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Dietary Treatments and New Therapeutic Perspective in GLUT1 Deficiency Syndrome

Pierangelo Veggiotti, MD[1,2,*]
Valentina De Giorgis, MD[2]

Address
*,[1]Department of Child Neurology and Psychiatry C. Mondino National Neurological Institute, Via Mondino, 2, 27100, Pavia, Italy
Email: pveggiot@unipv.it
[2]Brain and Behaviour Department, University of Pavia, Pavia, Italy
Email: valentina.degiorgis@mondino.it

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Opinion statement

GLUT1 deficiency syndrome (GLUT1DS) results from impaired glucose transport into the brain: awareness of its wide phenotypic spectrum is a prerequisite in order to ensure an early diagnosis, treating the patients is the subsequent challenge to allow prompt compensation for the brain's lack of fuel. The ketogenic diet (KD) plays a primary role in the treatment of GLUT1DS because it provides ketone bodies as an alternative source to meet the demands of energy of the brain. Therefore, we recommend early initiation of the KD based on the assumption that early diagnosis and treatment improves the long term neurological outcome: the classic KD (4:1 or 3:1) at the present time is the most proven and effective in GLUT1DS. A KD should be continued at least until adolescence, although there are reports of good tolerability even in adulthood, possibly with a less rigorous ratio; in our experience seizure and movement disorder control can be achieved by a 2:1 ketogenic ratio but the relationship between ketosis and neurodevelopmental outcome remains undetermined. Other types of KDs can, therefore, be considered. The Modified Atkins diet, for example, is also well tolerated and provides effective symptom control; furthermore, this diet has the advantage of being easy to prepare and more palatable, which are important requirements for good compliance. Nevertheless, about 20 % of these patients have compliance trouble or the same diet loses its effectiveness over time; for these reasons, new therapeutic strategies are currently under investigation but further studies on pathophysiological mechanisms and potential effects of novel "diets" or "therapies" are needed for this new pathology.

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Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is caused by impaired glucose transport across the blood brain barrier and into astrocytes, due to heterozygous mutations in the SLC2A1 gene (1p34.2) encoding the glucose transporter GLUT1. GLUT1 is a membrane-bound glycoprotein that provides base rate glucose transport across blood-tissue barriers. It is expressed in erythrocytes, brain microvessels and astroglia, and is exclusively responsible for glucose transport to the brain across the blood-brain barrier [1]. The defect in this transporter results in low levels of glucose in the cerebrospinal fluid, hypoglycorrhachia. The brain is a highly energetic organ; in an adult, although the brain represents only 2 % of the body weight, it receives 15 % of the cardiac output and accounts for 20 % of total body oxygen consumption, and 15 % of total body energy glucose utilization.

GLUT1DS was first described in 1991 in two patients with intractable epilepsy, global developmental delay, movement disorder and acquired microcephaly [2]. During the past few decades, it has been increasingly evident that there is a great variation in the clinical presentation of GLUT1DS [3–5]. Now clinical presentation of these patients could vary from paroxysmal exercise-induced dyskinesias with or without epilepsy [6, 7], cognitive impairment, and other various carbohydrate-responsive symptoms [8, 9].

Clinical severity varies from mild motor dysfunction to severe and diffuse neurological disability. The phenotype varies according to the age at onset; epilepsy is more frequent in children, whereas movement disorders are the main manifestations in adults [10•].

The clinical spectrum of GLUT1 deficiency is important to know for clinical practice since the disease is potentially treatable. Likewise, diagnostic delays are deleterious [11]. To date, more than 200 patients have been identified [12], but a large number of patients might be undiagnosed due to the pleiotropic and complex phenotype.

Lumbar puncture, a simple investigation, is the first diagnostic step, mutational analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene should be performed in patients with highly suggestive clinical findings and low cerebrospinal fluid glucose (<50 mg/dl or ratio <0.60) [10•].

Treatment

The diagnosis of GLUT1DS is often made late, much later than the onset of clinical manifestations such as seizures and mental retardation; for this reason, seizures are often treated with a number of antiepileptic medications.

When the diagnosis is established, the KD represents the first choice of treatment in GLUT1DS patients. It has been demonstrated to be effective in the control of epileptic and movement disorders [11, 13, 14••, 15, 16].

A KD is more important to provide sufficient metabolic fuel to support optimal brain growth and development during infancy and childhood.

An accurate clinical evaluation is the starting point in order to define the therapeutic strategy. It is crucial to determine the major symptoms that are determinants in patients' quality of life.

The KD needs close monitoring by a multidisciplinary team, including neurologists and trained dieticians.

The KD represents the first choice of treatment in GLUT-1 patients. However, about 20 % of these patients have compliance trouble or the same diet has lost its effectiveness over time; for these reasons new therapeutic strategies must be identified. Furthermore, another important question should be solved: how long can the diet be continued without creating any side effects? All these issues will be dealt with in separate chapters and the overall strategy will be discussed in the conclusion.

Ketogenic diets

The KD is the gold standard treatment for GLUT1DS. When the glucose supply is insufficient, ketone bodies are the only relevant alternative fuel source for brain metabolism. A KD is a high-fat, adequate protein, carbohydrate-restricted diet that mimics the metabolic state of starvation, in which glucose metabolism is switched to ketone bodies metabolism. The diet forces the body to burn fats rather than carbohydrates, thereby producing ketone bodies to penetrate the blood-brain barrier and serve as alternative fuel for the brain metabolism.

Classic KD

Basically, the diet consists in 3 to 4 g of fat – depending on the age of the patient – to every 1 g of carbohydrate and protein combined (classic 3:1 or 4:1 KD). This is achieved by excluding high-carbohydrate foods, while increasing the consumption of high-fat foods that provide 87 – 90 % of daily calories. To date, most patients with GLUT1DS are treated with the classic 3:1 or 4:1 KD. In infants below the age of 2 years, a 4:1 KD can be more effective in stimulating ketosis but might not provide sufficient protein for growth [17•]; our experience enables us to affirm that a 4:1 KD could be effective in severe phenotype infants, a 3:1 ratio should be proposed in mild phenotype in infants, and in mild and severe phenotype of all ages [10•, 18••].

Originally, patients were made to fast for the initiation of the diet; calories as well as fluid were restricted and the diet was started in a hospital setting [19]. In 2004, Kim et al. [16] showed that initial fasting and fluid restriction are not essential for the KD and that the tolerability of this treatment may be improved by not fasting. Despite these changes, the strict limitation of both carbohydrates and proteins and the high fat content in the classic KD prove it difficult to produce tasty and variable meals. The diet is a genuine medical nutrition therapy and should follow a well-defined protocol of introduction and maintenance. A discipline is needed to maintain the KD and it is often a challenge to maintain compliance to the diet.

For this reason, in the last few years, several "novel" KDs have been developed: the medium chain triglyceride (MCT) KD, the Modified Atkins diet (MAD), and the low glycemic index treatment (LGIT).

Medium chain triglyceride KD

The MCT KD uses more ketogenic triglycerides so the fat-to-carbohydrates and protein ratio could be lowered approximately to 1,2:1 and be more palatable. However, the MCT diet has potential gastrointestinal side effects, and clinical experience, especially in GLUT1DS, is limited.

Modified Atkins diet

The MAD is relatively new [20] and it could be a less restrictive alternative to the traditional KD. It could be started as an outpatient treatment, without fasting, it allows unlimited proteins, about 10 g of carbohydrates with a fat-to-nonfat 1:1 ratio. The ketosis achieved is significantly lower

than classic KD but a comparable efficacy has been demonstrated [21•] also in GLUT1DS patients [5, 22]. Moreover, the acceptance of this diet is higher as the daily management and the choice of dietary foods is easier, and the taste is improved.

Low glycemic index treatment

Unlike diets previously described, LGIT liberalizes the carbohydrate restriction and selects the type of carbohydrate-containing food to those that produce relatively small changes in blood glucose [23]. Of all ketogenic diets the LGIT achieves the lowest ketosis and the best tolerability, but there are still limited data on the comparable efficacy to the classic KD [18••], especially on GLUT1DS.

Mechanism of action

Although, in epilepsy, the mechanism of action underlying the effectiveness of the KD is not yet clear [24••], in GLUT1DS it essentially provides an alternative fuel source. The effectiveness of the KD in GLUT1DS might be enhanced by its anticonvulsant action.

So far, the symptom domain in which the effect of the KD has been most systematically assessed is the control of seizures. The majority of patients with seizures experience an improvement in seizure control on initiation of the KD [5, 14••, 15, 25]. The vast majority of GLUT1DS patients obtain seizure freedom with the classic 4:1 or 3:1 formula, allowing anticonvulsant therapy to be withdrawn [26]. The improvement is often rapid. In a retrospective study by Pong et al. [14••], two-thirds of the 41 patients who experienced a complete resolution of seizures (28/41) did so within 1 week of diet initiation.

The KD also has a positive effect on another peculiar symptom of GLU1DS: the paroxysmal movement disorder and, in particular, paroxysmal dyskinesia (PED), which has been reported to respond very well to the diet [5, 13, 27, 28].

The effect of the KD on other motor and cognitive symptoms is more variable, and has been characterized in less detail than the seizure or PED response. A clear improvement in motor symptoms has been documented in individual patients with persistent movement disorders, including chorea, dystonia, and ataxia [29, 30•]. However, the benefit is not universally observed [5].

The impact of KD treatment on developmental delay appears to be less prominent [4]. However, many parents noticed an improvement on their child's alertness, activity, attention and concentration upon starting the KD, probably due to an increased availability of fuel to burn in the central nervous system. However, the effect on cognition in the long term has been harder to quantify and distinguish from the benefit attributable to the control of refractory seizures. The literature contains numerous reports of improved psychomotor impairment, but these are hard to verify in case–control

studies, and further studies are needed to understand better the mechanism of action of the diet.

Our own experience has shown that introduction of the KD in the first years of life in patients with GLUT1DS guarantees a better cognitive outcome. As the developing brain in the young child requires more energy, the KD should be started as early as possible whenever GLUT1DS is suspected. There are also reports of voluntary intake of large amounts of fat-containing food in patients subsequently diagnosed as GLUT1DS [31].

Finally, there are patients in which the KD was not fully effective [29, 32]; side effects related to the KD occurred, such as elevated blood lipids or growth retardation, or there were significant compliance problems in adolescence or simply resulting from years on a strict KD. Here, MAD could be considered an attractive option and several recent report on GLUT1DS showed its efficacy [21•, 22, 33, 34].

However, further studies on pathophysiological mechanisms and potential effects of novel "diets" or "therapies" are needed for this recently new pathology.

Treatments other than diet

Antiepileptic drugs

Medications remain an additional strategy for controlling seizures in patients with milder symptoms. Phenobarbital, valproate, carbamazepine, lamotrigine, topiramate and clonazepam are the most frequently used antiepileptic drugs (AEDs) [35].

However, in GLUT1DS, seizures are typically refractory to medical treatment. Only 8 % of patients may reach seizure freedom with antiepileptic drug treatment alone [14••].

Recently, many patients are diagnosed in adulthood as family members of young GLUT1DS. These subjects often have minimal symptoms (e.g., infrequent seizures); for them, an AED treatment, without introduction of a KD, is sufficient to manage their disease.

Moreover, it should be kept in mind that in GLUT1DS, certain antiepileptic drugs have the potential to exacerbate seizures. For example, barbiturates can competitively inhibit the GLUT1 transporter [36] and result in increased seizure frequency. Conversely, transient improvement in seizures and EEG findings have been described during the postprandial phase [37].

Drugs potentially altering GLUT1 function should be avoided, including caffeine, phenobarbital, diazepam, valproate and tricyclic antidepressants [4, 38]. However, in our experience, we have not noticed worsening of symptoms under these drugs (especially valproic acid).

Acetazolamide

Paroxysmal dyskinesias have been reported to respond well to treatment with acetazolamide in some cases [11, 18••, 30•, 39, 40]. This may be an

alternative treatment for dyskinesias when compliance with the diet is difficult. In any case, medications do not correct inadequate nourishment necessary for brain growth and development, the central mechanism underlying the GLUT1DS. Fuel availability remains central to the optimal long term outcome in this treatable clinical condition.

Other

Appropriate rehabilitation may include physiotherapy, speech therapy and occupational therapy. It is important to prevent complications and to promote school or professional integration and mixing with peers.

New perspectives

Alpha lipoic acid

Alpha lipoic acid and triheptanoin have been also proposed as treatment options in GLUT1DS.

Alpha lipoic acid is an antioxidant that serves as a co-enzyme in energy metabolism. It neutralizes free radicals, improves cellular glucose uptake by stimulating the insulin signal cascade, reduces inflammation, and binds with metals. Its supplementation has been recommended in GLUT1DS on the basis of the observation that it improves glucose transport in cultured muscle cells via mobilization of the GLUT4 transporter from intracellular pools [14••, 41]; however, to date, there are no published data in humans to demonstrate its effectiveness.

UX007

UX007 (triheptanoin) is a triglyceride that has been used as an anaplerotic substrate in humans to treat inherited metabolic diseases such as pyruvate carboxylase deficiency [42] and carnitine palmitoiyltransferase II deficiency [36]. The rationale for UX007 in GLUT1DS is that triheptanoin is metabolized to heptanoate, and C4 and C5 carbon compound ketone bodies that easily cross the blood–brain barrier via monocarboxylate transporters and may enhance the effect of the regular ketones as an alternative fuel for the brain [43, 44]. It could provide anaplerotic substrates to resupply intermediates of the tricarbocylic acid (TCA) cycle and it can support gluconeogenesis in the brain.

Nonclinical studies evaluating UX007 and its metabolites in mice and rats have been published. Triheptanoin was effective in four animal models of epilepsy, similar to that of other AEDs [45–48]. Until now, approximately 150 subjects with various diseases have been treated with triheptanoin during the last decade and 30 GLUT1DS subjects are in an ongoing clinical trial (no published data).

Triheptanoin treatment allows for greater carbohydrate intake and higher serum glucose levels relative to KD and thus does not exacerbate the deficiency of glucose transport into the brain.

Optimal therapeutic management

An early diagnosis of GLUT1DS is a prerequisite in order to obtain adequate treatment. If the diagnosis is delayed, patients have a higher risk of developing symptoms such as seizures or movement disorders and an irrecoverable cognitive delay. In fact, in GLUT1DS, seizure control is not the only treatment goal. It is more important to provide sufficient metabolic fuel to support optimal brain growth and development during infancy and childhood.

The KD is the mainstay of therapy in GLUT1DS. It provides an alternative source of fuel for the brain in order to support both brain growth (which is particularly vital in the first decade of life) and the normal neuronal function thereby controlling symptoms. We recommend early initiation of the KD based on the assumption that early diagnosis and treatment improves the long term neurological outcome; the classic KD (4:1 or 3:1) at the present time is the most proven and effective in GLUT1DS (Fig. 1).

The diet is a genuine medical nutrition therapy and should be followed with the same care as other antiepileptic drugs (AEDs). Because of the particularity and multidisciplinary nature of the therapy, a team composed of a neurologist, a dietician, a nurse and a pediatrician is needed to obtain proper management [49•].

It remains unclear whether a rigorous KD is essential in GLUT1DS. Discipline needed to maintain the KD is often challenging for patients and compliance to the diet is difficult to maintain. To avoid compliance difficulties, a gradual reduction of the ketogenic ratio should be considered, and frequently it can be achieved without loss in effectiveness; in our experience seizure and movement disorder control can be achieved by a 2:1 or 3:1 ketogenic ratio but the relationship between ketosis and neurodevelopmental outcome remains undetermined.

Other types of KDs can, therefore, be considered. The MAD, for example, is also well tolerated and provides effective symptom control; furthermore, this diet has the advantage of being easy to prepare and more palatable, which are important requirements for good compliance. On the contrary, there are no data about the LGIT in GLT1DS and studies are needed to investigate the possible effectiveness of this treatment. Finally, we have little direct experience with MCT therapy and, therefore, cannot express an opinion on this option. We feel that MCTs could be integrated into the above diets to make them more manageable; however, it is not our practice to use only MCTs in our drug-resistant epilepsy or GLUT1DS patients. Factors such as age, epilepsy type, lifestyle, and resources also increasingly encourage the use of novel ketogenic diets. When we are faced with loss of compliance and long-term side effects, a novel KD might be better than no diet at all.

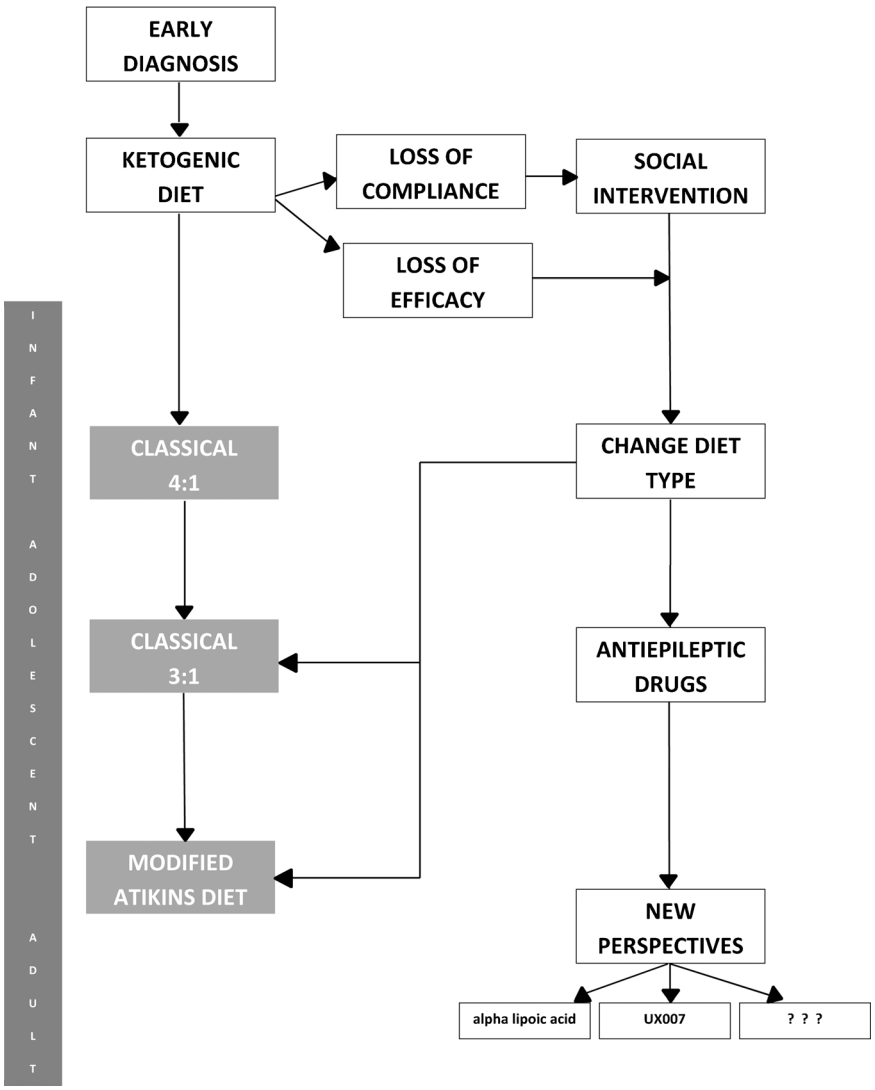

Fig. 1. Optimal therapeutic management in GLUT1DS

KD treatment can be useful in adulthood, too, because the KD might exert neuroprotective effects; low glucose concentrations in the CSF can lead to oxidative DNA damage and lipid peroxidation. Chronic ketosis limits the generation of reactive oxygen species and boosts energy reserve capacity, which is important in sustaining the electrophysiological activities essential for performing brain function [10•]. For these reasons, if there are no serious side effects, we recommend lifelong KD treatment in GLUT1DS patients: the classic ketogenic diet (3:1 ratio) for children and symptomatic adults, and MAD (or other "new" diets) for adolescents and adults with minimal symptoms. The change from one diet to another in case of ineffectiveness or lack of compliance should be done after at least 6 months from the start of the KD.

In our experience, the main difficulty with compliance is represented by those families in which multiple subjects are affected by GLUT1DS, so

even parents frequently have a lower cognitive level. In these families, the dietary management often becomes complicated, compliance is poor and, therefore, the response is insufficient.

In these cases - about 15 % of our patients - a multidisciplinary trained team is often not sufficient given the particular day to day management of KD; collaboration, helpfulness and a proper preparation of the family, with social intervention and possibly support by the family associations, is essential for a positive outcome (Fig. 2).

Moreover, in recent years, we found a significant number of patients who do not respond to the KD; seizures, movement disorders and/or paroxysmal events persist despite adequate ketosis. Particularly, in our experience, we have also noticed that over the years the KD may lose its effectiveness, especially with regard to epileptic symptoms. The reason why is hard to explain; the original concept that brain energy failure is reversible by means of a ketogenic diet with adequate ketosis apparently is far too simplistic. There is more to GLUT1DS than just cerebral energy failure [17•].

Non-specific drugs may be used for the pharmacological treatment of the residual symptoms but their effects are often disappointing. Lamotrigine, carbamazepine, phenytoin and zonisamide may be preferred to treat epilepsy [14••, 38]; acetazolamide may be the first choice to treat paroxysmal movement disorders [11, 40, 50]. New therapeutic perspectives appear, however, essential in order to face the lack of effectiveness of ketogenic diets and AEDs.

Again, even in those cases where the KD is effective and well tolerated, still an important and debated matter is how long the diet should be carried out. Currently, an alternative to the diet, with proven and comparable efficacy, does not exist; therefore, it is recommended to maintain the KD at least until puberty, to provide sufficient energy to the developing brain [17•]. As far as our experience is concerned, we can affirm that the KD has adequate efficacy and tolerance also in GLUT1DS young adults

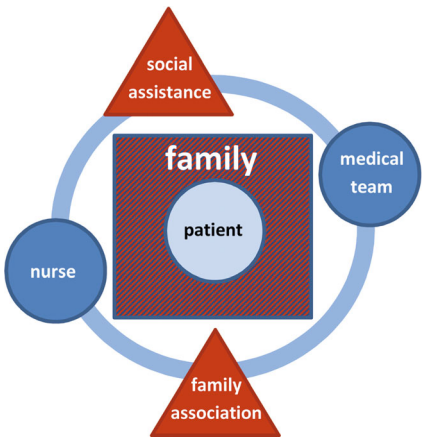

Fig. 2. In those GLUT1DS families where we see a difficulty in compliance, the dietary management of a multidisciplinary team is not sufficient; therefore, social intervention and the support of family associations are indispensable for a good outcome

(Tagliabue et al., 2014 in press); we have three patients who have been treated for more than 5 years with classic KD 3:1 who show excellent compliance and no significant adverse events or metabolic complications.

Conclusions

GLUT1DS results from impaired glucose transport into the brain; an early diagnosis is essential to allow prompt compensation for the brain's lack of fuel. Awareness of the wide phenotypic spectrum of GLUT1DS is a prerequisite, treating the patients is the subsequent challenge. While continuous clinical research has markedly widened our knowledge concerning the phenotypic variability of GLUT1DS, treatment is still largely based on the KD, as introduced 20 years ago [51].

The standard classic KD with a 4:1 ratio is actually a very restrictive diet and many patients cannot sustain it; therefore, the idea of carrying it out for the long term has to be overcome. The necessary multidisciplinary team should consider an adaptable and individualized therapy with different diet options.

New therapeutic strategies are needed in order to improve compliance and quality of life for those patients. For this reason, ongoing research to better discovery of the KD mechanism of action and the availability of long-term follow-up are essential in this relatively new disease.

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Compliance with Ethics Guidelines

Conflict of Interest

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Pierangelo Veggiotti and Valentina De Giorgis declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This is an interesting review that provides a consensus statement regarding the clinical management, patient selection, counseling and follow-up of the ketogenic diet in the Italian experience.

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