & OT
Dental issues w/L-serine oral therapy	Preventative dental care	There appears to be ↑ risk for dental caries in persons treated w/oral L-serine powder.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. • Provide family support in transition to adult care.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics for persons w/milder or adult-onset phenotypes.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; 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.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - Physical, occupational, and speech therapies 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, botulinum toxin, 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 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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Serine Deficiency Disorders

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & contractures.	At each visit
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Behavioral assessment for anxiety, ADHD, ASD, aggression, or self-injury	At each visit in persons of school age
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation & feeding tube issues when present.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Dental	Dental eval for ↑ risk of caries assoc w/oral L-serine powder	Every 6 mos
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).	At each visit
	Assess transitional care needs.	At time of transition from pediatric to adult care

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Avoid known triggers of seizure activity (e.g., infection, physical stress, emotional stress).

Evaluation of Relatives at Risk

It is appropriate to evaluate newborn sibs and apparently asymptomatic older and younger sibs of a proband to identify as early as possible those who would benefit from prompt initiation of L-serine treatment. Early treatment with L-serine can prevent the onset of neurologic abnormalities.

Prenatal testing of a fetus at risk. When the serine deficiency-causing pathogenic variants in the family are known, prenatal testing of fetuses at risk may be performed via amniocentesis or chorionic villus sampling to allow L-serine treatment of the mother during pregnancy as a potential treatment for the fetus [de Koning et al 2004, de Koning & Klomp 2004] and initiation of L-serine treatment as soon as possible after birth [Hart et al 2007]. There appears to be a narrow window of opportunity to prevent neurologic damage. Newborns treated within the first month of life have better neurologic outcomes than those treated later.

Newborn sibs and apparently asymptomatic older and younger sibs

- If the pathogenic variants in the family are known, molecular genetic testing of younger at-risk sibs who have not undergone prenatal testing should be performed immediately after birth. Those with biallelic serine deficiency-causing pathogenic variants should be treated with L-serine immediately.
- If the pathogenic variants in the family are not known and genetic testing is not possible, biochemical tests should be performed immediately after birth. Some diagnostic centers have reference ranges for umbilical cord blood amino acids; this can be used as the least invasive testing in combination with fasting plasma serine. When this is not feasible CSF serine is most reliable to diagnose serine deficiency.

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

Pregnancy Management

There is very limited experience in the management of pregnancies in women with serine deficiency. The authors are aware of these pregnancies resulting in healthy newborns, but long-term follow up on the outcome of children born to mothers with serine deficiency is lacking. Affected pregnant females were monitored regularly to ensure that plasma serine concentrations remained within the normal range with L-serine therapy and that fetal growth parameters remained within the normal range.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

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. 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

Serine deficiency disorders are 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 a *PHGDH*, *PSAT1*, or *PSPH* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *PHGDH*, *PSAT1*, or *PSPH* 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 two 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) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a serine deficiency-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and

being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Sibs who inherit biallelic pathogenic variants are expected to have a clinical phenotype similar to that observed in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with severe serine deficiency are not known to have offspring.
- The offspring of an individual with a milder or adult-onset serine deficiency disorder are obligate heterozygotes (carriers) for a pathogenic variant in *PHGDH*, *PSAT1*, or *PSPH*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a serine deficiency-causing pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *PHGDH*, *PSAT1*, or *PSPH* 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 carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the serine deficiency-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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**
  Phosphoglycerate dehydrogenase deficiency
- **Serine Deficiency Foundation**
  www.serine.org
- **Patiëntenvereniging voor Stofwisselingsziekten**

Dutch Patient Organization for Inborn Errors of Metabolism
Netherlands
www.stofwisselingsziekten.nl

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. Serine Deficiency Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PHGDH	1p12	D-3-phosphoglycerate dehydrogenase	PHGDH database	PHGDH	PHGDH
PSAT1	9q21.2	Phosphoserine aminotransferase	PSAT1 database	PSAT1	PSAT1
PSPH	7p11.2	Phosphoserine phosphatase	PSPH database	PSPH	PSPH

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 Serine Deficiency Disorders (View All in OMIM)

172480	PHOSPHOSERINE PHOSPHATASE; PSPH
256520	NEU-LAXOVA SYNDROME 1; NLS1
601815	PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY; PHGDHD
606879	PHOSPHOGLYCERATE DEHYDROGENASE; PHGDH
610936	PHOSPHOSERINE AMINOTRANSFERASE 1; PSAT1
610992	PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY; PSATD
614023	PHOSPHOSERINE PHOSPHATASE DEFICIENCY; PSPHD
616038	NEU-LAXOVA SYNDROME 2; NLS2

Molecular Pathogenesis

L-serine is classified as a nonessential amino acid (i.e., humans can synthesize serine from available cellular precursors). However, given L-serine's many important cellular functions, it is considered a conditionally essential amino acid. Synthesis of L-serine from the glycolytic intermediate 3-phopshoglycerate is the major source of L-serine (see Figure 1). Other sources include absorption from the diet, synthesis from glycine through serine hydroxymethyl transferases, and synthesis from breakdown of proteins and phospholipids.

L-serine cellular functions include:

- Nucleotide synthesis and cellular proliferation;
- Folate and single-carbon metabolism (methylation);
- Phosphatidylserine, sphingolipid, and ceramide synthesis;
- Synthesis of NMDA receptor agonists glycine and D-serine.

The manifestations of serine deficiency are due to dysfunction of these metabolic pathways. The neurodevelopmental manifestations of prenatal- and infantile-onset serine deficiency, including microcephaly,

are due to defective prenatal and postnatal neuronal proliferation and migration. Defective phospholipid synthesis results in hypomyelination and skin abnormalities. Seizures are likely related to disturbances in NMDA receptor activation due to insufficient synthesis of D-serine and potentially glycine.

Treatment with L-serine restores these metabolites and normalizes serine, glycine, 5-methyltetrahydrofolate, and D-serine levels. Phospholipids cannot be quantified after L-serine treatment, but it has been shown that cerebral white matter expands significantly following treatment, serving as a measure of phospholipid synthesis [de Koning et al 2000b].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Saskia N van der Crabben is a clinical geneticist working in cardiogenetics with a subspecialty in inborn errors of metabolism. Her research focus is on inherited cardiac arrhythmia syndromes and (re)classification of genetic variants. She works in the Department of Human Genetics in the Amsterdam University Medical Centers and is localized in the AMC in Amsterdam, the Netherlands. Email: s.n.vandercrabben@amsterdamumc.nl

Tom J de Koning is a full professor in neurometabolic and neurogenetic disorders and is trained as a pediatrician for inborn errors of metabolism. He is based at Lund University in Sweden, but also has an affiliation at the movement disorders expertise center in the University Medical Center in Groningen, the Netherlands. He is involved in translational research and exploring treatment modalities in neurometabolic and neurogenetic disorders. Emails: tom.j_de_koning@med.lu.se and t.j.de.koning@umcg.nl

Dr de Koning is actively involved in clinical research regarding individuals with serine deficiency disorders. He would be happy to communicate with persons who have any questions regarding diagnosis of serine deficiency disorders or other considerations.

Dr de Koning is also interested in hearing from clinicians treating families affected by serine deficiency disorders in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr de Koning or Dr van der Crabben to inquire about review of *PHGDH*, *PSAT1*, or *PSPH* variants of uncertain significance.

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References

Literature Cited

Abdelfattah F, Kariminejad A, Kahlert AK, Morrison PJ, Gumus E, Mathews KD, Darbro BW, Amor DJ, Walsh M, Sznajer Y, Weiß L, Weidensee S, Chitayat D, Shannon P, Bermejo-Sánchez E, Riaño-Galán I, Hayes I, Poke G, Rooryck C, Pennamen P, Khung-Savatovsky S, Toutain A, Vuillaume ML, Ghaderi-Sohi S, Kariminejad MH, Weinert S, Sticht H, Zenker M, Schanze D. Expanding the genotypic and the phenotypic spectrum of severe serine biosynthesis disorders. Hum Mutat. 2020;41:1615-28. PubMed PMID: 32579715.

Acuna-Hidalgo R, Schanze D, Kariminejad A, Nordgren A, Kariminejad MH, Conner P, Grigelioniene G, Nilsson D, Nordenskjöld M, Wedell A, Freyer C, Wredenberg A, Wieczorek D, Gillessen-Kaesbach G,

Kayserili H, Elcioglu N, Ghaderi-Sohi S, Goodarzi P, Setayesh H, van de Vorst M, Steehouwer M, Pfundt R, Krabichler B, Curry C, MacKenzie MG, Boycott KM, Gilissen C, Janecke AR, Hoischen A, Zenker M. Neu-Laxova syndrome is a heterogeneous metabolic disorder caused by defects in enzymes of the L-serine biosynthesis pathway. Am J Hum Genet. 2014;95:285-93. PubMed PMID: 25152457.

Brassier A, Valayannopoulos V, Bahi-Buisson N, Wiame E, Hubert L, Boddaert N, Kaminska A, Habarou F, Desguerre I, Van Schaftingen E, Ottolenghi C, de Lonlay P. Two new cases of serine deficiency disorders treated with l-serine. Eur J Paediatr Neurol. 2016;20:53-60. PubMed PMID: 26610677.

Damseh N, Simonin A, Jalas C, Picoraro JA, Shaag A, Cho MT, Yaacov B, Neidich J, Al-Ashhab M, Juusola J, Bale S, Telegrafi A, Retterer K, Pappas JG, Moran E, Cappell J, Anyane Yeboa K, Abu-Libdeh B, Hediger MA, Chung WK, Elpeleg O, Edvardson S. Mutations in SLC1A4, encoding the brain serine transporter, are associated with developmental delay, microcephaly and hypomyelination. J Med Genet. 2015;52:541-7. PubMed PMID: 26041762.

Debs S, Ferreira CR, Groden C, Jeffrey Kim H, King KA, King MC, Lehky T, Cowen EW, Brown LH, Merideth M, Owen CM, Macnamara E, Toro C, Gahl WA, Soldatos A. Adult diagnosis of congenital serine biosynthesis defect: a treatable cause of progressive neuropathy. Am J Med genet A. 2021;185:2102-7. PubMed PMID: 34089226.

de Koning TJ, Duran M, Dorland L, Jakobs C, Wevers RA, Berger R, Poll-The BT. Neurotransmitters in 3-phosphoglycerate dehydrogenase deficiency. Eur J Pediatr. 2000a;159:939-40. PubMed PMID: 11131361.

de Koning TJ, Jaeken J, Pineda M, Van Maldergem L, Poll-The BT, van der Knaap MS. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics. 2000b;31:287-92. PubMed PMID: 11508546.

de Koning TJ, Klomp LW. Serine-deficiency syndromes. Curr Opin Neurol. 2004;17:197-204. PubMed PMID: 15021249.

de Koning TJ, Klomp LW, van Oppen AC, Beemer FA, Dorland L, van den Berg I, Berger R. Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet. 2004;364:2221-2. PubMed PMID: 15610810.

El-Hattab AW, Shaheen R, Hertecant J, Galadari HI, Albaqawi BS, Nabil A, Alkuraya FS. On the phenotypic spectrum of serine biosynthesis defects. .J Inherit Metab Dis. 2016;39:373-81. PubMed PMID: 26960553.

Fu J, Chen L, Su T, Xu S, Liu Y. Mild phenotypes of phosphoglycerate dehydrogenase deficiency by a novel mutation of PHGDH gene: Case report and literature review. Int J Dev Neurosci. 2023;83:44-52. PubMed PMID: 36308023.

Hart CE, Race V, Achouri Y, Wiame E, Sharrard M, Olpin SE, Watkinson J, Bonham JR, Jaeken J, Matthijs G, Van Schaftingen E. Phosphoserine aminotransferase deficiency: a novel disorder of the serine biosynthesis pathway. Am J Hum Genet. 2007;80:931-7. PubMed PMID: 17436247.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Keularts IM, Leroy PL, Rubio-Gozalbo EM, Spaapen LJ, Weber B, Dorland B, de Koning TJ, Verhoeven-Duif NM. Fatal cerebral edema associated with serine deficiency in CSF. J Inherit Metab Dis. 2010;33:S181-5. PubMed PMID: 20300853.

Méneret A, Wiame E, Marelli C, Lenglet T, Van Schaftingen E, Sedel F. A serine synthesis defect presenting with a Charcot-Marie-Tooth-like polyneuropathy. Arch Neurol. 2012;69:908-11. PubMed PMID: 22393170.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Serrano Olave A, López AP, Cruz MM, Rodríguez SM, Narbona Arias I, López JSJ. Prenatal diagnosis of Neu-Laxova syndrome. Diagnostics (Basel). 2022;12:1535. PubMed PMID: 35885441.

Shaheen R, Rahbeeni Z, Alhashem A, Faqeih E, Zhao Q, Xiong Y, Almoisheer A, Al-Qattan SM, Almadani HA, Al-Onazi N, Al-Baqawi BS, Saleh MA, Alkuraya FS. Neu-Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. Am J Hum Genet. 2014;94:898-904. PubMed PMID: 24836451.

Shen Y, Peng Y, Huang P, Zheng Y, Li S, Jiang K, Zhou M, Deng J, Zhu M, Hong D. Juvenile-onset PSAT1-related neuropathy: A milder phenotype of serine deficiency disorder. Front Genet. 2022;13:949038. PubMed PMID: 36061210.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Tabatabaie L, Klomp LW, Rubio-Gozalbo ME, Spaapen LJ, Haagen AA, Dorland L, de Koning TJ. Expanding the clinical spectrum of 3-phosphoglycerate dehydrogenase deficiency. J Inherit Metab Dis. 2011;34:181-4. PubMed PMID: 21113737.

van der Crabben SN, Verhoeven-Duif NM, Brilstra EH, Van Maldergem L, Coskun T, Rubio-Gozalbo E, Berger R, de Koning TJ. An update on serine deficiency disorders. J Inherit Metab Dis. 2013;36:613-9. PubMed PMID: 23463425.

van Karnebeek CDM, Ramos RJ, Wen XY, Tarailo-Graovac M, Gleeson JG, Skrypnyk C, Brand-Arzamendi K, Karbassi F, Issa MY, van der Lee R, Drögemöller BI, Koster J, Rousseau J, Campeau PM, Wang Y, Cao F, Li M, Ruiter J, Ciapaite J, Kluijtmans LAJ, Willemsen MAAP, Jans JJ, Ross CJ, Wintjes LT, Rodenburg RJ, Huigen MCDG, Jia Z, Waterham HR, Wasserman WW, Wanders RJA, Verhoeven-Duif NM, Zaki MS, Wevers RA. Bi-allelic GOT2 Mutations Cause a Treatable Malate-Aspartate Shuttle-Related Encephalopathy. Am J Hum Genet. 2019;105:534-48. PubMed PMID: 31422819.

Shapira Zaltsberg G, McMilan HJ, Miller E. Phosphoserine aminotransferase deficiency: imaging findings in a child with congenital microcephaly. J Matern Fetal Neonatal Med. 2020;33:1033-35. PubMed PMID: 30122079.

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