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THE GOLD STANDARD FOR THE MANAGEMENT OF GLUT1 DEFICIENCY SYNDROME

An overview for healthcare professionals

Glut1DS booklet is reviewed and endorsed by Prof Jörg Klepper, MD,
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INTRODUCTION

Glut1 Deficiency Syndrome (Glut1DS) is a rare genetic disorder caused by a deficient glucose transport into the brain resulting in impaired brain function and growth. This chronic condition, often dominated by epilepsy in infancy and movement disorders thereafter, was first diagnosed in 1991[1]. Life-long age-specific ketogenic diet therapies (KDT) are the standard of care and currently the most effective treatment for Glut1DS, providing supplemental fuel – ketones – for brain energy metabolism[2].

Since its first discovery, Glut1DS diagnosis and treatment become increasingly complex. Initially under-diagnosed[3], the number of affected individuals has grown steadily[2] emphasizing the need for an international consensus statement, summarising current Glut1DS knowledge and bringing together collective professional experience and expertise. In 2020, the *'Glut1 Deficiency Syndrome (Glut1DS): State of the art in 2020 and recommendations of the international Glut1DS study group[2]'* was published in Epilepsia Open (link to the full paper: scan the QR-code) with the key conclusions regarding the standard of care for Glut1DS summarised in this booklet.

← Link to the full paper
https://onlinelibrary.wiley.com/doi/10.1002/epi4.1241

ABOUT GLUT1 DEFICIENCY SYNDROME (GLUT1DS)

Pathophysiology

Glucose is essential for brain energy metabolism. It enters the brain by the glucose transporter type 1 (GLUT1) protein. GLUT1 exclusively facilitates glucose transport across the blood-brain barrier – this explains why Glut1 haploinsufficiency results in disease – and into brain cells in concert with other GLUTs.

Genetics

GLUT1 is encoded by *SLC2A1*, a small gene on chromosome 1 (1p35-31.3) SCL2A1. Pathogenic *SLC2A1* variants cause quantitative or functional Glut1 defects resulting in a brain 'energy crisis'[2]. It affects males and females in equal numbers[4]. In the majority of cases Glut1DS results from non-inherited spontaneous "de novo" *SLC2A1* variants[2]. Glut1DS patients transmit the disease in an autosomal dominant pattern with a 50 per cent risk for each pregnancy[5]. In approx. 5-10% of Glut1DS patients *SLC2A1*-analysis is normal indicating disease mechanisms on the RNA/protein level[6]. Autosomal-recessive Glut1DS has been described in single families[7].

Incidence

The estimated worldwide incidence of Glut1DS is 1.65-2.22 per 100,000 births[2]. This figure is considered to be a huge underestimate as the condition remains largely undiagnosed, often misdiagnosed or unrecognised[4].

Phenotype

Glut1DS was first discovered in 1991 by Dr De Vivo[1]. Since, the condition is now considered a spectrum of disorders as the clinical presentation can vary significantly, including atypical phenotypes[8,9]. The classical phenotype presents with the trias of early-onset epilepsy, developmental delay, and a complex movement disorder:

Epilepsy – seizures are the most common symptom. In the vast majority of cases, they occur in infancy. Seizures are unresponsive to antiepileptic medication but respond to KDT[9]. For some children, seizures develop later at the age of two to four years of age and in some cases, epilepsy doesn't develop at all[4]. When present, seizures may be of any type but usually myoclonic and, atonic,[2] can be a daily occurrence for some but for others can be separated by days, weeks or even months[5].

Developmental delay – varying degrees of cognitive impairment, ranging from mild learning disabilities to severe intellectual disability, often exacerbated by delays in diagnosis and treatment are common[5]. Speech and language impairment is usually present with infants experiencing both speech delays, dysarthria, and dysfluency[4]. Cognitive dysfunction persists throughout life although there is no evidence for progressive worsening[2].

Movement disorder – permanent movement disorders include impairment of balance, coordination, limb movements, and gait resulting from elements of hypotonia, ataxia, spasticity, and dystonia[5]. Paroxysmal movement disorders affect approximately 75 per cent of patients[2]. Episodes include sudden loss of posture or gait control, dizziness, and emotional disturbances and are often triggered by fasting or exercise. They often resolve on 20-30 min rest. Abnormal paroxysmal eye-head movements may be noticed before the seizures start and are considered specific for Glut1DS[2]. Sometimes referred to as 'aberrant gaze saccades', early recognition of these particular ocular movements could enable early diagnosis and treatment initiations, significantly improving prognosis and neurological development[10,11].

Glut1DS symptoms develop in an age-specific pattern. Seizures are predominant in infants and young children and tend to decline or disappear in later childhood, to be replaced by movement disorders and dysarthria as the predominant clinical feature in adolescents and adults[2]. Deceleration of head growth is seen in some patients[2].

International Glut1DS study group conclusions on the clinical features of Glut1DS[2]

The Glut1DS phenotype changes with advancing age. Clinical features consistent with Glut1DS include the following:

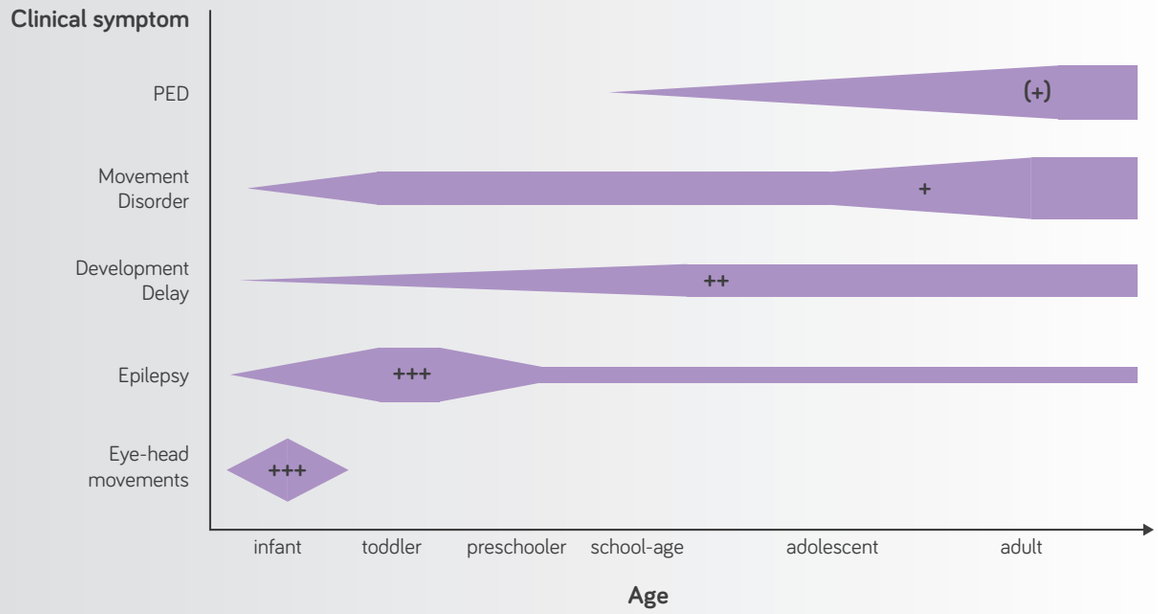
- Any unexplained movement disorder with spasticity, dystonia, and ataxia
- Complete seizure control by KDT in children with drug-resistant epilepsy
- Unexplained paroxysmal events at any age
- Early-onset absence epilepsy (under 4 years of age)
- Myoclonic-atonic epilepsy (Doose syndrome)

Paroxysmal eye-head movements in infancy were felt to be specific for Glut1DS.

Diagnosis

Diagnosis of Glut1DS rests on i) characteristic clinical symptoms, ii) low glucose concentrations in the cerebrospinal fluid (CSF) termed hypoglycorrhachia and determined by lumbar puncture, and iii) pathogenic *SLC2A1* variants.

Figure 1: Glut1 Deficiency Syndrome: Phenotype[2]



Legend: PED: paroxysmal exercise-induced dystonia
Response to KDT: **+++** very good, **++** good, + reasonable, **(+)** poor

International Glut1DS study group conclusions on the diagnosis of Glut1DS[2]

Glut1DS diagnosis is confirmed by presence of characteristic clinical features, hypoglycorrhachia documented by lumbar puncture, and genetic analysis showing pathogenic *SLC2A1* variants.

Investigations

CSF – CSF glucose is gender-independent, but age-specific. Low CSF glucose (hypoglycorrhachia) in Glut1DS ranges from 0.9 to 2.8 mmol/L (16.2 to 50.5 mg/dL). The CSF glucose/blood glucose ratio varies from 0.19 to 0.59.45. CSF lactate levels are always low-to-normal differentiating this condition from other diseases resulting from impaired brain energy metabolism.

EEG - interictal EEG often is normal. Focal slowing or epileptiform discharges are more prevalent in infants, generalized 2.5- to 4-Hz spike-wave patterns in school-age children. Abnormal fasting EEGs sometimes improve on food intake reflecting impaired glucose availability in Glut1DS when fasting.

Neuroimaging - nonspecific cranial MRI findings can be observed in about 25 % of patients.

Diagnostic algorithm

The heterogeneity of symptoms makes the diagnosis of Glut1DS challenging – therefore an algorithm based on the three key diagnostic criteria was developed characterizing diagnostic probability in confirmed, probable, possible or negative (table 1).

Table 1: Probability for Glut1DS diagnosis based on three key diagnostic criteria: characteristic clinical features, definite hypoglycorrhachia, and pathogenic SLC2A1 variants[2]

Symbol	Diagnosis	Start KDT
√√√	Confirmed	Yes
√√	Probable	Yes
√	Possible	Consider
X	Negative	Not required

Hypoglycorrhachia \ Characteristic clinical features	+	–	Pathogenic *SLC2A1*-variant
+	√√√	√√	+
+	√√	√	–
–	√	√	+
–	X	X	–

KETOGENIC DIET THERAPIES (KDT) ARE THE GOLD STANDARD TREATMENT FOR GLUT1DS

Since the discovery of Glut1DS in 1991, KDTs have been well-established as the standard of care and the only known successful therapy to significantly improve quality of life and long-term outcome. Ketones generated from nutritional fat provide alternative fuel for the brain. The KDT effectively controls seizures and improves movement disorder and cognitive issues (see figure 1). Consequently, KDTs should be initiated as early as possible. Early KDT initiation predicts better cognitive outcome and results in better intellectual and social adaptive skills.

KDTs for Glut1DS are a lifelong therapy. In contrast to KDT for children with intractable epilepsy, the recommendation for KDT in Glut1DS extends into adulthood despite its difficulties.

International Glut1DS study group conclusions on the therapy of choice for Glut1DS[2]
Ketogenic diet therapies remain the treatment of choice for Glut1DS and should be started as early as possible.

No effective pharmacological treatments exist

Epilepsy in Glut1DS does not respond to antiseizure medication. As seizures are often the presenting symptom, many infants are treated unsuccessfully with antiseizure medication, contributing to the long-term disease burden. Ineffective medications may do harm and there are concerns regarding possible interactions with KDT. The available data is very limited and currently no recommendation for any antiseizure medication in the management of Glut1DS can be made. Other such as triheptanoin for which expectations were high failed to demonstrate efficacy in two significant phase 3 trials. Therefore, the best and only effective treatment for Glut1DS remains KDT. Such is its effectiveness that the international Glut1DS study group concluded that KDT, the current standard of care for Glut1DS, should not be discontinued in favour of clinical trials that are designed to investigate novel treatments[2].

International Glut1DS study group conclusions on pharmacological treatments for Glut1DS[2]

- Currently, there is no basis to recommend any antiseizure drug in the management of Glut1DS, and there are concerns regarding potential harmful interactions.
- No recommendations can currently be made regarding effective paroxysmal exercise-induced dyskinesias (PED) treatment or the use of oral ketones or keto esters.
- Discontinuing KDT, the current standard of care for Glut1DS, in favour of clinical trials that are designed to investigate novel treatment considerations was rejected strongly by the group.

About the classical ketogenic diet therapy (KDT)

KDT is established internationally as a non-pharmacological intervention in children and adults with drug resistant epilepsy since the 1920s[12]. It is a high-fat, carbohydrate restricted diet with a fat to carbohydrate and protein ratio of 3:1 or 4:1, although a 3:1 ratio is preferable for infants in order to provide adequate protein to support optimal growth[12].

In the treatment of Glut1DS specifically, KDT raises levels of ketones such as β-hydroxybutyrate and acetoacetate - substitutes for brain glucose - in blood and brain[12,13]. Maintaining the highest degree of ketosis is recommended as it improves brain energy metabolism[2].

About the modified Atkins diet (MAD)

The modified Atkins diet (MAD) achieves a ketosis similar to a 1:1 ratio classical KDT. It is less high-fat and carbohydrate restricted and as such easier to adhere to, but also requires supplements and medical supervision. MAD limits carbohydrates and encourages fat intake but doesn't require the same weighing and measuring of foods as classical KDT making it a viable option for those finding classical KDT difficult to maintain long-term[2,12].

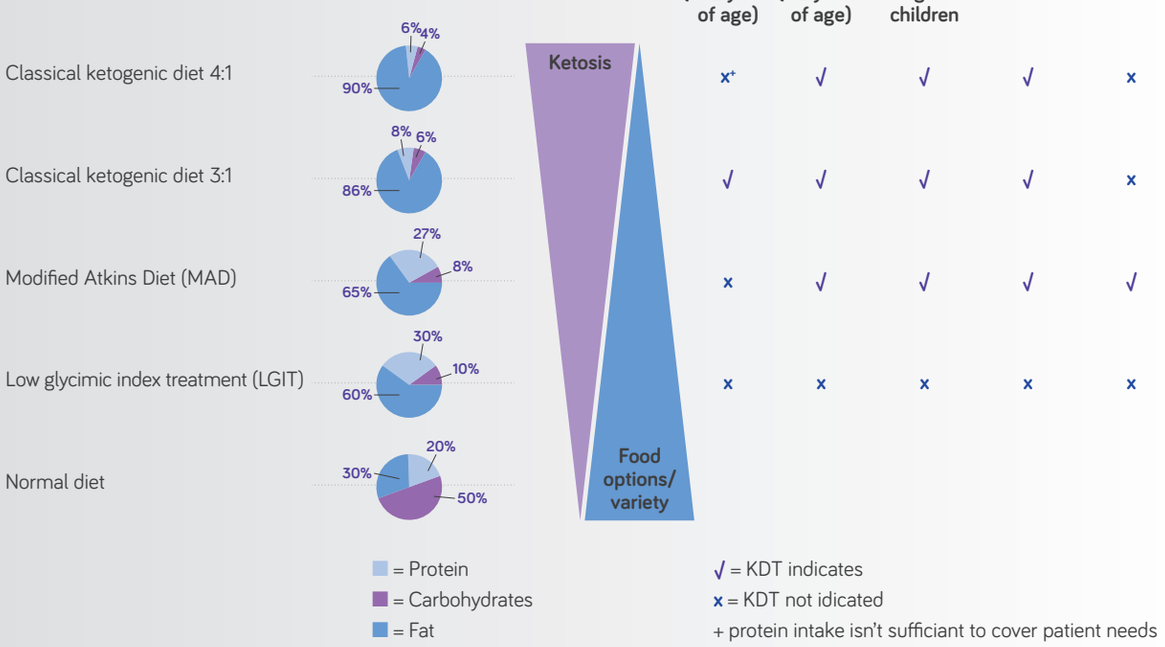
About the low glycemic index treatment (LGIT)

The low glycemic index treatment (LGIT) liberalizes carbohydrate restriction but restricts the type of carbohydrate-containing foods to those that produce relatively small changes in blood glucose (glycemic index < 50)[14]. It does not produce a significant degree of ketosis and therefore is not recommended for Glut1DS but has proven effective in the treatment of intractable childhood epilepsy.

Which diet is best for Glut1DS?

Children and adults have distinct needs including age-specific brain energy requirements. Classical KDT typically provide higher levels of ketosis to meet the higher energy demand of the developing brain in younger children. Adolescents and adults may require a more feasible, less restrictive approach for quality of life and to aid compliance[15].

Figure 2: Varying the dietary interventions of Glut1DS patients by age[15]



Adapted from the Ketogenic Diet Guildelines - Germany

International Glut1DS study group conclusions on the adaptation of KDTs for Glut1DS[2]

- In children under age two years, a classical 3:1 KDT is the treatment of choice.
- A classical KDT should be continued, for as long as it can be tolerated, to obtain a high degree of ketosis to meet the energy demands of the developing brain.
- For adolescents, adults, and noncompliant patients, the MAD provides a good alternative to the classical KDT.
- LGIT is not recommended as a management option for Glut1DS because it provides very low ketones and has no evidence of benefit in Glut1DS.

TREATMENT OF GLUT1DS WITH KDT

Ketogenic diet therapy (KDT) should be started as early as possible

The international consensus statement highlights that for Glut1DS 'the importance of early diagnosis and treatment cannot be exaggerated'[2]. It recommends that in classic cases KDT should be started as early as possible postnatally with the highest degree of ketosis maintained to mitigate brain energy deficiency by providing optimal concentrations of metabolic fuels (glucose and ketones) to the developing brain[2].

When administered early during the course of the disease, KDT attenuates the seizures associated with Glut1DS[16]. Data published in the last few years demonstrates that timing of KDT initiation is a predictive factor of cognitive outcome, confirming that the earlier introduction may prevent the onset of all Glut1DS symptoms including epilepsy, movement disorders and cognitive impairment[17]. Furthermore, a delay in the management of Glut1DS with KDT could lead to progressive neurological deterioration[13]. Consequently, KDT should be initiated KDT if Glut1DS is suspected - even if a diagnosis has not been confirmed (see table 1)[2].

Table 2: Summary of KDT treatment recommendations for Glut1DS from the international Glut1DS study group consensus[2]

Treatment recommendations for KDT in Glut1DS	
Initiation	At diagnosis, any age, as early as possible
Duration	Into adolescence/adulthood
Ketosis and KDT ratio	As high as tolerated
LGIT	Not recommended
Monitoring ketosis	Blood ketones
Carnitine levels	Recommended
Monitoring side effects	(+++)

Data shows that KDT in Glut1DS achieves excellent seizure control without antiepileptic drugs. In recent reports 60 % of patients became seizure-free after the implementation of KDT and in 80 % movement disorders improved[13]. The earlier the treatment with KDT the better the outcome[2,18].

Ketogenic diet therapy and breastfeeding

Previous recommendations suggested that infants be weaned before starting KDT. More recently this view has changed. Studies demonstrated the benefits of the early introduction of KDT together with the feasibility, effectiveness, and safety of simultaneous breastfeeding[19] by either calculating the amount of breastmilk into a 3:1 formula or potentially allowing it briefly on demand[12].

Efficacy of KDT for Glut1DS

KDT is effective and safe to use in infants. The latest recommendations from the international Ketogenic Diet study group highlight the increasing evidence for KDT across all epilepsy conditions. In specific epilepsy syndromes and metabolic conditions, including GLUT1DS, it is either the treatment of first choice or should be introduced very early[12].

Efficacy of KDT varies individually in Glut1DS, depending on phenotype, genotype, and time of diagnosis and initiation of KDT. In general, paroxysmal eye-head movements and seizures respond very well to KDT, with some studies demonstrating a >90 per cent reduction in seizures in 80 per cent of patients. There is also increasing data that intellectual development benefits from early KDT. The complex movement disorder also responds to KDT on an individual basis, but often symptoms are mitigated, not absent. The paroxysmal exercise-induced dystonia (PED) often increases with the onset of puberty despite KDT and remains the predominant problem in adult Glut1DS. (see also figure 1)[2].

Duration of KDT intervention for GLUT1DS

KDT for GLUT1DS should be used lifelong[2]. As a minimum it should certainly be maintained throughout childhood and teenage years, when a MAD can be considered to aid compliance[2].

Side effects and monitoring

Supplements are essential to avoid potential side effects and vitamin and mineral deficiencies as a result of KDT. Generally short-term adverse effects such as constipation or low/high ketosis are usually mild and easy to treat[2]. Long-term KDT in Glut1DS may generate more evident side effects such as kidney stones, dyslipidaemia, and growth retardation[2]. Dyslipidaemia may be transient and cardiovascular (CV) risk apparently does not increase with long-term KDT[13].

Monitoring should include anthropometric parameters (weight, height, BMI, blood pressure), blood tests (full blood count, liver and renal parameters, fasting lipids), ECG, EEG, renal ultrasound and carotid doppler at the age of 10 years at regular intervals, mostly biannual)[2].

International Glut1DS study group conclusions on management in Glut1DS[2]

There was general agreement that patients should be monitored regularly for long-term side effects of KDT such as kidney stones, growth retardation, and cardiovascular disease (blood pressure, fasting lipid profiles, carotid Doppler ultrasound from age 10 years). Long-term use of KDT in Glut1DS might generate long-term adverse effects not observed in the shorter-term use of KDT for drug-resistant childhood epilepsy.

Dietary supplement to support the use of ketogenic diet therapies in Glut1DS

Ketogenic infant formulas to support KTD

Ketogenic formulas are a valuable component of successful KDT[20,21,22] and can improve compliance and tolerability across all age groups[23]. The development of readily available, specific ketogenic formulas used as supplement of as a sole source of nutrition have facilitated the use of KDT. They provide a complete nutritional source and support the maintenance of consistent KDT ratios, be it 4:1 or 3:1 or MAD[20].

In Glut1DS, KDT initiation is recommended as early as possible to improve outcomes and avoid progressive neurological deterioration[2]. Ketogenic infant formulas can simplify and aid KDT initiation in infants and can be given orally as a bottle or tube feed. Indicated from 0 - 3 years of age and specifically developed to meet the nutritional requirements of very young patients, it can be combined with breastmilk and breastfeeding[19]. Multiple studies have shown ketogenic formulas to be safe, efficacious, and well tolerated by this age group.[21,22,24,25]

Other age groups

If possible, Glut1DS patients should follow a KDT for life[2]. Throughout life nutritional requirements change, requiring variations to the fat to carbohydrate and protein ratios and supplements throughout any age.

With increasing age there are times when consistent strict compliance to KDT is a challenge. Compliance is easier in younger children who develop their sense of taste and whose food intake is managed by parents or caregivers. Food preferences, social interactions, kinder garden and school as well as peers and other external influences increase with age making compliance with KDT challenging. Often several reasons require a less restricted diet. Available formulas can support the maintenance of KDT and boost ketosis in MAD[20] or some specifically meet the requirements of older children and adults. MCT (medium-chain-triglycerides) based products provide more ketones than long-chain triglycerides (LCT) enabling less restricted carbohydrate intake therefore making KDT more sustainable in the long term[26].

Summary points from Glut1 Deficiency Syndrome (Glut1DS): State of the art in 2020 and recommendations of the international Glut1DS study group[2]

- Early Glut1DS diagnosis is confirmed by characteristic clinical features, low CSF glucose, and pathogenic *SLC2A1* variants.
- Clinical features and treatment responses change with advancing patient age. Best outcomes correlate with early treatment.
- Age-specific ketogenic diet therapies remain the standard of care.
- Ongoing challenges are continuity of care during transition to adulthood, paroxysmal dyskinesias, intolerance to ketogenic diet therapies, and potential long-term complications.
- Future therapies will focus on small molecule restoration of Glut1 protein/function, supplemental metabolic augmentation, and *SLC2A1* transfer strategies.

Further information

For further information please refer to:

Glut1 Deficiency syndrome (Glut1DS): state of the art in 2020 and recommendations of the international Glut1DS study group led by Joerg Klepper et al. and accessible here:
https://onlinelibrary.wiley.com/doi/full/10.1002/epi4.12414

Optimal clinical management of children receiving dietary therapies for epilepsy; updated recommendations of the international Ketogenic Study Group led by Eric Kossoff et al. accessible here:
https://onlinelibrary.wiley.com/doi/full/10.1002/epi4.12225

GLUT1 DEFICIENCY SYNDROME (GLUT1DS)
An overview

Rare genetic metabolic disorder

- A faulty gene prevents transport of glucose, trough the blood-brain barrier[1]
- Glut1 is encoded by *SLC2A1*, on chromosome 1 (1p35-31.3)[1]
- Mostly caused by a spontaneous gene mutation, and is mostly inherited in an autosomal dominant manner[1]
- Incidence 1.65 – 2.22 per 100,000 births[1] (probably more often[2])

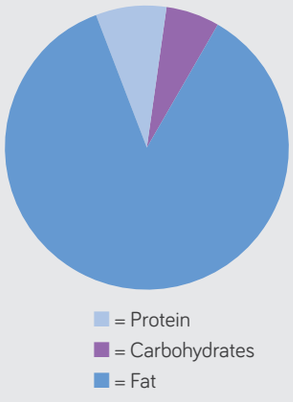
Many different presenting features makes diagnosis difficult

- Most common are[1]:
  - Paroxysmal eye-head movements in infancy
  - Early-onset epilepsy
  - Complex movement disorders predominantly with spasticity, dystonia and ataxia
- Diagnosis[1]:
  - Presence of clinical features
  - Hypoglycorrhachia (= low CSF glucose) documented by lumbar puncture
  - Pathogenic *SLC2A1* variant identified via genetic analysis

KETOGENIC DIET THERAPY
Standard of care in GLUT1DS

Only therapy to significantly improve quality of life and long-term outcomes[1]

- Ketones provide an alternative fuel for the brain
- Effectively controls seizures
  - >90% reduction in 80% of patients
- Improves movement disorders and cognitive issues



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KDT should be started as early as possible and is for life[1]

- Resulting in better long-term outcomes including intellectual and social adaptive skills[1]
- Delayed diagnosis and treatment can significantly affect outcomes and can result in irreversible brain disfunction[1] and progressive neurological deterioration[3]

There are no specific pharmacological treatments[1]

- Epilepsy in Glut1DS does not respond to antiseizure medication
- Many infants are initially treated with antiseizure medication but these can do more harm than good and can be withdrawn again under KDT

KTD can be adapted for different life stages[1]

- A classical KDT obtains the highest degree of ketosis to meet the energy demands
- In infants a 3:1 KDT is the treatment of choice
- For adolescents, adults and noncompliant patients the modified Atkins diet (MAD) provides a good alternative
- No other variations or diets have been shown to be effective

Life-long use of KDT is safe however, regular monitoring is recommended

- Side effects usually mild and easy to treat[1]
- Dyslipidaemia shown to be mostly transient[3]
- Long-term cardiovascular risk presumably doesn't increase with long-term KDT[3]
- More studies needed to understand impact of KDT on height[3]

DIETARY FORMULA FOOD TO SUPPORT KDT IN GLUT1DS

Can improve compliance and tolerability increasing treatment efficacy[4]

- Provide an invaluable nutritional source[5]
- Support maintenance of correct KDT 4:1 or 3:1 ratios and MAD[5]
- Simplify and aid initiation in infants[4]
- Can be given orally, as a bottle or tube feed[4]
- Are diets of choice in patients with PEG

Nutricia has a portfolio of products to support effective KDT in patients with Glut1DS throughout their life

The Ketogenics range offers evidence-based complete nutritional solutions, aiding compliance and ensuring nutritional requirements are met and correct ratios maintained.

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NOTES


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