GLUT1 Deficiency Syndrome
Glut1DS

Medical Guide

2024

by METAFORA

Agenda

About Glut1DS

Glut1DS, or **De Vivo disease**, is a rare **neurometabolic** genetic disorder caused by a defect in the glucose transporter **GLUT1***, resulting in a cerebral energy deficit. This syndrome was first described in 1991 by Professor Darryl De Vivo.

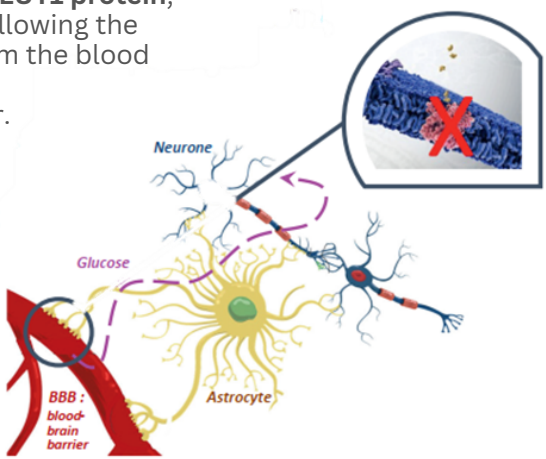
Etiology

The ***SLC2A1* gene** which encodes the transport protein GLUT1 undergoes an alteration which can either be transmitted by one of the parents (autosomal dominant transmission variant), or new in the patient (*de novo* mutation).

Several hundred mutations are listed, of different natures including missense, nonsense variants or even deletions.

A pathogenic variant of ***SLC2A1*** causes a **malfunction of the GLUT1 protein**, the main transporter allowing the passage of glucose from the blood to the brain across the blood-brain barrier.

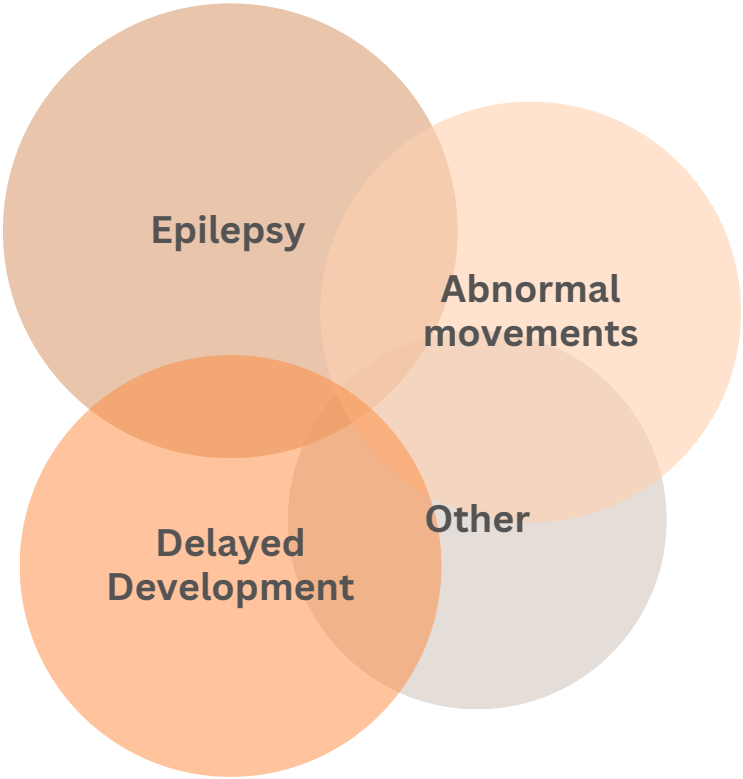
This notably causes a cerebral energy deficiency.



* Glucose transporter deficiency syndrome type 1 (Glut1DS) or De Vivo disease (OMIM606777).

Symtoms

Glut1DS is characterized by a **wide phenotypic spectrum**. The combination and severity of symptoms greatly vary from one patient to another, ranging from a severe phenotype with early onset to moderate symptoms with late onset.



These symptoms can be aggravated by fasting, fatigue, exercise or stress.

Symptoms

Age 0 1 2 3 4 5 6 7 8 9 10 ... 15 ... 30 ..

Epilepsy

- **EOAE** Early-onset absence epilepsy — 0-4 y.o.
- **CAE** Childhood absence epilepsy — 4-10 y.o.
- **JAE** Juvenile absence epilepsy — 10-15 y.o.

- Different forms
- Onset at any age
- Tends to improve with age

Any other type of epilepsy may be observed (generalized epilepsy, focal epilepsy, myoclonic-atonic seizures, spasms, etc.).

Key factors: early-onset epilepsy, seizures favored by fasting, seizures occurring in the early morning, drug resistance, good response to ketogenic diet.

Abnormal movements (AM) → **Paroxysmal eye movements** — 0-1 y.o.

- Different forms
- Onset at any age
- Tends to increase with age

Paroxysmal AM (favored by fasting, stress, physical exertion, etc.)

- Non-kinesigenic paroxysmal AM, exercise-induced paroxysmal dyskinesias, paroxysmal ataxia, paroxysmal parkinsonism, acute speech disorder
- Paroxysmal attacks of weakness or paralysis
- Paroxysmal attacks of pain, migraine
- Paroxysmal attacks of lethargy, somnolence, confusion, vomiting
- Acute mood disturbance

Permanents AM:

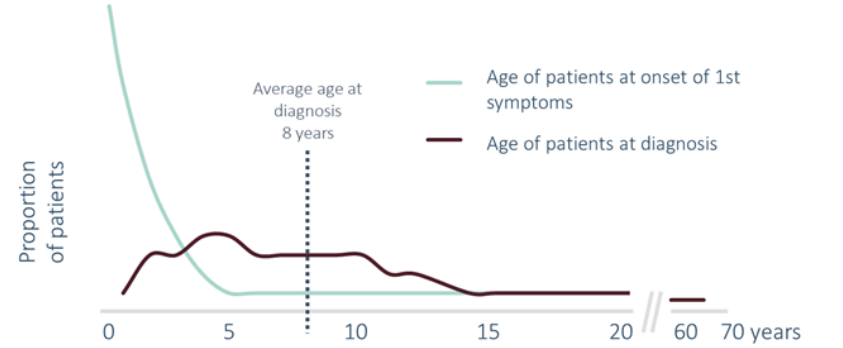
- Spasticity
- Cerebellar syndrome
- Complex permanent abnormal movements: dystonia, choreoathetosis, myoclonus, tremor

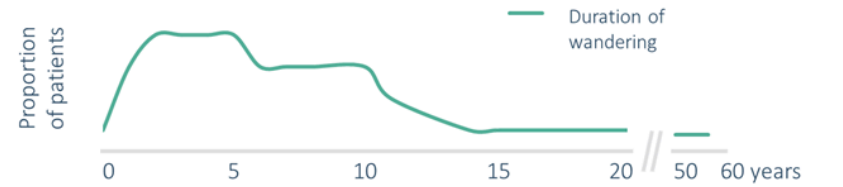
Neuro-developmental disorders

- Mild to severe intellectual disability
- Other neurodevelopmental disorders (complex cognitive disorders including attentional, executive and praxis disorders)
- May be associated with acquired microcephaly or a dip in the head circumference curve

Epidemiology

- The prevalence of the disease is estimated at 1/24,000.
- 90% of patients are undiagnosed[1].
- No sex ratio has been observed, the disease is detected in all ethnic origins.
- Neurological symptoms, occurring in 1/3 of cases before the age of 1 year old.
- A major diagnostic wandering for most patients, delaying treatment

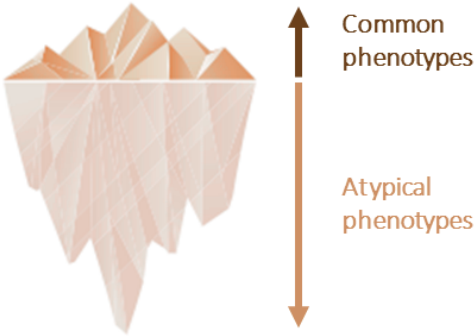




- Early diagnosis is a main healthcare challenge.
- The development of a simple, rapid and non-invasive tool, accessible to all, is therefore very useful for a diagnosis early.

Challenges

Hardly known by health professionals, this **rare proteiform disease** is largely under-diagnosed. However, for the proper development of children, it is important that they are treated (in particular with a **ketogenic diet**) from a very young age, in order to offer their brain an energy alternative to glucose.



The results of a large French study[2] showed that among newly diagnosed patients:

50%

Have **epilepsy**

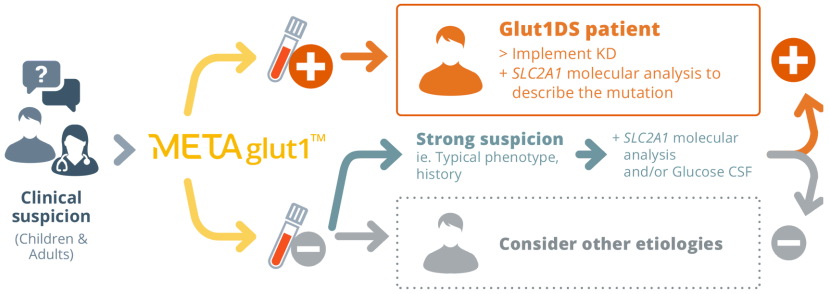
50%

Have **abnormal movements (AM)**

20%

Are **adults**

The **METAglut1™ TEST** is a **first-line simple test** to screen for Glut1DS patients*:



Clinical suspicions are symptoms such as: epilepsy, abnormal movements (AM) and/or neuro-developmental disorders.

* Strategy published in the journal Neurology[2] and recommended by the HAS:
Opinion n°2023.0011/AC/SEAP of March 30, 2023 from the college of the High Authority of Health relating to registration on the list of procedures and services mentioned in the article L. 162-1-7 of the social security code for the METAglut1™ test.

** In France, the glucose absorption test is only available at the Institute of Molecular Genetics of Montpellier (IGMM). The request for this analysis can be made to METAFORA biosystems

Diagnosis

The diagnosis of this syndrome is based on a range of arguments. There is no “gold standard”.

The French study[2] showed that:

- The METAglut1™ test, like cerebrospinal fluid (CSF) glucose measurement, is reliable in 80% of cases.
- The METAglut1™ test can aid interpret the molecular analysis when the result is uncertain or inconclusive.

METAglut1™ is therefore designed as a first-line test as part of the Glut1DS diagnostic strategy*.

METAglut1™

Already reimbursed for children and adults in France

Simple blood draw, no fasting required

Enable early testing for any phenotype

Performance equivalent to glycorrhachia

Fast results (24-72 hours)

Can help characterize Variants of Uncertain Significance

Quantification of GLUT1 expression on the surface of red blood cells.

- Inpatients or outpatients settings
- Blood collection using an EDTA tube (1 pediatric EDTA tube of 3 mL is sufficient. In case of difficulty, 1 microtube can be used. For patients from 3 months old)
- No need to fasting
- Analysis up to 7 days after sampling
- Storage of the sample at 4°C
- Results available in 24h-48h
  The positivity threshold is < -24%

METAglut1™ is a CE marked in vitro diagnostic medical device used to aid the diagnosis of the Glut1 Deficiency Syndrome

Diagnosis

In **case of strong suspicion**, patients can be referred to the hospital for a **CSF glucose measurement** and/or a **molecular analysis** of the *SLC2A1* gene to complete the diagnostic strategy.

CSF Glucose - Glycorrhachia (lumbar puncture)

Principle:
Search for hypoglycorrhachia, suggestive of the disease.

Procedure:
Collection of cerebrospinal fluid (CSF) by lumbar puncture. The blood sugar measurement must be coupled, after an 8-hour fast.

Results:
Available within hours.
The value suggestive of pathogenicity is < 2.2 mmol/L (40mg/dL) and/or a CSF Glucose / Blood Glucose ratio < 0.45

Molecular Analysis of the *SLC2A1* Gene

Principle:
Molecular analysis of the *SLC2A1* gene by NGS and/or Sanger sequencing, more or less associated with MLPA (Multiplex Ligation-dependent Probe Amplification) analysis.
It makes it possible to detect pathogenic variants of the gene.

Procedure:
Blood collection on EDTA tube after obtaining consent

Results:
Very variable availability ranging from a few weeks to several months. The interpretation of the result can be confirmed by the reference center

Useful Contacts

METAglut1™ MANUFACTURER

METAFORA biosystems
100 S. State Street, PO 417, Chicago, IL 60603, USA
29 rue du Faubourg Saint-Jacques, Paris 75014, France
contact@metafora-biosystems.com

PATIENT ASSOCIATIONS

Glut1 Deficiency Foundation
PO Box 737 Owingsville, KY 40360 - United States
https://www.g1dfoundation.org/

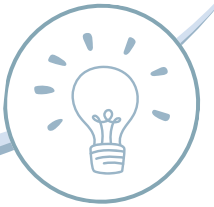
Association sur le Syndrome du Déficit en Glut1
4A, Allée des Sports 64600 ANGLET – France
https://asdglut1.wixsite.com/asdglut1

References

1. Symonds JD et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019.

2. . Mochel et al. Prospective Multicenter Validation of a Simple Blood Test for the Diagnosis of Glut1 Deficiency Syndrome. Neurology. 2023.

Glut1DS
To sum up



1 Causes

Malfunction of the glucose transporter Glut1

2 Symptoms

- Drug-resistant epilepsy (all types of seizures)
- Shift in psychomotor acquisitions
- Acquired microcephaly
- Permanent and/or paraxysmal motor disorders (ataxia, dystonia, spasticity)

A wide phenotypic spectrum with a combination and severity of symptoms that greatly vary from one patient to another, often aggravated with fasting, physical effort, stress.

3 Diagnosis

1. METAglut1™ blood test as a primary intention
2. Molecular Analysis of the *SLC2A1* Gene
3. CSF Glucose - Glycorrhachia (lumbar puncture)

4 Treatment

Ketogenic diet (KD) to restore brain energy