Aicardi-Goutières Syndrome (AGS)
Speakers

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AGS is an often but not always progressive disorder that affects the brain, and many other organs (heart, lung, skin, eyes, kidneys, liver and others) via a genetic dysregulation of the immune system.

- Mutations in one or more of the following genes cause accumulation of DNA/RNA or abnormal sensing of the DNA/RNA: TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, and IFIH1.
  - This causes an immune response by a molecule called interferon.
  - Interferon causes injury of multiple cell types, including those of the brain.
How do you get AGS?

- Often Autosomal recessive disease
  - The child can only inherit the disease when both parents carry the mutation
- Can also be caused by inheritance of the gene from one parent, but this is rare; often these cases are milder and parents may also be affected
- De novo mutations can also occur, in particular for *IFIH1* and *ADAR*

Even though there are identified genes, many families have a long journey to diagnosis
How Does AGS Affect the Individual?

• In AGS Interferon causes injury to the blood vessels and cells of the brain, as well as injury to other organs
• First symptoms can include encephalopathy (severe brain dysfunction) within the first few months of life
• Can also affect children later, with loss of previously acquired milestones
• Can be mistaken for viral encephalitis or ADEM
What are Initial Symptoms of AGS?

• Can be neurologic
  • Encephalopathy, irritable or jittery behavior in infants, excessive sleepiness
  • Feeding difficulties
  • Seizures
  • Developmental delay
  • Spasticity or dystonia
• Can be liver dysfunction (autoimmune hepatitis)
• Can be blood cells (anemia, low platelets)
• Can be skin (unusual rashes, chilblains)

AGS affects multiple organ systems.
How is AGS Diagnosed?

• Blood tests suggesting a combination of abnormal blood cells and abnormal liver tests, tests for interferon in the blood
• Genetic testing to identify changes in the 7 genes associated with AGS
• Spinal tap
  • Test for elevated levels of lymphocytes and interferon-alpha in CSF
  • Test for elevated neopterin or tetrahydrobioterin
• MRI or CT scan
  • Look for areas of calcification or atrophy
What are the Different Forms of AGS?

- Early Onset: beginning in infancy
  - Characterized by liver and neurological issues
  - More serious form of the disease as loss of myelin at an early age leads to severe physical and intellectual issues as well as permanent brain damage

- Later Onset: beginning after the first few months of life
  - Loss of previously attained milestones
  - Characterized by feeding difficulties, irritability, seizures, and developmental delays
  - Symptoms may last for several weeks or months but eventually stabilize in most cases

The irritability associated with AGS is often misdiagnosed as colic
Medical Issues

- **Encephalopathy/irritability and sleep** should be screened and managed with medications to improve comfort.
- **Recurrent aseptic febrile illnesses** can occur though infection needs to be excluded.
- **Eyes**: Yearly screening for glaucoma and artificial tears is needed. Patients often also have cortical visual impairment.
- **Swallowing** dysfunction is frequent and children may need G tubes to support feeding.
- **Respiratory** risks including recurrent pneumonia/aspiration
  - Depending upon the severity of symptoms, children may require chest physiotherapy and treatment for respiratory complications, including nebulizer treatments and the use of an ABI Vest.
- **Cardiac**: screen for pulmonary hypertension and cardiomyopathy with echocardiogram at baseline and yearly if any abnormalities.
Medical Issues continued

• **Nutrition and GI**: risk for reflux, constipation and autoimmune hepatitis. Check yearly blood liver tests
  • To ensure adequate nutrition and caloric intake, some infants may require special accommodations for diet and feeding, including placement of a feeding tube.

• **Endocrine**: check for thyroid disease, diabetes and diabetes insipidus; check yearly TSH

• **Hematologic**: risk of low platelets and anemia, check yearly CBC

• **Orthopedic**: risk of autoimmune joint disease and contractures.
  • Attention should be given to the prevention and treatment of orthopedic problems, such as hip dislocation and scoliosis. Most children require the use of a wheelchair.

• **Skin**: avoid exposure to cold weather and pressure to prevent chilblains.

• **Dental**: risk of root resorption; needs to be seen by dentistry Q3-6 months

• **Spasticity/Dystonia**: due to basal ganglia injury, should be managed by medications to improve comfort and function

• **Seizures**: manage with anticonvulsants.

• **Autonomic dysfunction**: may have problems maintaining temperature
Symptom Management

- Frequently changing positions to help prevent skin infections, rashes and pressure sores.
- Chest physiotherapy, nebulizer treatments and suctioning for respiratory issues.
- Testing for and management of scoliosis and dislocated joints.
- Testing for and controlling seizures with medications.
- Testing for acid reflux and treating with medications.
- Aspiration precautions with use of feeding tube.
- Testing for vision problems, especially glaucoma.

With proactive, comprehensive medical care, affected individuals can avoid unnecessary suffering and complications to have the best quality of life possible.
Is There a Treatment for AGS?

• No currently approved treatments but symptoms can be managed
• Research and clinical trials are moving forward for AGS
• Recent publications suggest role for blocking interferon receptor via a group of medications called Janus Kinase inhibitors, which are also used in rheumatologic conditions
Is there NBS for AGS?

• No available test developed for NBS
• Not currently on Recommended Uniform Screening Panel (RUSP)
NBS Follow-up Protocols for AGS

• No newborn screening so no newborn screening protocols
Research and Clinical Trials

• Research

• Clinical Trials
  • Reverse Transcriptase Inhibitors in Aicardi Goutières Syndrome (RTIAGS)
    • Active, not Recruiting
    • Testing efficacy of Tenofovir (TDF) and Emtricitabine (FTC) in AGS patients ages 2-18 in decreasing endogenous retroelement accumulation

• JAK Inhibitor Treatment in AGS
  • Recruiting
  • Testing efficacy of Baricitinib in reducing interferon production, a substance that controls immune system response and causes AGS symptoms to occur
LCN & Other Centers with Expertise in AGS

- Eunice Kennedy Shriver National Institute of Child Health and Human Development
- Children's Hospital of Philadelphia
Family Advocate Organizations for AGS

- Leukodystrophy Care Network
- The M.O.R.G.A.N. Project
- Hunter’s Hope
- National Organization for Rare Diseases
- Leukodystrophy Family Forum
- Mission Massimo
- Aicardi Goutieres Association of Americas
- International AGS Association
LCN Care Coordinator Shared Files for AGS
Resources for Medical Professionals

- Genetic and Rare Diseases Information Center: AGS
- Genetics Home Reference
Resources for Families

- Leukodystrophy Care Network
- Hunter’s Hope Foundation – Family Care
- Hunter James Kelly Research Institute
- Duke Children’s Hospital: Bone Marrow and Stem Cell Transplantation
- Genetics Home Reference
- United Leukodystrophy Foundation
- AGS Facebook Group
- The Morgan Project: Resource Library
Thank you!

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