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Aspartylglucosaminuria

Synonyms: AGA Deficiency, Aspartylglucosaminidase Deficiency, Aspartylglycosaminuria, Glycoasparaginase Deficiency, Glycosylasparaginase Deficiency

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Summary

Clinical characteristics

Aspartylglucosaminuria is a lysosomal storage disorder characterized by developmental delay, intellectual disability, behavioral manifestations (hyperactivity in young children, anxiety and restlessness in adolescence, and apathy in adulthood), recurrent infections, musculoskeletal features, and characteristic craniofacial features (prominent supraorbital ridges, hypertelorism, periorbital fullness, short nose with broad nasal bridge, thick vermilion of the upper and lower lips, and macroglossia) that become more prominent with age. Additional neurologic manifestations can include seizures, poor balance and coordination, and progressive cerebral atrophy in adulthood. Macrocephaly is common. Musculoskeletal features include lordosis, scoliosis, and arthritis in adolescents and young adults; vertebral dysplasia and/or rib cage abnormalities; and progressive muscle wasting, joint contractures, bursitis, and osteoporosis in adulthood. Skin manifestations (facial seborrhea, rosacea, and angiofibromas), gastrointestinal manifestations, neutropenia, and thrombocytopenia occur in some individuals. The clinical manifestations of aspartylglucosaminuria worsen with age, and adults have progressive psychomotor decline.

Diagnosis/testing

The diagnosis of aspartylglucosaminuria can be established in a proband with characteristic clinical and laboratory findings by identification of decreased aspartylglucosaminidase enzymatic activity in serum, leukocytes, or fibroblasts and/or biallelic pathogenic variants in *AGA* by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational services; standardized treatments for seizures, behavioral manifestations, sleep issues, dental manifestations, recurrent infections, scoliosis, joint swelling and

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mobility problems, osteoporosis, and gastrointestinal manifestations; social work support and care coordination as needed.

Surveillance: At each visit, assess for developmental progress, educational needs, seizures, balance and coordination issues, recurrent infections, spine issues, muscle wasting, joint manifestations, chronic diarrhea or constipation, and family needs. Assess behavioral and sleep issues annually or as needed. Dental examination every six months. Assess bone density every five years, or every two years in those treated for osteoporosis. Complete blood count with differential to assess for neutropenia and thrombocytopenia in those with any clinical manifestations of cytopenia.

Evaluations of relatives at where risk: It is appropriate to clarify the genetic status of apparently asymptomatic younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of supportive treatments.

Genetic counseling

Aspartylglucosaminuria is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *AGA* 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 *AGA* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for aspartylglucosaminuria have been published.

Suggestive Findings

Aspartylglucosaminuria **should be suspected** in probands with the following clinical, laboratory, imaging, and family history findings.

Clinical findings

- Mild-to-moderate developmental delay
- Mild-to-moderate intellectual disability
- Other neurologic manifestations (seizures, poor balance, and coordination)
- Behavioral manifestations (hyperactivity in young children, anxiety and restlessness in adolescence, and apathy in adulthood; disruptive sleep patterns)
- Recurrent infections (typically respiratory tract, ear, or skin infections)
- Characteristic craniofacial features (macrocephaly; coarsening of the facial features through childhood and adolescence progressing to characteristic facial features in adults, including prominent supraorbital ridges, hypertelorism, periorbital fullness, short nose with broad nasal bridge, relatively small ears, thick vermilion of the upper and lower lips, and macroglossia) (See Figures 1 and 2.)
- Skin manifestations (facial seborrhea, rosacea, and angiofibromas)
- Musculoskeletal manifestations (lordosis, scoliosis, and arthritis in adolescents and young adults; progressive muscle wasting, joint contractures, bursitis, and osteoporosis in adulthood)
- Gastrointestinal manifestations (chronic diarrhea or constipation, abdominal or inguinal hernias)
- Neutropenia and thrombocytopenia in some individuals

Laboratory findings

- Elevated aspartylglucosamine and other glycoasparagines on urinary oligosaccharide analysis
- Vacuoles and large lysosomes in analysis of leukocytes or fibroblasts [Goodspeed et al 2021]

Imaging findings

- **Brain MRI.** Increased signal intensity of subcortical and periventricular white matter and decreased T_2 and SWI signal intensity in the thalami (especially pulvinar nucleus), poor grey-white differentiation, thinning of the corpus callosum, cerebral/cerebellar atrophy on T_2-weighted images, and progressive iron accumulation [Tokola et al 2015, Anna et al 2017, Tokola et al 2019, Sairanen et al 2020]. Progressive cerebral atrophy in adulthood.
- **Radiographs of the chest and spine.** Broad and misshapen ribs, vertebral dysplasia (flattened vertebral bodies with anterior wedging), spondylolisthesis, lordosis, scoliosis, and kyphosis [Arvio & Mononen 2016]

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 aspartylglucosaminuria can be **established** in a proband with suggestive findings including elevated aspartylglucosamine and other glycoasparagines on urinary oligosaccharide analysis by identification of either:

- Reduced aspartylglucosaminidase enzymatic activity in serum, leukocytes, or fibroblasts [Banning et al 2023];

  AND/OR

- Biallelic pathogenic (or likely pathogenic) variants in *AGA* 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 *AGA* variants of uncertain significance (or of one known *AGA* pathogenic variant and one *AGA* variant of uncertain significance) does not establish or rule out the 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 Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *AGA* 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: Targeted analysis for *AGA* pathogenic variant c.488G>C (p.Cys163Ser) can be performed first in individuals of Finnish ancestry; individuals of Palestinian Arab ancestry from Jerusalem may also benefit from targeted analysis (see Table 7).

A lysosomal storage disorder multigene panel that includes *AGA* 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)

Figure 1. Two brothers with aspartylglucosaminuria demonstrate progression of facial features with age. One sib at age two years (A), three years (B), four years (C), six years (D), and ten years (E). Second sib at age four months (F), one year (G), two years (H), five years (I), and nine years (J).

Figure 2. Two unrelated individuals with aspartylglucosaminuria demonstrate progression of facial features with age, notably periorbital fullness, short nose, thick vermilion of the upper and lower lips, and obesity. First individual at age two years (A), four years (B), five years (C), nine years (D), 14 years (E), and 17 years (F). Second individual at age three years (G), four years (H), five years (I), eight years (J), ten years (K), and 13 years (L).

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

When the phenotype is indistinguishable from many neurodevelopmental disorders, **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.

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 Aspartylglucosaminuria

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
AGA	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4]

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.

Clinical Characteristics

Clinical Description

Aspartylglucosaminuria is a lysosomal storage disorder characterized by developmental delay, intellectual disability, behavioral manifestations, recurrent infections, growth deficiency, musculoskeletal features, and characteristic craniofacial features that become more prominent with age. Adults have progressive psychomotor decline and eventually lose the ability to communicate verbally and remain completely dependent as adults. To date, approximately 500 individuals have been identified with biallelic pathogenic variants in *AGA* [Arvio & Mononen 2016, Goodspeed et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Aspartylglucosaminuria: Frequency of Select Features

Feature	% of Persons w/ Feature	Comment
Developmental delay	>90%	Mild to moderate

Table 2. continued from previous page.

Feature	% of Persons w/ Feature	Comment
Intellectual disability	>90%	Mild to moderate
Other neurologic manifestations	>50%	Seizures, poor balance & coordination, progressive cerebral atrophy in adulthood
Behavioral manifestations	>50%	Hyperactivity in young children, anxiety & restlessness in adolescence, & apathy in adulthood; disruptive sleep patterns
Characteristic craniofacial features	>90%	Macrocephaly; coarsening of facial features through childhood & adolescence progressing to characteristic facial features in adults: prominent supraorbital ridges, hypertelorism, periorbital fullness, short nose w/broad nasal bridge, relatively small ears, thick vermilion of the lips, & macroglossia
Recurrent infections	>50%	Typically respiratory tract, ear, &/or skin infections
Musculoskeletal manifestations	30%-50%	Lordosis, scoliosis, & arthritis in adolescents & young adults; vertebral dysplasia, rib cage abnormalities; progressive muscle wasting, joint contractures, bursitis, & osteoporosis in adulthood
Skin manifestations	<40%	Facial seborrhea, rosacea, & angiofibromas
Gastrointestinal manifestations	<40%	Chronic diarrhea or constipation, abdominal or inguinal hernias
Cytopenia(s)	<40%	Typically neutropenia or thrombocytopenia

Based on Arvio & Mononen [2016], Harjunen et al [2020], Goodspeed et al [2021], Goodspeed et al [2022]

Developmental delay. Individuals with aspartylglucosaminuria tend to have mild-to-moderate delays in early developmental milestones. The delay in acquisition of new developmental skills becomes more prominent over time, with a widening gap between chronologic age and developmental age equivalent as children get older. There is typically a plateau in new skill acquisition in late childhood to early adolescence that persists for the remainder of the individual's life. Periods of significant developmental regression in childhood are not typically seen [Arvio & Mononen 2016, Goodspeed et al 2021].

Intellectual disability. Individuals with aspartylglucosaminuria typically have mild-to-moderate intellectual disability. Earlier studies suggested that cognitive ability peaks in early adolescence; however, more recent studies suggest that the peak cognitive ability may be reached earlier (by ages seven to ten years) and remain stable throughout adolescence [Harjunen et al 2020]. There is typically a slow cognitive decline beginning in early adulthood [Arvio & Mononen 2016].

Other neurologic features. Some individuals with aspartylglucosaminuria will develop epilepsy, typically in adolescence or early adulthood [Goodspeed et al 2021]. Additionally, individuals with aspartylglucosaminuria are described as being clumsier than peers, with poor balance and coordination [Arvio & Mononen 2016, Goodspeed et al 2021].

Neurobehavioral/psychiatric manifestations. Children with aspartylglucosaminuria are typically described as hyperactive and may meet criteria for attention-deficit/hyperactivity disorder [Arvio & Mononen 2016, Goodspeed et al 2021]. Many individuals will also have disruptive sleep patterns. Beginning in adolescence, symptoms of restlessness or anxiety may emerge, and during adulthood, some individuals may experience psychotic episodes or develop apathy, withdrawing from social activities [Arvio & Mononen 2016]. Some individuals may also meet criteria for autism spectrum disorder.

Craniofacial features. Infants with aspartylglucosaminuria may not demonstrate any abnormal facial features until they are older. Characteristic facial features include hypertelorism, periorbital fullness, short nose with

broad nasal bridge, relatively small ears, thick vermilion of the upper and lower lips, macroglossia, and poor dentition in adulthood [Arvio & Mononen 2016, Goodspeed et al 2021]. All facial features tend to coarsen with age and are more noticeable in older individuals (see Figures 1 and 2).

Recurrent infections. Children tend to have recurrent ear and upper respiratory tract infections. Skin infections are also reported. Life span is reduced, as individuals often succumb to a respiratory tract infection in middle adulthood.

Growth. Individuals with aspartylglucosaminuria may have typical growth patterns through infancy and early childhood, but many will experience a stagnation in growth in puberty and have reduced adult height [Arvio & Mononen 2016]. Obesity is common in older individuals.

Musculoskeletal features. Individuals with aspartylglucosaminuria commonly have vertebral dysplasia (flattened vertebral bodies with anterior wedging) and rib cage abnormalities such as broad and misshapen ribs. They may develop lordosis, scoliosis, and/or kyphosis that progresses with age. Scoliosis can be severe and require bracing or surgical intervention, and may interfere with procedures such as lumbar puncture. Some individuals will also develop progressive muscle wasting, arthritis, bursitis, joint contractures, and osteoporosis with age [Arvio & Mononen 2016, Goodspeed et al 2021].

Skin manifestations. Some individuals have seborrhea, rosacea, and/or angiofibromas that become more apparent with age [Arvio & Mononen 2016, Goodspeed et al 2021].

Gastrointestinal manifestations include chronic diarrhea or constipation and abdominal or inguinal hernias.

Hematologic manifestations. Neutropenia and thrombocytopenia are most common, tend to be mild to moderate even in older individuals with aspartylglucosaminuria, and rarely require intervention.

Prognosis. Aspartylglucosaminuria is a slowly progressive neurodegenerative disorder with systemic manifestations. All clinical manifestations of aspartylglucosaminuria worsen with age, typically over the course of years to decades. Life expectancy is well into middle adulthood with proper care and preventive medicine. Most individuals are dependent upon caregivers throughout their entire life due to significant cognitive impairment that continues to worsen in adulthood [Arvio & Mononen 2016, Goodspeed et al 2021].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified. In a small study including both Finnish and non-Finnish individuals with aspartylglucosaminuria, there were no clear genotype-phenotype correlations identified [Goodspeed et al 2022].

Nomenclature

In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], aspartylglucosaminuria is referred to as *AGA*-related aspartylglucosaminuria and included in the lysosomal storage diseases with skeletal involvement group.

Prevalence

The vast majority of identified individuals with aspartylglucosaminuria are of Finnish descent, with a prevalence rate of 1.5-5:100,000 live births in Finland [Arvio & Mononen 2016].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Aspartylglucosaminuria

Gene(s)	Disorder	MOI	Clinical Findings	Laboratory Findings	Comment
GNPTAB	ML II (See *GNPTAB*-Related Disorders.)	AR	Significant bony malformations at birth w/subsequent neurodegeneration & death in early childhood	• ↑ oligosaccharides & GAGs in urine • ↑ lysosomal hydrolases	• ML II has a more severe neurodegenerative phenotype than AGU. • ML III has more cardiorespiratory symptoms than AGU. • Urinary testing may be similar.
	ML IIIα/β (See *GNPTAB*-Related Disorders.)	AR	• Emergence of joint deformities in early childhood • Significant cardiorespiratory disease w/death in early adulthood		
GNS *HGSNAT* *NAGLU* *SGSH*	MPS III (Sanfilippo syndrome)	AR	• Neurodevelopmental delay & challenging behaviors w/progressive mobility impairment • Clinical severity can vary.	↑ GAGs in urine	Phenotypic presentation may be similar to AGU in those w/milder forms of MPS III.
GUSB	MPS VII (Sly syndrome)	AR	• Intellectual decline in some • Coarse features • Dysostosis multiplex • Organomegaly	• ↑ urinary chondroitin, heparan, & dermatan sulfates • Beta-glucuronidase deficiency	
IDS	MPS II (Hunter syndrome)	XL	• Neurodevelopmental delay & challenging behaviors w/progressive mobility impairment in males • Clinical severity can vary.	↑ GAGs in urine	• Phenotypic presentation may be similar to AGU in those w/milder forms of MPS II. • However, AGU will typically have earlier cognitive impairment compared to mild MPS II.
IDUA	MPS I	AR	• Severe form has neurodegeneration from early childhood & death by adolescence. • Attenuated form may have normal early development w/ psychomotor decline beginning in adolescence or adulthood.	↑ GAGs in urine	The severe form has a more rapid decline in neurologic function than AGU, & the attenuated form is much milder in early childhood.
MAN2B1	Alpha-mannosidosis	AR	• Coarse features • Progressive ataxia • ID • Hearing loss • Skeletal abnormalities • Recurrent infections	• ↑ urinary oligosaccharides • Acid alpha-mannosidase deficiency	

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Findings	Laboratory Findings	Comment
NGLY1	*NGLY1*-related congenital disorder of deglycosylation	AR	• Mild-to-profound DD/ID • ↓ tear production • Liver dysfunction • Hyperkinetic movements (choreoathetosis, dystonia, myoclonus, tremor, dysmetria) • Seizures • Sleep disorders • Neuropathy	• ↑ ALT & AST in early childhood that resolves spontaneously • ↑ urine mucopolysaccharides • Mild elevation of lactate • Generalized aminoaciduria	
SUMF1	Multiple sulfatase deficiency	AR	• Childhood-onset neurodegenerative disorder w/varying severity • Neonatal form is most severe, w/death by age 2 yrs. • Infantile form has a slower progression w/ variable rates of psychomotor decline beginning in early childhood.	• ↓ activity of at least 2 sulfatases • ↑ GAGs in urine • ↑ sulfatides in urine	The phenotypic presentation & rate of neurodegeneration is typically more severe & rapid than AGU.

AGU = aspartylglucosaminuria; ALT = alanine transaminase; AR = autosomal recessive; AST = aspartate transaminase; DD = developmental delay; GAGs = glycosaminoglycans; ID = intellectual disability; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis; XL = X-linked

Management

No clinical practice guidelines for aspartylglucosaminuria have been published.

Evaluations Following Initial Diagnosis

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

Table 4. Aspartylglucosaminuria: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Development/ Cognition	Developmental & cognitive assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Consider brain MRI. • Consider EEG if seizures are a concern.
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Dental	Assessment for dental issues	
ENT	Eval for recurrent ear & upper respiratory infections	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
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)
Gastroenterology	• Gastrointestinal eval • Assessment for hernias	To incl assessment of chronic diarrhea or constipation
Hematology	Complete blood count w/differential	To assess for neutropenia &/or thrombocytopenia
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of AGU 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

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; AGU = aspartylglucosaminuria; 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

There is no cure for aspartylglucosaminuria. 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 5).

Table 5. Aspartylglucosaminuria: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Behavioral manifestations / Sleep issues	Standardized treatment w/combination of behavioral therapy & psychopharmacology w/ experienced providers	No specific therapies or medications have been proven more effective in this population.
Dental	Routine dental care	
Recurrent infections	Eval for ear myringotomy, adenoidectomy, or tonsillectomy w/experienced ENT specialist	Many persons require repeated ear myringotomy in early childhood.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Musculoskeletal manifestations	Mgmt of scoliosis as per orthopedist	
	Standardized mgmt of joint swelling & mobility problems	No specific agents have been proven more effective in this population.
	Mgmt of osteoporosis per endocrinologist	Standard treatments may be used (e.g., bisphosphonates).
Gastrointestinal manifestations	Standardized mgmt of diarrhea or constipation by experienced primary care or GI specialist	No specific agents have been proven more effective in this population.
Neutropenia/ Thrombocytopenia	Typically no treatment required	
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.

ASM = anti-seizure medication; ENT = ears, nose, and throat; GI = gastrointestinal
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.
  - Hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected

individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

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

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

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

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric 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 6 are recommended.

Table 6. Aspartylglucosaminuria: Recommended Surveillance

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, balance, & coordination issues.	
Neurobehavioral/ Psychiatric	Assessment for anxiety, attention, & sleep issues	Annually or as needed
Dental	Dental exam	Every 6 mos
ENT	Assessment for recurrent infections	At each visit
Musculoskeletal	• Assessment for spine issues, muscle wasting, & joint manifestations • Physical medicine, OT/PT assessment of mobility, self-help skills	
	DXA scan	Every 5 yrs; or every 2 yrs in those being treated for osteoporosis
Gastrointestinal	Assessment for chronic diarrhea or constipation	At each visit
Hematologic	Complete blood count w/differential to assess for neutropenia & thrombocytopenia	In those w/any clinical manifestations of anemia, recurrent infection, or bleeding abnormality
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

DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic younger at-risk sibs of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of supportive treatments. Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Biochemical testing, including urinary oligosaccharide analysis to identify elevated aspartylglucosamine and other glycoasparagines, if the pathogenic variants in the family are not known.

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

Therapies Under Investigation

Early studies of bone marrow transplantation demonstrated no benefit in individuals with aspartylglucosaminuria. However, a case series of four children treated with hematopoietic stem cell transplant at an early age (age five months to nine years) demonstrated reduction in aspartylglucosamine and favorable neurodevelopmental outcomes [Arvio & Mononen 2016, Selvanathan et al 2021].

There are also many small molecules that show promise as chaperone therapies to increase aspartylglucosaminidase activity [Banning et al 2016, Banning et al 2018]. For certain missense variants, glycine, asparagine, and betaine can increase aspartylglucosaminidase activity in cell culture, while amlexanox appears to rescue nonsense-mediated decay of nonsense variants [Banning et al 2018]. For splice site variants, methylxanthine derivatives and food-derived flavonoid luteolin enhance correct splicing to facilitate translation of a full-length, functional aspartylglucosaminidase [Banning & Tikkanen 2021]. Additionally, there is an ongoing clinical trial to assess the safety and efficacy of Cystadane® (betaine) for the treatment of aspartylglucosaminuria (EudraCT 2017-000645-48).

Furthermore, early initiation of enzyme replacement therapy (ERT) in mice with aspartylglucosaminuria has been shown to reduce accumulation of aspartylglucosamine, but clinical development of ERT is complicated by the need to deliver high doses of recombinant aspartylglucosaminidase at an early age to improve penetration of the blood-brain barrier in individuals with aspartylglucosaminuria [Dunder et al 2010].

Finally, gene transfer therapy using an adeno-associated viral type 9 (AAV9) vector carrying codon-optimized human *AGA* has shown promise in preclinical studies. *Aga* knockout mice treated with AAV9/*AGA* demonstrated favorable toxicity profiles, restoration of aspartylglucosaminidase enzyme activity, reduction of aspartylglucosamine accumulation, and rescue of the behavioral phenotypes [Chen et al 2021]. The Rare Trait Hope Fund is supporting a toxicology, dose determination, and biodistribution study in larger animals and preparing an investigational new drug application for FDA approval to start clinical trials in individuals with aspartylglucosaminuria.

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.

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

Aspartylglucosaminuria 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 *AGA* 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 *AGA* 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 an *AGA* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with aspartylglucosaminuria are not known to reproduce.

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

Carrier Detection

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

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Carrier testing for the reproductive partners of known carriers should be considered, particularly if both partners are of the same ancestry. *AGA* founder variants have been identified in the Palestinian Arab community in Jerusalem and in individuals from eastern Finland (see Table 7).

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 *AGA* 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**
  Aspartylglucosaminuria
- **Rare Trait Hope Fund**
  Phone: 504-408-1126
  Email: info@raretrait.com
  www.raretrait.com
- **International Advocate for Glycoprotein Storage Diseases (ISMRD)**
  Email: info@ismrd.org
  www.ismrd.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.org
- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
  Email: mps@mpssociety.org.uk
  mpssociety.org.uk
- **National MPS Society**
  Phone: 877-MPS-1001
  mpssociety.org

Molecular Genetics

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

Table A. Aspartylglucosaminuria: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
AGA	4q34.3	N(4)-(beta-N-acetylglucosaminyl)-L-asparaginase	AGA	AGA

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 Aspartylglucosaminuria (View All in OMIM)

208400	ASPARTYLGLUCOSAMINURIA; AGU

Table B. continued from previous page.

613228	ASPARTYLGLUCOSAMINIDASE; AGA

Molecular Pathogenesis

AGA encodes aspartylglucosaminidase (AGA), which is initially synthesized in an inactive form. Subsequent autoproteolysis results in an active hydrolase with separate alpha and beta subunits. Mature AGA hydrolyzes glycoasparagine N(4)-(β-N-acetylglucosaminyl)-L-asparagine, which connects carbohydrate to the side chain of an asparagine [Pande et al 2018]. This allows for free sugars and amino acids to be degraded through their respective pathways within the lysosome.

AGA pathogenic variants impair the autoproteolysis of AGA precursors. The abnormal AGA molecules are misprocessed and retained at the pre-autoproteolysis stage as single-chain precursors, which results in reduced production or activity of AGA [Sui et al 2014]. Deficiency of AGA causes impaired degradation of glycoproteins within the lysosome and toxic accumulation of glycoasparagines, which impair cellular function [Goodspeed et al 2021].

Mechanism of disease causation. Loss of function

Table 7. *AGA* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000027.4 NP_000018.2	c.214T>C	p.Ser72Pro	Founder variant in Palestinian Arab community in Jerusalem [Zlotogora et al 1997]
	c.488G>C	p.Cys163Ser	Founder variant in persons from eastern Finland that accounts for 98% of pathogenic variants in the Finnish population [Arvio & Mononen 2016]

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 Kimberly Goodspeed (kimberly.goodspeed@utsouthwestern.edu) is actively involved in clinical research regarding individuals with aspartylglucosaminuria. Dr Goodspeed would be happy to communicate with persons who have any questions regarding diagnosis of aspartylglucosaminuria or other considerations.

Dr Goodspeed (kimberly.goodspeed@utsouthwestern.edu) and Dr Michel Tchan (michel.tchan@health.nsw.gov.au) are also interested in hearing from clinicians treating families affected by aspartylglucosaminuria in whom no causative variants have been identified through molecular genetic testing.

Contact Dr Xin Chen (xin.chen@utsouthwestern.edu) to inquire about review of *AGA* variants of uncertain significance.

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