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.

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+ Informational Guide

FOR *GNAO1*-ASSOCIATED NEURODEVELOPMENTAL DISORDERS (*GNAO1*-NDD)

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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 [1]. 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 [1,2,5]. The movement disorder may be mixed, consisting of dystonia (most common), dyskinesia, chorea, stereotypies, ataxia, and/or hypotonia [3,5]. 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 [1]. 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.
Drooling
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

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4) Saitsu, et al. ""Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay.“" European Journal of Human Genetics 24.1 (2016): 129-134.
5) Schirinzi, et al. ""Phenomenology and clinical course of movement disorder in GNAO1 variants: Results from an analytical review.“" Parkinsonism & Related Disorders 61 (2019): 19-25.