Clinical Characteristics

GNAO1 is a gene which provides instructions to make the Gαo protein which is found in the central nervous system.

Pathogenic variants (also known as ‘mutations’) in GNAO1 can affect patients differently, depending on the location of the mutation in the gene, causing a spectrum of mild to severe epilepsy, movement disorder, or a combination of both.

GNAO1-NDD is a rare neurodevelopmental disease that was first described in 2013 and affects hundreds of individuals across the world.

The natural course of the disease is not well known, and researchers are working to better understand the disease to find appropriate treatments for its symptoms.

The most common initial symptoms of GNAO1-NDD include low muscle tone (hypotonia), not meeting developmental milestones, seizures, difficulty feeding, and abnormal involuntary movements. These concerns are usually reported within the first year of life (1).

Genetic testing should be considered for patients who show early signs of seizures and/or involuntary movements with global developmental delays (4).

This guide details the clinical characteristics of GNAO1-NDD and up-to-date research information.

Treatment Consultants

Amy Viehoever, M.D., Ph.D.
Pediatric Neurologist
Director of the Pediatric DBS Program
Cerebral Palsy & Movement Disorders
Washington University School of Medicine in St. Louis

Erika Axeen, M.D.
Epileptologist
Pediatric Neurologist
Department of Neurology
University of Virginia | UVA Health

Patient and Family Support
Emily Bell
The Bow Foundation
emily@bowfoundation.org
www.gnao1.org

GNAO1-NDD is a gene which provides instructions to make the Gαo protein which is found in the central nervous system.

Pathogenic variants (also known as ‘mutations’) in GNAO1 can affect patients differently, depending on the location of the mutation in the gene, causing a spectrum of mild to severe epilepsy, movement disorder, or a combination of both.

GNAO1-NDD is a rare neurodevelopmental disease that was first described in 2013 and affects hundreds of individuals across the world.

The natural course of the disease is not well known, and researchers are working to better understand the disease to find appropriate treatments for its symptoms.

The most common initial symptoms of GNAO1-NDD include low muscle tone (hypotonia), not meeting developmental milestones, seizures, difficulty feeding, and abnormal involuntary movements. These concerns are usually reported within the first year of life (1).

Genetic testing should be considered for patients who show early signs of seizures and/or involuntary movements with global developmental delays (4).

This guide details the clinical characteristics of GNAO1-NDD and up-to-date research information.

Disclaimer

The aim of this informational document is to promote an awareness and understanding of GNAO1-NDD. Always seek guidance from your (or your child’s) physician for any questions you may have. Do not disregard professional medical advice because of what you have read in this guide.

The information provided here is for clinical reference only and should not be considered as a replacement for published data, clinical practice guidelines, diagnosis and/or treatment of GNAO1-NDD. This knowledge is based on early research on GNAO1-NDD and may evolve over time as we learn more about this disorder. The reader should not take the information from this guide as complete.

The reader assumes all responsibility and risk for using this guide. Under no circumstances shall The Bow Foundation, Washington University in St. Louis, sponsors, or any contributors to this guide be liable for any direct, indirect, incidental, or consequential damages that result from the use of this guide.
Epilepsy
For individuals with an epilepsy predominant presentation, seizure onset typically occurs within the first year of life. In that year, the majority of seizure presentations are within the first 3 months. Types of seizures range from motor (clonic, myoclonic), nonmotor (absence), and generalized (tonic-clonic). Seizures may be well-controlled or resistant to medications.

Movement Disorder
The average age of onset is 24 months, with a wide range between 3 months to 8 years. The movement disorder may be mixed, consisting of dystonia (most common), dyskinesia, chorea, stereotypies, ataxia, and/or hypotonia. Involuntary movements may be triggered by intentional movement, excitement, stress, illness, bowel movements/GI discomfort, or pain. They also may be spontaneous.

Hyperkinetic Movement "Storms"
- These are exacerbations of hyperkinetic movements dominated by chorea and dystonia that can lead to ICU admission and can be life-threatening.
- They are severe and continuous, and may cause ballismus, autonomic dysfunction, and/or rhabdomyolysis, or the breakdown of muscle fibers with leakage into the bloodstream.
- Treatment should start with aggressive hydration and initiation of IV and benzodiazepines, preferably diazepam. Often, large doses are needed to stabilize the patient. Risperidone or haloperidol can also be considered.
- Deep Brain Stimulation should be considered early when severe hyperkinetic movements are present.

Medications
There is no single most effective medication to treat symptoms of GNAO1-NDD. Treatment is often symptomatic and sometimes ineffective. The following are suggestions for treatment of specific symptoms:

Movement Disorder
If primarily dystonia:
- Trihexyphenidyl (Artane)
  *can make chorea worse
- Carbidopa/Levodopa (Sinemet)
  *can make chorea worse
- Botulinum Toxin injections
If primarily chorea:
- Tetrabenazine (Xenazine)
  *often the most effective for long-term management, but side effects can limit use
- Diazepam (Valium)
- Deep Brain Stimulation (DBS)
  *can be life-saving in emergencies

Epilepsy
Treatment for individual patients should be targeted towards their specific seizure type and/or electro-clinical syndrome. Commonly used medications include:
- Levetiracetam (Keppra)
- Clobazam (Onfi)

Drooling
- Glycopyrrolate (Cuvposa, Robinul)

Constipation
- Polyethylene glycol (Miralax)

Therapy
It is important to start aggressive physical, occupational, and speech therapies as soon as possible to receive maximum benefit of therapy.

Common Symptoms
Individuals with GNAO1-NDD may or may not experience some or all of the following:

Global Developmental Delay
Learning and motor disabilities.

Gastrointestinal Complications
Constipation; feeding difficulties leading to G-tube placement.

Speech and Language Deficiencies
Augmentative communication devices are helpful for children who have difficulty speaking.

Autonomic Dysregulation
Patients often have unexplained fluctuations in body temperatures, leading to sudden fevers, sweating, and/or cold extremities.

Sleeping Difficulties
Sleep apnea; insomnia; awakenings sometimes due to involuntary movements.

Orthopedic Complications
Scoliosis, joint contractures, and hip displacement will often require braces.

Daytime Fatigue

Psychiatric Manifestations
Anxiety; irritability.

Works Cited