EpiCARE

Glut1 Deficiency syndrome

Also known as: Glut1DS, G1D, De Vivo Disease

Overview

Glut1 Deficiency Syndrome is a rare, genetically determined disease affecting brain metabolism. It is caused by a mutation in the SCL2A1 gene which may be either de novo or inherited. The consequence of haploinsufficiency is decreased availability of glucose to the brain and resultant encephalopathy, due to impaired transport of glucose across the blood-brain barrier.

Currently, GLUT1DS is recognized to have a wide spectrum of manifestations with variable degrees of severity and different timing of presentation through a patient's life. Common manifestations are represented by microcephaly, cognitive impairment, epilepsy, and paroxysmal movement disorder.

Although there is currently no cure for Glut1DS, Ketogenic dietary therapies (KDTs), consisting of high fat content, restricted carbohydrates, and adequate proteins, are the current standard of treatment for the syndrome: ketone bodies can cross the blood-brain barrier and be used as an alternative fuel for brain metabolism.

Disease course and long-term outcome are variable. To date, GLUT1DS natural history, epidemiology, response to KDTs, and their long term consequences are yet to be fully elucidated.

Incidence and prevalence

GLUT1 Deficiency Syndrome is a rare disorder. The recently predicted incidence is 1.65- 2.22 per 100,000 births. In retrospective studies, the prevalence of GLUT1DS was estimated to be around 1:90,000. However, due to the progressive broadening of the recognized phenotype, the actual prevalence of GLUT1DS might be underestimated.

Diagnosis

Diagnosis can be suggested by the presence of characteristic clinical features and confirmed by the evidence of hypoglycorrhachia (low CSF glucose) in a setting of normoglycemia. To date, the only known gene associated with the disease is the SLC2A1 gene. Mutations are mainly autosomal dominant de novo, but familial cases are possible. The type of genetic mutation might correlate with phenotypic severity. Molecular diagnosis remains elusive in 10% of patients with clinical features supporting GLUT1DS and typical CSF profile. Intronic variants have been reported as cause of GLUT1DS, but detailed evidence is still lacking

Early diagnosis of Glut1DS is essential for early treatment during the stages of brain development when symptoms can be prevented. A correct diagnosis requires knowledge of the symptoms of Glut1DS, but these may be very similar to other disease and often are not specific enough to allow for an immediate diagnosis.

Age of onset

Glut1 deficiency is an inborn error of metabolism, so it is present from birth. However, there is a wide variation in age of onset. Symptoms may not be immediately evident and may change with age.

Symptoms at presentation

The most common symptom at presentation is represented by epileptic seizures, and most frequently by early onset absence seizures (before 4 years of age) and myoclonic-atonic seizures, whereas focal seizures are less common. The second most frequent initial sign of Glut1DS is represented by paroxysmal eye-head movement, usually characterized by repeated multidirectional saccadic, conjugate movements of the eyes and head, without loss of consciousness. Psychomotor developmental delay might be present at onset.

Most patients also present with movement disorders (which may be the symptom of onset when the disease becomes manifest later in life), classically which present preprandially and are mitigated by meals. Movement disorders may be persistent or paroxysmal. Persistent movement disorders include ataxia, spasticity, and dystonia with gait disturbances; chorea or tremor are less common. Paroxysmal movement disorders are mainly represented by paroxysmal exercise-induced dyskinesia, paroxysmal major motor dysfunction, and paroxysmal events with complex neurological symptoms, often triggered by stress, fever, fatigue, fasting, or insufficient ketosis. Most patients have some degree of dysarthria with some degree of speech impairment.

Acquired microcephaly may become evident during childhood.

Intellectual disability is common, yet highly variable, ranging from mild to severe. Performance skills are usually more affected than verbal ones. Adaptive behavior and social skills are considered a strength for the group.

Alternating hemiplegia, hemiplegic migraine, cyclic vomiting, stroke-like episodes, writers' cramp, intermittent ataxia, Parkinsonism and nocturnal painful muscle in legs are rare features.

How do seizure types change over time?

Clinical manifestations shift over time from the infantile-childhood onset epilepsy to the adolescent-adult movement disorder.

Epileptic manifestations of Glut1DS tend to improve over time, as seizures may decline or disappear in late childhood, adolescence, or adulthood. However, in adolescence or adulthood the movement disorder tends to become more prominent.

EEG features

Similar to clinical findings, also neurophysiological findings are complex and variable. Electroencephalographic (EEG) findings may change in a single individual over time and may encompass focal, multifocal, generalized, or normal activity in the same patient at different times. In infants, the most common findings are represented by focal slowing and epileptiform discharges, whereas in children ages two years or older, 2.5- to 4- Hz generalized spike- wave pattern is observed. Moreover, in a study comparing pre and postprandial EEG recordings, a significant reduction in epileptiform discharges was noted in the postprandial recording.

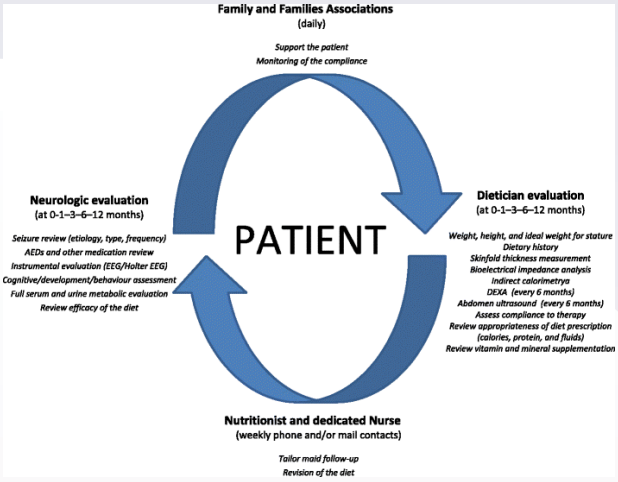
Treatment

Ketogenic dietary therapies (KDTs), consisting of high fat content, restricted carbohydrates, and adequate proteins, are, to date, the gold standard treatment for the syndrome: ketone bodies can cross the blood brain barrier and can be used as alternative fuel for brain metabolism. Therefore, KDT should be started as early as possible. KDTs are usually effective in controlling seizures, and some patients may no longer require anti-seizure medications. Furthermore, cognitive delay and movement disorders may also improve with the ketogenic diet. The classic KDT (with a 3:1 or 4:1 fat-to-carbohydrate-plus-protein ratio), which provides higher levels of ketosis, is generally preferred in younger patients, while a more liberal versions – i.e. the modified Atkins diet – may be adequate alternatives and promote compliance in adolescents or adults. Dietary therapy should be maintained indefinitely, continuing into adulthood, as symptoms may return upon discontinuation.

Some patients receive treatment with anti-seizure medications , and may be already in treatment at the time of diagnosis. These drugs do not address the metabolic defect which is the underlying cause of Glut1DS, but may be used as an add-on to the ketogenic diet for seizure control, although there are concerns regarding the interaction of these drugs with the diet.

Follow-up evaluations

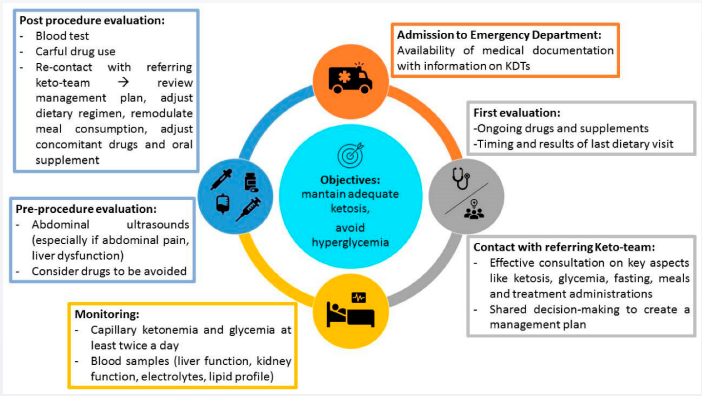
Aimed at monitoring the evolution of GLUTDS1 symptoms and the efficacy / tolerability of the KDT:



Pasca L, De Giorgis V, Macasaet JA, Trentani C, Tagliabue A, Veggiotti P. The changing face of dietary therapy for epilepsy. Eur J Pediatr. 2016 Oct;175(10):1267-76. doi: 10.1007/s00431-016-2765-z. Epub 2016 Sep 1.

Individualized emergency protocols

Individualized emergency protocol is mandatory for those patient treated with KDT.



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Provide patient/carer with:

- Adequate support for the application of dietary therapy (multidisciplinary ketogenic diet team)
- Indications for rehabilitation and support (neuropsychological evaluation, physical therapy, speech therapy, support for intellectual development)
- Genetic counselling

Authors: Monica Lucente (Italian GLUT1DS Association); Valentina De Giorgis and Costanza Varesio (IRCCS Mondino Foundation, Pavia; Brain and Behavioral Department, University of Pavia, Italy). The European Commission support for the production of this publication does not constitute endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

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Overview

Glut1 Deficiency Syndrome is a rare genetic disease affecting brain metabolism. Glut1 is the protein responsible for the transport of glucose, the brain's main source of energy, across the blood-brain barrier. It is produced by the SLC2A1 gene on Chromosome 1. If this gene is damaged by a mutation, enough of the transporter protein might not be produced, or else what is produced might not be effective enough to ensure sufficient glucose transport. Since glucose is the main fuel source for the brain, and it is important for cerebral metabolism and neural function, in patients with Glut1 deficiency, the brain doesn't receive enough energy for normal development and function: a Glut1DS brain is always hungry and might not function properly. The predominant symptoms are represented by epilepsy, developmental delay, cognitive impairment, language impairment and movement disorders.

There is currently no known cure for Glut1DS, but there are methods of treatment, namely represented by a special diet called Ketogenic Dietary Therapy (KDT), which may help nourish the brain and prevent or improve symptoms, providing alternative fuel to the brain. The disease course is variable among affected people, and information on long-term outcome, frequency of the disease and efficacy of KDTs still need to be further studied.

How common is GLUT1DS?

GLUT1DS is a rare disease, which means it affects a small number of people compared to the general population (a disease is defined rare if it affects less than 1:2,000 people). GLUT1DS affects an estimated 1.65-2.22 in 100,000 live births. Its prevalence (population affected at a given time) is estimated to be around 1:90,000. However, its prevalence is thought to be underestimated especially in adults.

When do symptoms first appear?

Glut1 deficiency is an inborn error of metabolism, so it is present from birth. However, symptoms may not be immediately evident and may change with age. Symptoms may begin in early infancy with paroxysmal eye-head movements, early-onset epilepsy or delay in acquisition of psychomotor milestones, or later in childhood with cognitive delay and motor disturbances.

How is Glut1DS diagnosed?

A correct diagnosis requires knowledge of the symptoms of Glut1DS, but these may be very similar to other disease and often are not specific enough to allow for an immediate diagnosis. When symptoms lead to the suspicion of Glut1DS, a sample of cerebrospinal fluid (CSF) when fasting might be collected, in order to compare the glucose levels to those in the blood. In GLUT1DS patients, the CSF glucose levels are abnormally low. Alternatively, or after CSF sampling, genetic testing looking for causative variants in the SLC2A1 gene might be performed. However, some patients with Glut1DS may not have an identified mutation in SLC2A1, and research is ongoing into potential alternative genes which may lead to Glut1DS.

Early diagnosis of Glut1DS is essential for early treatment during the stages of brain development when symptoms can be prevented; however, Glut1DS manifestations may be very similar to other disease and often are not specific enough to allow for an immediate diagnosis.

What are the symptoms at onset in Glut1DS?

The most common symptoms at presentation are drug-resistant seizures, usually characterized by absence seizures (the child may suddenly have a blank stare for a few moments) or myoclonic-atonic seizures (the child presents with massive jerks of muscles, followed by loss of muscle tone causing a drop). The second most frequent early sign of Glut1DS is the paroxysmal eye-head movement, characterized by involuntary repeated multidirectional movements of the eyes and head as if "watching a fly", without loss of consciousness. Most patients also present with a motor impairment, which may be fixed and persistent or paroxysmal. Patients may experience ataxia, spasticity, and dystonia, thus leading to unstable and uncoordinated gait. Patients may also experience episodic movement disorders, mainly represented by paroxysmal exercise-induced dyskinesia, paroxysmal major motor dysfunction, and paroxysmal events with complex neurological symptoms, often stimulated by stress, fever, fatigue, fasting, or insufficient ketosis. Most patients present also with variable degrees of psychomotor delay and cognitive impairment, speech and language are also involved. Acquired microcephaly (a progressive slowdown of head growth) may become evident during childhood.

How do symptoms change over time?

Epileptic manifestations of Glut1DS tend to improve over time, as seizures may decline or disappear in late childhood, adolescence, or adulthood. However, as epileptic manifestations decrease, there is a shift in adolescence or adulthood towards a more prominent movement disorder. The language disorder doesn't worsen but it could be more prominent and affect social functioning in adolescence or adulthood.

Why should EEG be performed?

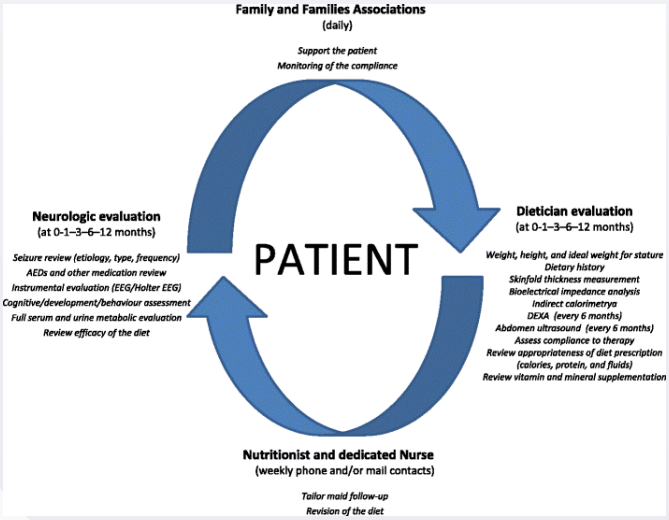
Electroencephalography (EEG) should be regularly performed to detect the presence of epileptic seizures and to characterize abnormal brain electrical activities.

How can Glut1DS be treated?

Ketogenic diet therapy (KDT) is the first choice for treatment of Glut1DS, and should be started as early as possible to provide alternative fuel to the developing brain. KDT, characterized by high fat content with normal protein and restricted carbohydrates, stimulates the production of ketone bodies which provide an alternative fuel source to the brain. Dietary therapy is usually effective in controlling seizures, and some patients may no longer require anti-epileptic drugs. Furthermore, cognitive delay and movement disorders may also improve with KDT. Different types of KDTs exist. The classic ketogenic diet, which provides higher levels of ketosis is generally preferred in younger patients, while less restrictive KDT – a modified Atkins diet – may be adequate and promote compliance in adolescents or adults. Dietary therapy should be maintained indefinitely, continuing into adulthood, as symptoms may return upon discontinuation. Some patients receive treatment with anti-seizure medications, and many are already in treatment at the time of diagnosis. These drugs do not address the metabolic defect which is the underlying cause of Glut1DS, but may be used as an add-on to the ketogenic diet for seizure control.

What are the follow-up assessments over time?

The aim is to monitor the evolution of GLUTDS1 symptoms and the efficacy / tolerability of the KDT:



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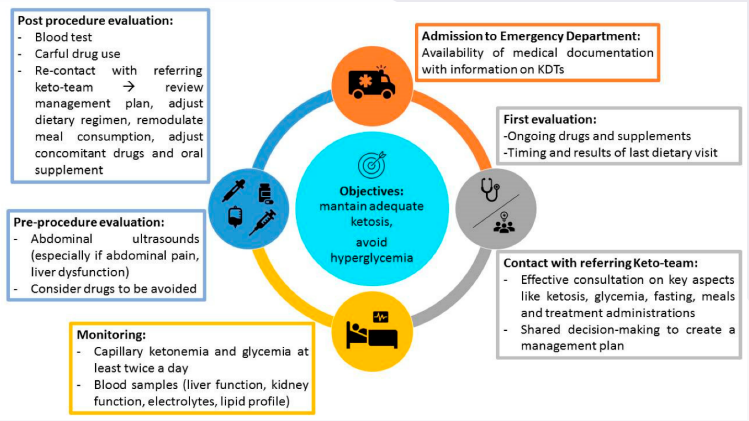
What to do in case of an emergency?

It could be useful to provide an individualized emergency protocol for those GLUT1DS patient treated with KDT.



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What could I ask my doctor about?

- Adequate support for the application of dietary therapy (multidisciplinary ketogenic diet team)
- Indications for rehabilitation and support (neuropsychological evaluation, physical therapy, speech therapy, support for intellectual development)
- Genetic counselling

Patient group

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GLUT1 ASSOCIAZIONE ITALIANA

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