Understanding AGU

Aspartylglucosaminuria (AGU) is a rare, neurodegenerative lysosomal storage disorder (LSD). LSDs are a group of inherited metabolic diseases caused by a genetic variant resulting in a deficiency or absence of a critical enzyme, leading to the accumulation of toxic deposits in cells throughout the body.

AGU is caused by a deficiency or lack of activity in the aspartylglucosaminidase (AGA) enzyme. The deficiency of this enzyme activity leads to toxic deposits in cells, causing cellular dysfunction across multiple organ systems, the most debilitating of which is in the central nervous system, including the brain. Both males and females may be affected.

Signs and symptoms of AGU vary with age. Developmental issues include speech delay, poor motor coordination, difficulty understanding simple instructions, behavioral and emotional issues, and intellectual disability. Other medical issues have been reported such as gastrointestinal disturbances, respiratory infections including recurrent ear infections, and in some cases, seizures in older patients (> age 20). People with AGU have a shortened lifespan.


History of AGU

AGU was first reported in 1968 in England. AGU cases have been documented throughout the world and across ethnicities, races, heritages, and geographies including North America, Europe, Asia, and the Middle East with the highest known prevalence in Finland.

Places Reported to Include People Diagnosed with AGU (1975 – 2019):
Sources:


How AGU Affects the Body

AGU affects children both cognitively and physically. Aspects of the disease may include:

- progressive thickening of facial features: widely-spaced eyes, small ears, full lips, acne, broad nose
- dental problems, tooth decay, enlarged tongue and tonsils
- rib and breast plate deformities, scoliosis and other bone deformities of the long bones (i.e. humerus or femur)
- gastrointestinal (GI) problems, including diarrhea or constipation
- unusually large range of motion in joints (hypermobility)
- developmental delay, speech delay, progressive intellectual decline, confusion with simple instructions, anxiety, behavioral issues, sleep problems, seizures (> 20 years old)
- chronic ear infections in early childhood often starting (< 5 years old) requiring multiple ear tube placements
- frequent respiratory infections that may lead to the removal of tonsils
- hernias around belly button or groin
- walking difficulties: including rolling in step, toe walking*, and “knock knees”

Science Behind AGU

The underlying cause of AGU is found in an individual’s chromosomal structure. In humans, each cell contains 23 pairs of chromosomes for a total of 46:23 from their mother and 23 from their father. The first 22 pairs of chromosomes are called autosomes, and they look the same in both males and females. The 23rd pair are called sex chromosomes, which are different between males and females. Females have two copies of the X chromosomes (XX), and males have one X and one Y chromosome (XY). A pathogenic variant in a gene on one of the first 22 non-sex chromosomes can lead to an autosomal disorder.

A child must inherit one pathogenic variant of the AGA gene from each parent for AGU to develop.

Autosomal recessive describes one of several ways that a disorder or disease is passed down through families. An autosomal recessive disorder occurs when a child inherits two copies of an abnormal gene, one from the mother and one from the father. The biological parents oftentimes have no symptoms of disease because the one functional gene is able to compensate for the defective gene. This means that two healthy people can produce a child or multiple children with the same genetic disorder.

AGU is inherited in an autosomal recessive pattern, meaning both copies of the AGA gene variant (one from each parent) must be present in the person diagnosed with AGU.
Healthy AGA Gene

People with AGU have two defective copies of the AGA gene. The AGA gene provides the body with instructions for building the AGA enzyme, aspartylglucosaminidase, which is important in breaking down aspartylglucosamine. When the AGA enzyme is built correctly, aspartylglucosamine is broken down in the lysosomes and waste is recycled or disposed of properly resulting in normal cellular function.

AGU Gene

When there are two defective copies of the AGA gene, the body creates a defective AGA enzyme that cannot perform an essential function of clearing toxic waste from the lysosomes and ultimately leads to cell death. Over time, this accumulated cell death in people with AGU leads to progressive damage in the brain and other organs.

Sources:
Signs and Symptoms

Birth Through Age 5

Children experience developmental delays. Common signs and symptoms include:

- Delayed speech
- Sleep disturbance
- Chronic ear infections, often requiring multiple ear tube placements
- Frequent upper respiratory infections often resulting in tonsillectomy
- Delay in sitting up
- Clumsy walking

Childhood Years

The most common sign of AGU is the lack or delay of speech. In addition, other signs and symptoms that become apparent in AGU children throughout the elementary school-age years include:

- Speech delay: support needed for missing words or letters
- Sleep disturbance
- Inability to learn shapes or trace figures
- Inability to follow simple directions and trouble managing daily tasks
- Thickening of facial features: widely-spaced eyes, small ears, full lips, large tongue, broad nose
- Upper respiratory infections, specifically ear infections
- Hernias around the belly button or in the groin area
- Gastrointestinal symptoms including diarrhea or constipation
- Orthopedic challenges, which may require surgery, including rolling instep, toe walking, knock knees, or spastic running

“Our daughter struggled with orthopedic challenges. She was continuously falling and was unable to brace herself when she fell. We added supportive soles to her shoes that went ankle high. Her kindergarten teachers also indicated that she was learning slower than her classmates.”
- Eeva, mother living in Finland reflecting on her daughter’s younger years living with AGU

Adolescent Years

As the disease continues to progress through the adolescent years, other signs and symptoms may become apparent:

- Intellectual disability will progressively worsen
- Sleep disturbance
- Anxiety, restlessness, and inability to understand the concept of time
- Emotional, behavioral, and psychiatric issues can arise
- Dental complications such as tooth decay, large tongue, and enlarged tonsils
- Progressive thickening of facial features: widely-spaced eyes, small ears, full lips, large tongue, broad nose
- Gastrointestinal symptoms including diarrhea or constipation
- Gait (walking) disturbance
Adulthood

People in their 20s and 30s may lack self-care skills and independence. Common signs and symptoms during this time include:

• Seizures
• Acceleration of cognitive decline
• Sleep disturbance
• Continued regression of previously mastered skills to the point of loss of ability
• Gait (walking) disturbance
• AGU-specific facial features become more apparent for example: widely-spaced eyes, small ears, full lips, large tongue, broad nose

Common Signs & Symptoms

While the signs and symptoms of AGU can vary and progress at each stage of a child’s life, there are some common signs and symptoms that are consistent across many cases of AGU.

• Delay in speech
• Speech disturbance
• Characteristic facial appearance (widely spaced eyes, small ears, full lips, broad nose, coarsening of hair)
• Slow learning of language and simple concepts
• Problems with motor skills
• Frequent ear infections, often requiring multiple ear tubes
• Frequent upper respiratory infections
• Diarrhea or constipation
• Hernias (umbilical/belly button and inguinal/inner groin)
• Clumsy walking (gait issues)

Sources:

3. Field research conducted by Neurogene and Ten Bridge Communications, February 2019.
Diagnosis and Testing

Obtaining a definitive genetic diagnosis is an important first step in seeking appropriate care and treatment, learning about potential research or therapies that may become available, and preparing for the future. Patients and their families should consider discussing the implications of obtaining a diagnosis of AGU with their physician and a genetic counselor or other specialists who are familiar with the disease management of AGU.

Because of low awareness and the fact that developmental delay is among the earliest observed symptoms, common misdiagnoses may include autism and attention deficit hyperactivity disorder (ADHD).³

If you believe your child is showing signs or symptoms of AGU, tests are available for a physician or other healthcare professional to order to help confirm a diagnosis.⁴,⁵,⁶

Testing for AGU may not be included in standard testing panels; however, upon request, a diagnostic genetic test for AGU can confirm a diagnosis. Your physician can help you navigate the process or refer you to a geneticist. Many academic and commercial laboratories offer genetic blood testing.

For additional details about a no-charge genetic testing and counseling program, visit www.Invitae.com/en/detectLSDs. To order the genetic test, physicians can download the requisition form here.

A representative is available to help you by calling 1-877-237-5020 or via email at medicalinfo@neurogene.com.

Legal disclosure: While third parties and commercial organizations may provide financial support for this program, tests and services are performed by Invitae. Healthcare professionals must confirm that patients meet certain criteria to use the program. Third parties and commercial organizations may receive de-identified patient data from this program, but at no time would they receive patient identifiable information. Third parties and commercial organizations may receive contact information for healthcare professionals who use this program. Genetic testing and counseling are available in the US and Canada. Healthcare professionals and patients who participate in this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use or support any other products or services from Invitae or from third parties or commercial organizations.

Sources:
Understanding AGU: Disease Management

While there is currently no cure for people living with AGU, there are a number of specialists today with expertise who can help you manage this disease and its symptoms.

People living with AGU benefit from having a team of healthcare professionals to help manage the progressive impact of their disease. The daily needs of an individual with AGU can be supported by some or all of the following healthcare providers. These needs may change or evolve as a child moves into adulthood.

Click on each circle below for more information about the role each healthcare provider may play to support the daily needs of an individual living with AGU:

- **Pediatrician or primary care**: A pediatrician or primary care doctor supports AGU children and families in managing their medical care and monitoring their growth and development. Young children often develop hernias, which can be diagnosed by pediatricians or primary care doctors who will refer out for treatment.

- **Allergist**: An allergist can help with the management of allergies and food sensitivities. A family may see an allergist thinking respiratory infections are food or other allergies.

- **Neurologist**: The neurologist plays a critical role in determining an AGU diagnosis and keeping track of the progression of the disease over time.

- **Speech therapist**: A speech therapist is crucial in supporting the lack of or delay in speech development reported in people living with AGU. Speech therapists can also help those who are struggling with other communications issues such as confusion with simple directions or inability to learn shapes or concepts.

- **Orthopedist**: An orthopedist focuses on the bones, joints and muscles (musculoskeletal system) and provides management strategies to people living with AGU who are suffering from common symptoms related to delayed walking and knock knees.

- **Psychiatrist and psychologist**: Psychiatrists and psychologists help to manage many of the psychiatric issues that are common with AGU, especially as the patient gets older. Anxiety, restlessness, fear of crowds, and sleeping disturbances are only some of the challenges with which these therapists can help.

- **Gastroenterologist**: These providers can help navigate symptoms such as diarrhea and sensitivity to dairy products like cow’s milk or gluten.

- **Geneticist**: A geneticist, an expert on genes and hereditary patterns, can help with testing to diagnose and provide potential options for next steps.

- **Dentist and oral surgeon**: As people with AGU reach later teens, many need more extensive dental work. Challenges may include tooth decay, enlarged tonsils, large tongue, and tooth extractions. A dentist or oral surgeon can address these concerns.
Understanding AGU: Disease Management

• **Otorhinolaryngologist (ENT):** Ear, nose, and throat specialists assist with managing symptoms related to ear infections and tubes as well as ear tube replacement.

• **Occupational therapist:** Occupational therapists focus on improving the fine motor skills and activities from the waist up (dressing, feeding, writing, etc.). These specialists help individuals living with AGU to develop, recover, improve, and maintain the daily fine motor skills that may regress with time.

• **Physical therapist:** Physical therapists focus on improving the gross motor skills and activities from the waist down (walking, toileting, stairs, etc.). These specialists help individuals living with AGU to develop, recover, improve, and maintain the daily gross motor skills that may regress with time.

In addition to the care team that can help to manage the various symptoms associated with AGU, people living with AGU may also find support through social and educational plans. These plans can help cultivate independent living skills as a person gets older and their symptoms progress.

Sources:
