

# ★ Treatment

## 1. ketogenic diet

There is currently no cure for Glut1 Deficiency. The recommended standard of care treatment is a medically supervised ketogenic diet, which can improve most symptoms for most patients, even in adulthood. A ketogenic diet is a high fat, moderate protein, low carbohydrate diet that provides alternative fuel to the brain with ketones instead of glucose. The earlier the diet is implemented, the better the outcomes for patients in improving seizure control, movement disorders, and cognitive abilities. Studies show that 4 out of 5 children who have epilepsy caused by Glut1 Deficiency will become seizure-free on dietary therapy.

In infancy and childhood, a classical 3:1 or 4:1 ketogenic is recommended to ensure the highest level of ketone energy to meet the metabolic fuel demands of the developing brain. Although it is recommended to continue the classical ketogenic diet for as long as is tolerated, alternative ketogenic diet versions such as the Modified Ketogenic (2:1 and 1:1 ratios) or the Modified Atkins Diet may be more feasible for quality of life and compliance considerations and are often used by teenagers and adults.

All patients on a ketogenic diet should be under the care of an experienced dietitian and neurologist and have regular laboratory screenings to help monitor for potential side effects. Blood ketone levels, as opposed to urine, should also be monitored and can be correlated to optimal brain energy supply and symptom control.

For a small subset of patients, a ketogenic diet proves ineffective despite adequate levels of ketosis. Medications to address the symptoms of seizures or movement disorders may provide some benefit, although there is currently no clear basis for specific recommendations and there are concerns to consider regarding potential harmful interactions with ketogenic diets.

## 2. other therapies

Occupational therapy, physical therapy, and speech and language therapies are often recommended for supporting optimal development in children and remain beneficial into adulthood. Families also report benefits from additional forms of regular therapy, particularly hippotherapy, aqua therapy, and mindfulness.

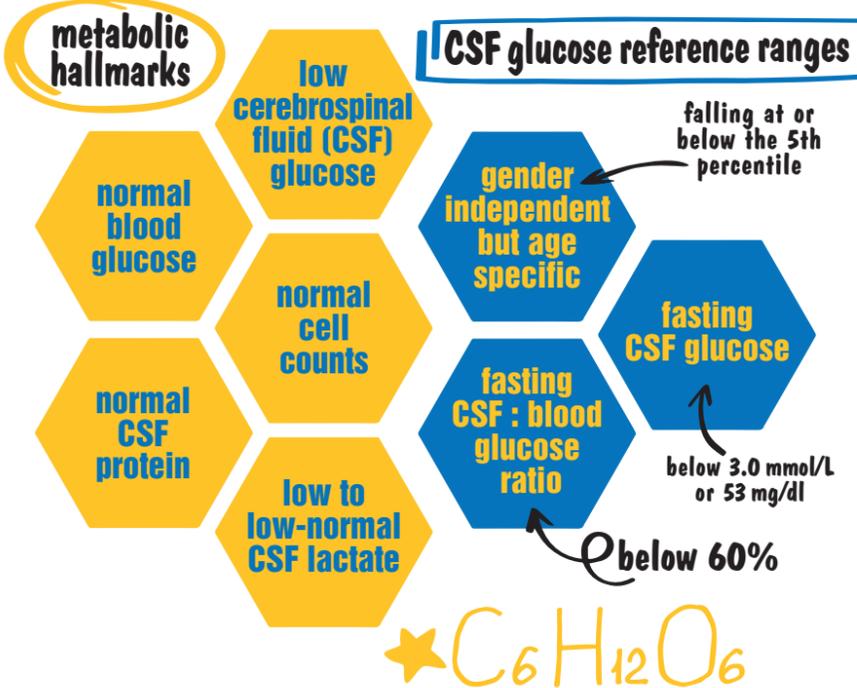
Many adult patients have reported that regular physical exercise can help reduce movement disorder symptoms.

# Diagnosis

Early diagnosis is critical in order to initiate treatment so brain growth and development may be optimized during important early growth stages of life. Proper diagnosis and treatment can lead to dramatic improvements in symptoms and quality of life at any age.

## 1. lumbar puncture

When Glut1 Deficiency is suspected, glucose should be measured in the spinal fluid and in the blood simultaneously after a 4-6 hour fast. Blood samples should be drawn first to avoid stress-related elevations in blood glucose, and a lumbar puncture (spinal tap) should quickly follow.



## 2. genetic analysis

Genetic testing can also help confirm the diagnosis by detecting a mutated SLC2A1 gene, although current testing does not identify a mutation in 10-15% of cases. The combination of suggestive clinical symptoms and the characteristic CSF findings indicate a Glut1 Deficiency diagnosis, even in the absence of an identified SLC2A1 mutation.

Distinct patterns of brain glucose uptake on PET scans and specialized red blood cell uptake assays are also useful in the absence of an otherwise clear diagnosis but might be available in specialized centers only.

Dystonia 9 and 18 are associated with mutations in the SLC2A1 gene.

# Research

Ongoing research aims to better understand the mechanisms of Glut1 Deficiency in the brain and throughout the body, develop better diagnostic tools, and identify more potential treatments for the future, including:

- Exploring methods to enhance glucose transport
- Identifying the safest and most effective medications for seizures and movement disorders
- Using supplemental oils and synthetic ketones to boost the effectiveness of the ketogenic diet
- Repairing or replacing the faulty gene or manipulating its expression

# Resources

The Glut1 Deficiency Foundation is a non-profit family organization dedicated to improving lives in the Glut1 Deficiency community through its mission of:

- Increased awareness
- Improved education
- Advocacy for patients and families
- Support and funding for research

## Expert Consensus Guidelines:

- Glut1 Deficiency Syndrome: State of the Art in 2020 and Recommendations of the International Glut1DS Study Group

## Ketogenic Diet Resources:

- The Charlie Foundation for Ketogenic Therapies
- Matthew’s Friends Ketogenic Dietary Therapies
- Epilepsy.com “KetoNews”

## Medical Advisory Board:

- Mackenzie Cervenka MD
- Darryl De Vivo MD
- Kristin Engelstad MS, CGC
- Prof. Dr. Jörg Klepper
- Eric Kossoff MD
- Juan Pascual MD, PhD
- Toni Pearson MBBS, MD
- Prof. Dr. Michèl Willemsen
- Beth Zupec-Kania RDN, CD

## Patient Registry:

www.G1DRegistry.org

## BioBank Repository:

Coriell Institute for Medical Research

## New Specific ICD-10-CM Code: E74.810



www.G1DFoundation.org



# A GUIDE TO UNDERSTANDING GLUT1 DEFICIENCY



www.G1DFoundation.org



## What is **Glut1** Deficiency?

Glut1 Deficiency is a rare, genetic disorder that impairs brain metabolism. Glucose isn't properly transported into the brain, leaving it starving for the metabolic fuel it needs to grow, develop, and function normally and causing a wide range of neurological symptoms.

**Did you know? Glut1 Deficiency is also known as:**

- Glucose Transporter Protein Type 1 Deficiency Syndrome**
- Glut1DS**
- G1D**
- De Vivo Disease**

## Cause **SLC2A1**

Glut1 Deficiency is caused by mutations in the **SLC2A1** gene, which regulates production and activity of the glucose transporter protein type 1 (Glut1). Since it is an autosomal dominant disorder, just one mutation in one of the two copies of the gene is enough to cause disease. Mutations most often occur spontaneously and are not inherited, but people with Glut1 Deficiency do have a 50% chance of passing the altered gene on to each offspring.

## Understanding **Symptoms**

Glut1 is the only transport protein that moves glucose across the blood brain barrier, where the brain uses it as its main source of energy. Without enough glucose, brain growth and function are impaired, resulting in symptoms that can vary widely between individuals and may change over time as a patient ages. Puberty often brings changes in symptoms and treatment response.

Symptoms may be present all the time, occur as temporary episodes, and may fluctuate in severity. Not all patients experience all symptoms, especially in milder cases. The range of symptoms may vary from mild to severe, sometimes making Glut1 Deficiency difficult to diagnose. Any combination of suggestive symptoms in any range of severity should be considered for diagnostic workup.

### 1. movement disturbances

Movement symptoms relate to the quality of motor functions, and most people with Glut1 Deficiency have some form of complex movement disorder that may include one or more type listed below. Movement disturbances tend to become the dominant feature in adolescence and adulthood, and new types of movement episodes may appear.

- **Ataxia** — impaired balance and movement coordination
- **Athetosis** — involuntary twisting and writhing movements
- **Ballismus** — large amplitude flinging movements of a limb
- **Chorea** — brief, involuntary movements that appear to flow randomly from one body part to another
- **Dysarthria** — unclear speech articulation
- **Dyspraxia** — impaired coordination and organization of movement and/or speech
- **Dystonia** — involuntary muscle contractions that lead to abnormal posture and movements
- **Eye-head movements** — characteristic episodes, typically lasting for minutes, of repeated eye and head movements in multiple directions. These start in infancy and may be the first symptom to appear.
- **Hemiplegia** — temporary episode of paralysis on one side of the body
- **Hypotonia** — decreased muscle tone, floppiness
- **Paroxysmal Exercise-Induced Dyskinesia (PED)** — involuntary movement disorder episodes triggered by prolonged and excessive physical exertion, hunger, illness, or stress
- **Spasticity** — stiff muscles, predominantly in the legs, often causes toe-walking
- **Tremor** — involuntary, rhythmic trembling or shaking

### 2. seizures

Seizures are common but not always present, and multiple types of seizures may occur with both focal and generalized onset. Typically, seizures first begin in infancy or early childhood and tend to stabilize, decline, and sometimes eventually resolve beyond puberty and into adulthood. Most seizures in Glut1 Deficiency are not easily treated with medication.

### 3. cognition & learning

Most patients experience some degree of cognitive impairment ranging from subtle learning difficulties to severe intellectual disabilities. While there are individual differences, some general patterns that impact learning and performance are found in patients across all ages:

#### **weaknesses**

- Lowered IQ and adaptive behavior scores
- Executive function
- Expressive language and verbal memory
- Abstract analytical skills
- Visuospatial, visuomotor, and visual attention skills
- Transfer of learning to new contexts
- Fine motor skills and coordination

#### **strengths**

- Receptive language skills
- Sequential, step-by-step processing
- Sociability
- Developmental gains are seen over time
- Perseverance
- Fun-loving, empathetic personalities
- No evidence of loss of skills over time for patients on a ketogenic diet

When planning instruction and interventions, it is important to build upon strengths as weaknesses are remediated. The most appropriate school setting, accommodations, and support services vary based on individual needs and available resources. Family members play an important role in educating school personnel and in forming partnerships to help develop and implement plans to best meet the unique and individual educational and medical needs of Glut1 Deficiency patients.

In adulthood, the extent of cognitive and medical challenges experienced by each individual can impact various aspects of their lives, including the level of independence patients can attain, the types of volunteer and vocational opportunities available to them, and the services and supports they may be eligible to receive.

### 4. behavioral

Behavioral symptoms affect relations with other people and may include short attention span, obstinance, and delays in achieving age-appropriate behaviors. Some patients have been additionally diagnosed with attention deficit and/or autism spectrum disorders. Anxiety, obsessive-compulsive tendencies, mood disorders, and behavioral outbursts are also reported. Sociability, however, is often reported as a strength in many Glut1 Deficiency patients.

### 5. developmental

Global developmental delays are typical for Glut1 Deficiency patients due to the many symptoms experienced. Young patients may reach developmental milestones such as walking, speaking, and toilet training at a delayed rate. Fine motor and visual motor skills may be affected, including writing. Gross motor delays may affect core body strength, balance, and coordination. Speech delays may affect articulation of expressive language.

#### **additional possible symptoms**



- migraines**
- episodic confusion**
- lack of physical endurance or stamina**
- microcephaly**
- memory problems**
- sleep disturbances**
- cyclic vomiting**

## Triggers

Symptoms can be triggered or worsened by excessive exercise, illness, hunger, weather and temperature changes, hormones, fatigue, anxiety, excitement, and other strong emotional reactions.



## Prevalence

The number of people diagnosed with Glut1 Deficiency is currently thought to number in the hundreds. Recent studies have estimated true prevalence to be at least 1:24,000, so the vast majority remain undiagnosed. There's no known susceptibility related to gender or race.