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Canavan Disease

Synonyms: ASPA Deficiency, Aspartoacylase Deficiency

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Summary

Clinical characteristics

Canavan disease is a leukodystrophy characterized by neurodevelopmental delays, macrocephaly, and tone abnormalities. The phenotypic spectrum ranges from the more severe typical Canavan disease (85%-90% of individuals) to the less severe atypical Canavan disease (10%-15%). Typical Canavan disease is characterized by neurodevelopmental impairment evident by ages three to five months, followed by neurodegeneration and developmental regression. The clinical course of atypical Canavan disease is more variable, with neurodevelopmental delay usually becoming evident in the first years of life and frequently followed by developmental regression later in childhood or adolescence. All individuals with Canavan disease have reduced life expectancy, with the majority surviving to age ten years and the minority living to adulthood.

Diagnosis/testing

The diagnosis of Canavan disease is established in a proband with suggestive findings either by biochemical testing or by molecular genetic testing. The biochemical diagnosis is established in an individual with suggestive clinical findings and elevated N-acetylaspartic acid (NAA) in urine (using gas chromatography-mass spectrometry) or in the brain by proton magnetic resonance spectroscopy. The molecular diagnosis is established in an individual with suggestive clinical findings and biallelic *ASPA* pathogenic variants identified by molecular genetic testing. Frequently, both types of testing are performed; turnaround time, which varies among laboratories, should be considered when determining the order of testing.

Management

Treatment of manifestations: Multidisciplinary care by specialists in neurology (to manage spasticity and seizures if present); orthopedics, physical medicine and rehabilitation, physical therapy, and occupational therapy (to minimize contractures, optimize abilities and seating posture); feeding therapy (to assure adequate nutrition and weight gain, minimize risk of aspiration); and education (to support appropriate learning goals).

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Surveillance: Regularly scheduled evaluations of growth, nutrition, and safety of oral intake; respiratory function; seizure control and neurologic findings; developmental progress and educational needs; assessment of mobility and self-help skills; and need for social services such as palliative/respite care.

Genetic counseling

Canavan disease is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ASPA* 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 being unaffected and not a carrier. Once the *ASPA* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

GeneReview Scope

Canavan Disease: Phenotypic Spectrum

Phenotype	Proportion [1]	Comments
Typical Canavan disease	85%-90%	Infantile onset: hypotonia, macrocephaly, nystagmus / visual impairment, poor head control, significant developmental delay, followed by regression
Atypical Canavan disease	10%-15%	Clinical spectrum: onset from infancy to childhood or adolescence, milder developmental delay, with or without regression

For synonyms and outdated names see Nomenclature.
1. Bley et al [2021]

Diagnosis

No consensus clinical diagnostic criteria for Canavan disease have been published.

Suggestive Findings

Canavan disease **should be suspected** in a proband with the following clinical and imaging findings and family history.

Typical Canavan Disease

Clinical findings

- The triad of hypotonia, head lag, and macrocephaly after age three to five months
- Poor visual tracking and nystagmus
- Difficulties with suck and swallow
- Seizures
- Developmental delays that become apparent in the first few months of life, with most not achieving developmental milestones beyond a six-month level
- Developmental regression with onset in the first years of life

Laboratory findings. Biochemical and molecular genetic testing are used to establish the diagnosis (see Establishing the Diagnosis).

Imaging findings

- Brain CT or MRI performed in early infancy may be interpreted as normal [Matalon & Michals-Matalon 2000]. Neuroimaging changes reveal generalized leukodystrophy characterized by diffuse, symmetric changes observed in subcortical white matter and cortical areas as well as the brain stem and cerebellum [Matalon et al 1995]. Involvement of the globus pallidus with sparing of caudate nucleus and putamen is

usually seen [Van der Knaap & Valk 2005]. Cytotoxic edema is frequently present early in the disease course [Merrill et al 2016].

- Brain magnetic resonance spectroscopy to detect N-acetylaspartic acid has been reported as a method of diagnosing Canavan disease in infants, even those with normal serum and urine N-acetylaspartic acid levels [Karimzadeh et al 2014].

Atypical Canavan Disease

Clinical findings

- Developmental delay with onset in the first years of life; may not experience regression
- May be normocephalic or macrocephalic
- Nystagmus and/or vision impairment
- Ataxia or coordination difficulties

Laboratory findings. Biochemical testing and molecular genetic testing are used to establish the diagnosis (see Establishing the Diagnosis).

Neuroimaging. Brain MRI may not show generalized white matter changes; however, subcortical white matter involvement has been reported [Zafeiriou et al 1999, Yalcinkaya et al 2005, Sarret et al 2016]. T^2/FLAIR hyperintensities are common in the basal ganglia, thalami, brain stem (particularly involving the pontine tegmentum), and cerebellum [Nguyen & Ishak 2015, Kimiskidis et al 2017, Jauhari et al 2018, Çakar & Aksu Uzunhan 2020].

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. Of note, most new diagnoses of Canavan disease are made in individuals with no known Ashkenazi Jewish ancestry [Bley et al 2021], likely due to increased carrier screening done in individuals of Ashkenazi Jewish ancestry as well as the relatively small Ashkenazi Jewish population compared to the worldwide non-Ashkenazi Jewish population.

Establishing the Diagnosis

The diagnosis of Canavan disease **is established** in a proband with suggestive findings either by biochemical testing or by molecular genetic testing [Monaghan et al 2008]. Frequently, both types of testing are performed. Of note, turnaround time, which varies among laboratories, should be considered when determining the order of testing.

The **biochemical diagnosis** of Canavan disease **is established in a proband** with elevated N-acetylaspartic acid (NAA) in urine (using gas chromatography-mass spectrometry [GC-MS]) or in brain by proton magnetic resonance spectroscopy. Note that use of blood samples may become more relevant as testing on dried blood spots becomes available.

The **molecular diagnosis** of Canavan disease **is established in a proband** with biallelic pathogenic (or likely pathogenic) variants in *ASPA* 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 likely pathogenic variants. (2) Identification of biallelic *ASPA* variants of uncertain significance (or of one known *ASPA* pathogenic variant and one *ASPA* variant of uncertain significance) does not establish or rule out the diagnosis. (3) See Molecular Genetics, **_ASPA_-specific laboratory technical considerations** for information on evaluation of variants of uncertain significance.

Biochemical Diagnosis

Elevated NAA in urine using GC-MS is diagnostic of Canavan disease [Matalon & Michals-Matalon 2000, Janson et al 2006].

- In typical Canavan disease urine NAA is significantly elevated, often >100-fold.
- In atypical Canavan disease urine NAA is mildly elevated (~10-fold).

Note: (1) Although NAA concentration is also elevated in the blood and cerebrospinal fluid (CSF) of children with typical Canavan disease, elevated concentration of NAA in urine is sufficient for the diagnosis of typical Canavan disease in affected individuals [Michals & Matalon 2011]. (2) Although Canavan disease is associated with decreased aspartoacylase activity, the enzyme activity fluctuates with culture conditions such that enzyme activity may be unmeasurable in individuals with either typical or atypical Canavan disease. Thus, measurement of the urinary concentration of NAA is the preferred biochemical diagnostic method for individuals with typical Canavan disease [Matalon et al 1993].

Molecular Genetic Diagnosis

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Tier 1), whereas comprehensive genomic testing does not (see Tier 2).

Tier 1

When the clinical and biochemical findings suggest the diagnosis of Canavan disease, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *ASPA* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: If an individual has a biochemical diagnosis of Canavan disease (see Biochemical Diagnosis) and only one or no variant in *ASPA* is identified on single-gene testing, comprehensive genomic testing to more thoroughly interrogate *ASPA* (e.g., detect deep intronic variants or structural variants) is another option (see Tier 2).

- **A leukodystrophy or cerebral palsy multigene panel** that includes *ASPA* 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.

Tier 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

To date, the majority of *ASPA* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing. Although most pathogenic *ASPA* variants identified to date are within coding or canonical splice site regions, genome sequencing could aid in detecting deep *ASPA* splicing variants or structural variants when clinical suspicion for Canavan disease is high and exome sequencing does not identify an *ASPA* pathogenic variant.

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 Canavan Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ASPA	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	~1% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Exome and genome sequencing may be able to detect deletions/ duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Shaag et al [1995], Elpeleg & Shaag [1999], Zeng et al [2006], Caliebe et al [2010], Cozzolino et al [2011], Hogan et al [2018]

Clinical Characteristics

Clinical Description

Canavan disease is a leukodystrophy characterized by neurodevelopmental delays, macrocephaly, and tone abnormalities. The phenotypic spectrum ranges from the more severe typical Canavan disease (~85%-90% of individuals) to the less severe atypical Canavan disease (10%-15%) [Bley et al 2021].

In typical Canavan disease, neurodevelopmental impairment becomes evident by ages three to five months and is followed by neurodegeneration and developmental regression.

In atypical Canavan disease, neurodevelopmental delay usually becomes evident in the first years of life, frequently followed by developmental regression later in childhood or adolescence; however, the clinical course is more variable than in typical Canavan disease.

Individuals with Canavan disease have a reduced life expectancy, with 73% surviving to age ten years and a minority of individuals living to adulthood, as reported in a cohort comprising individuals with typical and atypical Canavan disease [Bley et al 2021].

Typical Canavan Disease

Presentation. Infants appear normal early in life, but by age three to five months, hypotonia, head lag, accelerated head growth leading to macrocephaly, and developmental delays become apparent.

Hypotonia is an early finding associated with poor head control. Inability to support the head is a constant feature of this disorder. With age, hypotonia evolves to spasticity.

Macrocephaly. Head circumference is typically normal at birth. However, in the course of typical Canavan disease, the majority of infants develop progressive macrocephaly between ages four and 18 months.

Developmental delay is an early finding but becomes more obvious with age. Children are delayed in their motor and language skills and are not able to sit, stand, walk, or talk.

More than half of affected children develop a social smile and laugh. The minority are able to reach for objects and use their hands purposefully.

Seizures are common and can include a variety of seizure types, including tonic spasms, generalized tonic-clonic, and infantile epileptic spasms syndrome [Karimzadeh et al 2014; Masri & Wahsh 2014; A Nagy, personal observation]. Seizures occur in the first year of life in one third of children with Canavan disease and become more prevalent over time, occurring in the vast majority by the end of the first decade and often persisting despite treatment with anti-seizure medications [Bley et al 2021].

Vision. Early in life there is a decreased ability to fix and follow, most commonly due to cerebral visual impairment [Bley et al 2021], broadly defined here as bilateral visual impairment due to a non-ocular cause (i.e., based in the brain) in the presence of normal ocular function. It may be due to involvement of the cortex (i.e., cortical visual impairment) or other parts of the brain as well. Optic atrophy has also been reported as a cause of visual impairment in Canavan disease. Nystagmus frequently develops early in infancy.

Hearing is usually not impaired.

Progression. With age, children with typical Canavan disease often become irritable and experience sleep disturbance, seizures, and feeding difficulties. Swallowing deteriorates, and some children require gastrostomy tube placement. Hypertonia increases over time, and previously acquired developmental skills are lost.

Prognosis. Most children with typical Canavan disease die in the first two decades of life [Bley et al 2021]. This survival is longer than previously reported and likely due to improved medical and nursing care.

Atypical Canavan Disease

Presentation. The spectrum of clinical presentations associated with atypical Canavan disease is wider than that of typical Canavan disease. Children with atypical Canavan disease may have normal or mildly delayed speech and/or motor development early in life.

Many children with atypical Canavan disease have normal head size, although macrocephaly is also seen.

In spite of developmental delay, most of these children participate in classroom settings and may benefit from an individualized education plan or other educational intervention [Matalon & Michals Matalon 2015].

Other findings in some individuals can include retinitis pigmentosa and seizures [Tacke et al 2005, Delaney et al 2015, Benson et al 2021].

Ataxia, coordination difficulties, and gait disturbances are frequently reported in atypical Canavan disease [Yalcinkaya et al 2005, Janson et al 2006, Nguyen & Ishak 2015, Sarret et al 2016, Kotambail et al 2023].

Progression. Children with atypical Canavan disease frequently continue to make slow developmental progress without regression until later in the disease course. Although these individuals often gain the ability to walk, some have significant language impairment and are diagnosed with intellectual disability [Sarret et al 2016, Kimiskidis et al 2017, Kotambail et al 2023].

Prognosis. The life span is not well-described; however, individuals with atypical Canavan disease may survive to adulthood.

Genotype-Phenotype Correlations

Genotype-phenotype correlations have been proposed with the following classes of variants depending on the effect of these variants on residual aspartoacylase enzyme activity (see Table 6).

The two common *ASPA* pathogenic variants in the Ashkenazi Jewish population, p.Tyr231Ter and p.Glu285Ala, cause complete loss of aspartoacylase activity and are associated with typical Canavan disease either in the homozygous or compound heterozygous state [Matalon & Michals-Matalon 1998].

The p.Ala305Glu pathogenic variant is a common variant in European individuals without Ashkenazi Jewish ancestry. This pathogenic variant is associated with very low aspartoacylase activity and has been identified in individuals with typical and atypical Canavan disease (both in the homozygous and compound heterozygous state with another mild variant) [Shaag et al 1995, Janson et al 2006, Mendes et al 2017].

ASPA pathogenic variants with higher residual aspartoacylase activity (e.g., p.Arg71His, p.Asp204His, p.Pro257Arg, p.Tyr288Cys) are associated with atypical Canavan disease [Mendes et al 2017]. Of note, these pathogenic variants can be associated with atypical Canavan disease whether in the homozygous or compound heterozygous state, including with pathogenic variants associated with complete loss of aspartoacylase activity [Surendran et al 2003, Yalcinkaya et al 2005, Kurczynski & Victorio 2011, Michals & Matalon 2011].

Nomenclature

Canavan disease has also been referred to as spongy degeneration of the brain (Van Bogaert and Bertrand type). Subcortical spongy degeneration is observed on neuropathology in typical Canavan disease; electron microscopy reveals swollen astrocytes and distorted mitochondria. See Differential Diagnosis for other disorders associated with spongy degeneration of the brain.

Typical and atypical Canavan disease may also be referred to as infantile and juvenile Canavan disease, respectively.

Prevalence

Canavan disease occurs in all populations.

Due to the founder *ASPA* pathogenic variants p.Glu285Ala and p.Tyr231Ter in individuals of Ashkenazi Jewish ancestry, estimates of carrier frequency in this population vary from 1/40 to 1/82 [Kronn et al 1995, Matalon et al 1995, Fares et al 2008].

Currently, most new diagnoses of Canavan disease are made in individuals with no known Ashkenazi Jewish ancestry [Bley et al 2021]. In non-Ashkenazi European populations, p.Ala305Glu is the most commonly reported pathogenic variant [Kaul et al 1994, Bley et al 2021].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Typical Canavan Disease

Table 2. Genetic Neurodegenerative Disorders of Infancy in the Differential Diagnosis of Typical Canavan Disease

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/Canavan disease [1]	Distinguishing from Canavan disease
AMT *GLDC* (*GCSH*) [1]	Nonketotic hyperglycinemia	AR	• Spongy degeneration of brain • Profound developmental delay	• Neonatal form manifests in 1st hrs/days of life w/ progressive lethargy, hypotonia, & myoclonic jerks. • Apnea • Intractable seizures
AQP4 *GPRC5B* *HEPACAM* (*GLIALCAM*) *MLC1*	Megalencephalic leukoencephalopathy w/ subcortical cysts	AR AD [2]	• Large head • Spasticity	• Ataxia • Occasional seizures • Mild cognitive decline
ARSA	Late-infantile metachromatic leukodystrophy (Arylsulfatase A deficiency)	AR	Normal or large head	Late-infantile onset (age <30 mos) after period of apparently normal development
GALC	Infantile-onset Krabbe disease	AR	Normal head	Peripheral neuropathy
GCDH	Infantile-onset glutaric acidemia type 1	AR	Normal or large head	Progressive movement disorder
GFAP	Infantile-onset Alexander disease	AD	Normal or large head	• Marked frontal predominance of white matter changes • Rostrocaudal progression of myelin loss on serial imaging studies
HEXA	Infantile Tay-Sachs disease (See *HEXA* Disorders.)	AR	Normal or large head	• ↑ startle response • Cherry-red spot of the macula of the retina
HEXB	Infantile Sandhoff disease	AR	Normal or large head	• ↑ startle response • Cherry-red spot of the macula of the retina

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/Canavan disease [1]	Distinguishing from Canavan disease
>100 assoc genes [3]	Leigh syndrome (See Mitochondrial DNA-Associated Leigh Syndrome and NARP & Nuclear Gene-Encoded Leigh Syndrome Spectrum Overview.)	AR AD Mat XL	Spongy degeneration of brain	Decompensation (often w/↑ lactate levels in blood &/or CSF) during intercurrent illness is typically assoc w/psychomotor delay or regression.

AD = autosomal dominant; AR = autosomal recessive; CSF = cerebrospinal fluid; Mat = maternal; MOI = mode of inheritance; XL = X-linked

1. In addition to being a neurodegenerative disorder of infancy

1. Biallelic pathogenic variants in *GCSH* (encoding the GCS H-protein component) have been proposed as a cause of nonketotic hyperglycinemia in two individuals; however, this remains unconfirmed.

2. Classic megalencephalic leukoencephalopathy with subcortical cysts (MLC) is most commonly caused by biallelic pathogenic variants in *MLC1* or *HEPACAM* and inherited in an autosomal recessive manner. Rarely, classic MLC occurs as an autosomal dominant disorder caused by a *de novo* heterozygous *GPRC5B* pathogenic variant. Improving MLC most commonly occurs as an autosomal dominant disorder caused by an inherited or *de novo* heterozygous pathogenic variant in *HEPACAM*. Rarely, improving MLC is caused by biallelic pathogenic variants in *AQP4* and inherited in an autosomal recessive manner.

3. See ClinGen: Leigh Syndrome Gene-Disease Validity.

Atypical Canavan Disease

Atypical Canavan disease may be misdiagnosed as a mitochondrial disorder given the overlapping neuroimaging features of bilateral deep gray matter involvement (see Primary Mitochondrial Disorders Overview).

Management

No clinical practice guidelines for Canavan disease have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 3. Canavan Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern		Evaluation	Comment
Neurologic	**Examination**	By pediatric neurologist	• Consider EEG if seizures are a concern. • Measurement of head circumference
	Imaging	MRI/MRS	To establish baseline imaging & confirm ↑ NAA levels
Development		Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention program • Atypical Canavan disease: eval for special education (IEP/504 plan)

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal/ADL	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures, hip development, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices / positioning & mobility devices, disability parking placard • Need for PT (to retain/improve gross motor skills) &/or OT (to retain/improve fine motor skills)
Ophthalmologic involvement	By pediatric ophthalmologist	Assess visual acuity & for evidence of optic atrophy.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• Monitor growth trajectory (length & weight). • To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Canavan disease to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADL = activities of daily living; IEP = individualized education plan; NAA = N-acetylaspartic acid; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for Canavan disease.

Supportive treatment for children with either typical Canavan disease or atypical Canavan disease is recommended to provide adequate nutrition and hydration, manage the risk of infections, and protect the airway (see Table 4).

Table 4. Canavan Disease: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neurologic	Neurologic eval	Consider Botox® injections to relieve spasticity.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none have been demonstrated specifically effective for this disorder. • Education of parents/caregivers [1]
Neuromuscular	Orthopedics / physical medicine & rehab / PT & OT	• PT to minimize contractures & optimize abilities & seating posture • Consider need for durable medical equipment (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers) & disability parking placard.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	- Feeding therapy - Gastrostomy tube placement may be required for persistent feeding issues.	- Low threshold for clinical feeding eval when showing clinical signs or symptoms of dysphagia - Radiographic swallowing study should be performed if there is diagnostic uncertainty &/or as recommended by speech-language pathologist to clarify tolerated consistencies.
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
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.	- Ongoing assessment of need for palliative care involvement &/or home nursing - Consider involvement in adaptive sports or Special Olympics for persons w/atypical Canavan disease.

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 United States; standard recommendations may vary from country to country.

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

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

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

- IEP services provide specially designed instruction and related services to children who qualify.
- 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.

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. AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

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. Canavan Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	Every 3-6 mos
Gastrointestinal	Monitor for constipation.	At each visit
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	Every 3-6 mos depending on seizure control
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	At each visit
Development	Monitor developmental progress & educational needs.	Every 6 mos
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	Every 3-6 mos
Ophthalmologic involvement	Ophthalmology exam	Per treating ophthalmologist(s)
	Low vision services	Per treating clinicians
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

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

A Phase I/II open label clinical trial to evaluate BBP-812, an AAV9-based gene therapy, is currently recruiting. See NCT04998396 for more details, including contact information for the research staff. Preliminary data in this trial has shown sustained reductions in urine, cerebrospinal fluid, and brain N-acetylaspartic acid (NAA) levels, improved myelination on brain MRI, and early positive trends in motor outcome data (see Aspa Therapeutics summary).

A Phase I/II open label clinical trial to evaluate rAAV-Olig001-ASPA, an oligodendrocyte-specific AAV-based gene therapy, is active but not currently recruiting. See NCT04833907 for more details, including contact information for the research staff. Preliminary data in this trial has shown reduction in NAA levels,

improvement in myelination on MRI, and early positive trends in functional domains (see American Society of Gene and Cell Therapy presentation).

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.

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

Canavan disease is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *ASPA* 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 an *ASPA* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant 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 an *ASPA* 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 being unaffected and not a carrier.
- The Canavan disease phenotype is consistent among affected family members.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with typical Canavan disease are not known to reproduce.
- Individuals with atypical Canavan disease are not known to reproduce; however, most individuals reported to date were not yet of reproductive age.

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *ASPA* pathogenic variants in the family. (See also Related Genetic Counseling Issues, **Family planning**.)

Carrier detection using biochemical assay is not routinely possible because it relies on a complex enzyme assay in cultured skin fibroblasts and enzyme activity fluctuates with culture conditions.

Population Screening

Individuals of Ashkenazi Jewish ancestry. Because of the presence of *ASPA* founder variants in individuals of Ashkenazi Jewish ancestry, estimates of carrier frequency in this population vary from 1/40 to 1/82 (see Table 6).

The ACMG includes Canavan disease among those disorders for which carrier screening should be offered to all individuals who are pregnant or planning a pregnancy [Gregg et al 2021]. Of note, most new diagnoses of Canavan disease are made in individuals with no known Ashkenazi Jewish ancestry [Bley et al 2021].

Related Genetic Counseling Issues

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.
- Carrier testing should be offered for the reproductive partners of individuals known to be carriers of Canavan disease. Of note, targeted analysis for common *ASPA* pathogenic variants is insufficient for carrier testing and full sequence analysis should be undertaken.

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

Once the *ASPA* pathogenic variants have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk 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.

- **Canavan Foundation**
  Phone: 866-907-1847
  Email: info@canavanfoundation.org
  www.canavanfoundation.org

- **MedlinePlus**
  Canavan Disease

- **National Tay-Sachs and Allied Diseases Association, Inc. (NTSAD)**
  Phone: 617-277-4463
  Email: info@ntsad.org
  www.ntsad.org

- **Norton & Elaine Sarnoff Center for Jewish Genetics**
  Phone: 312-357-4718
  Email: jewishgenetics@juf.org
  www.juf.org/cjg

- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  www.ulf.org

- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
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  Myelin Disorders Bioregistry Project

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. Canavan Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ASPA	17p13.2	Aspartoacylase	ASPA @ LOVD	ASPA	ASPA

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 Canavan Disease (View All in OMIM)

271900	CANAVAN DISEASE
608034	ASPARTOACYLASE; ASPA

Molecular Pathogenesis

ASPA encodes the enzyme aspartoacylase that catalyzes the conversion of N-acetylaspartic acid (NAA) to L-aspartate and acetate. NAA is abundant in the brain, where hydrolysis by aspartoacylase is thought to help maintain brain white matter. Loss or reduction of aspartoacylase activity causes Canavan disease. Although aspartoacylase is expressed widely throughout the body, its absence in the central nervous system leads to the specific buildup of NAA in the brain that causes demyelination and other signs of the disease.

Mechanism of disease causation. Loss of function

***ASPA*-specific laboratory technical considerations.** Although most *ASPA* pathogenic variants identified to date are within coding or canonical splice site regions, genome sequencing will aid in detecting deep *ASPA* splicing variants or structural variants.

Note: If a novel *ASPA* variant or an *ASPA* variant of uncertain significance (VUS) is identified, measurement of levels of urinary NAA or detection of brain NAA on magnetic resonance spectroscopy may aid in the interpretation of these variants.

Table 6. *ASPA* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000049.2 NP_000040.1	c.212G>A	p.Arg71His	Pathogenic variants resulting in relatively higher residual aspartoacylase activity & assoc w/atypical Canavan disease (See Genotype-Phenotype Correlations.)
	c.610G>C	p.Asp204His	
	c.693C>A	p.Tyr231Ter	Founder variant in Ashkenazi Jewish population resulting in complete loss of aspartoacylase activity & assoc w/ typical Canavan disease (See Genotype-Phenotype Correlations.)
	c.770C>G	p.Pro257Arg	Pathogenic variant resulting in relatively higher residual aspartoacylase activity & assoc w/atypical Canavan disease (See Genotype-Phenotype Correlations.)
	c.854A>C	p.Glu285Ala	Founder variant in Ashkenazi Jewish population resulting in complete loss of aspartoacylase activity & assoc w/ typical Canavan disease (See Genotype-Phenotype Correlations.)
	c.863A>G	p.Tyr288Cys	Pathogenic variant resulting in relatively higher residual aspartoacylase activity & assoc w/atypical Canavan disease (See Genotype-Phenotype Correlations.)
	c.914C>A	p.Ala305Glu	Common variant in Europeans of non-Ashkenazi Jewish ancestry resulting in complete loss of aspartoacylase activity; can be assoc w/either atypical or typical Canavan disease (See Genotype-Phenotype Correlations.)

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

Author Notes

Dr Nagy (anagy2@mgb.org), Dr Bley (abley@uke.de), and Dr Eichler (feichler@mgb.org) are actively involved in clinical research regarding individuals with Canavan disease. They would be happy to communicate with persons who have any questions regarding diagnosis of Canavan disease or other considerations.

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