Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

General review

GLUT1 deficiency syndrome: An update

Mise au point sur le syndrome de déficit en transporteur du glucose GLUT1

D. Gras [a,b], *E. Roze* [a,*,b,c,d], *S. Caillet* [c,f], *A. Méneret* [b,d], *D. Doummar* [e], *T. Billette de Villemeur* [e], *M. Vidailhet* [b,c,d], *F. Mochel* [b,d,f]

[a] *Service de neuropédiatrie et maladies métaboliques, hôpital Robert-Debré, 48, boulevard Sérurier, 75935 Paris cedex 19, France*
[b] *Inserm UMR S975, CNRS UMR7225, centre de recherche de l'institut du cerveau et de la moelle, groupe hospitalier Pitié-Salpêtrière, bâtiment ICM, 47, boulevard de l'Hôpital, 75651 Paris cedex 13, France*
[c] *Département de neurologie, hôpital Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, France*
[d] *Université Pierre-et-Marie-Curie, Paris-6, 4, place Jussieu, 75005 Paris, France*
[e] *Service de neuropédiatrie, hôpital Trousseau, 26, avenue du Docteur-Arnold-Netter, 75012 Paris, France*
[f] *Service de génétique, hôpital Pitié-Salpêtrière, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, France*

INFO ARTICLE

Article history:
Received 11 June 2013
Received in revised form
1 August 2013
Accepted 2 September 2013
Available online 20 November 2013

Keywords:
SLC2A1
Mental retardation
Epilepsy
Movement disorders
Ketogenic diet

Mots clés :
SLC2A1
Retard mental
Épilepsie
Mouvements anormaux
Régime cétogène

ABSTRACT

Introduction. – Glucose transporter type 1 deficiency syndrome is caused by heterozygous, mostly *de novo*, mutations in the *SLC2A1* gene encoding the glucose transporter GLUT1. Mutations in this gene limit brain glucose availability and lead to cerebral energy deficiency.
State of the art. – The phenotype is characterized by the variable association of mental retardation, acquired microcephaly, complex motor disorders, and paroxysmal manifestations including seizures and non-epileptic paroxysmal episodes. Clinical severity varies from mild motor dysfunction to severe neurological disability. In patients with mild phenotypes, paroxysmal manifestations may be the sole manifestations of the disease. In particular, the diagnosis should be considered in patients with paroxysmal exercise-induced dyskinesia or with early-onset generalized epilepsy. Low CSF level of glucose, relative to blood level, is the best biochemical clue to the diagnosis although not constantly found. Molecular analysis of the *SLC2A1* gene confirms the diagnosis. Ketogenic diet is the cornerstone of the treatment and implicates a close monitoring by a multidisciplinary team including trained dieticians. Non-specific drugs may be used as add-on symptomatic treatments but their effects are often disappointing.
Conclusion. – Glucose transporter type 1 deficiency syndrome is likely under diagnosed due to its complex and pleiotropic phenotype. Proper identification of the affected patients is important for clinical practice since the disease is treatable.
© 2013 Elsevier Masson SAS. All rights reserved.

* *Corresponding author.*
E-mail address: emmanuel.roze@psl.aphp.fr (E. Roze).
0035-3787/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.neurol.2013.09.005

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

RÉSUMÉ

Introduction. – Le déficit en transporteur du glucose GLUT1 est causé par des mutations hétérozygotes, souvent *de novo*, dans le gène *SLC2A1* qui code pour le transporteur du glucose GLUT1. Ces mutations entraînent une réduction de la disponibilité cérébrale du glucose et un déficit énergétique secondaire.

État de l'art. – Le phénotype est caractérisé par l'association variable d'un retard mental, d'une microcéphalie acquise, d'un syndrome moteur complexe et de manifestations paroxystiques qui peuvent être de nature épileptique ou non épileptique. La sévérité peut varier d'une atteinte motrice isolée peu invalidante à une atteinte neurologique diffuse et sévère. Chez les patients atteints de formes légères, les manifestations paroxystiques peuvent être la seule manifestation de la maladie. En particulier, ce diagnostic doit être systématiquement envisagé chez les patients ayant des dyskinésies induites par l'exercice ou une épilepsie généralisée de début précoce. Une glycorachie abaissée relativement à la glycémie constitue le meilleur indice biochimique en faveur de ce diagnostic, même si elle est absente chez certains patients. L'analyse moléculaire du gène *SLC2A1* permet de confirmer le diagnostic. Le régime cétogène est actuellement la pierre angulaire du traitement de la maladie et implique une surveillance étroite par une équipe multidisciplinaire comportant des diététiciens spécialisés. Des traitements pharmacologiques symptomatiques, non spécifiques, peuvent être utilisés, mais avec des résultats en général décevants.

Conclusion. – Le déficit en transporteur du glucose GLUT1 est probablement sous diagnostiqué en raison de son spectre phénotypique complexe et protéiforme. L'identification des patients atteints est importante en pratique clinique car il existe un traitement efficace.

© 2013 Elsevier Masson SAS. Tous droits réservés.

1. Introduction

Glucose transporter type 1 deficiency syndrome (GLUT1-DS, OMIM #606777) is caused by impaired glucose transport across the blood-brain barrier and into astrocytes, due to heterozygous, mostly *de novo*, mutations in the *SLC2A1* gene encoding the glucose transporter GLUT1. Mutations in this gene limit brain glucose availability and lead to cerebral energy deficiency, likely accounting for the clinical manifestations of the disease. The clinical spectrum of GLUT1 deficiency is important to know for clinical practice since the disease is potentially treatable; likewise, diagnostic delays are deleterious (Ramm-Pettersen et al., 2013). The disease was first described by De Vivo in 1991, who reported two patients with an infantile-onset epileptic encephalopathy associated with delayed neurological development and acquired microcephaly (De Vivo et al., 1991). Within the past few years, numerous reports have expanded the clinical spectrum of the disease, showing that patients may exhibit variable associations of permanent neurological disorders and paroxysmal events (Fig. 1). To date, about 200 patients have been identified (Klepper, 2012), but a large number of patients might be undiagnosed due to the pleiotropic and complex phenotype.

We thus thought it was important for clinical practice to raise awareness and recognition of GLUT1 deficiency. Based on a review of the literature through May 2013 and our personal experience, we describe in details the wide phenotypic spectrum of the disease and present the current knowledge on the diagnostic tools and therapeutic issues.

2. Clinical aspects

2.1. *A wide range of phenotypes*

The phenotype typically comprises psychomotor retardation with acquired microcephaly and motor disorders, associated with paroxysmal manifestations including seizures and non-epileptic paroxysmal episodes such as abnormal movements (Brockmann, 2009; Leen et al., 2012; Pons et al., 2010). Onset is usually in infancy or childhood but later onset of isolated paroxysmal manifestations, without mental retardation or microcephaly, can occur at any age. 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 (Fig. 2).

The ''classical'' severe phenotype is characterized by an infantile-onset chronic encephalopathy with pharmacoresistant epilepsy starting within the first months of life, psychomotor retardation, acquired microcephaly, spasticity, ataxia and mixed movement disorders (Graham, 2012; Klepper and Leiendecker, 2007). This phenotype is likely the most frequent, representing 84% of patients in a series of 57 patients (Leen et al., 2010; Pearson et al., 2013). Clinical severity varies from epileptic attacks on a background of mild motor and cognitive dysfunction to severe neurological disability, with some patients who never achieve language or unaided walking (Brockmann, 2009).

Milder forms of the disease include a broad phenotypic spectrum. Among patients with the classical phenotype, later

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

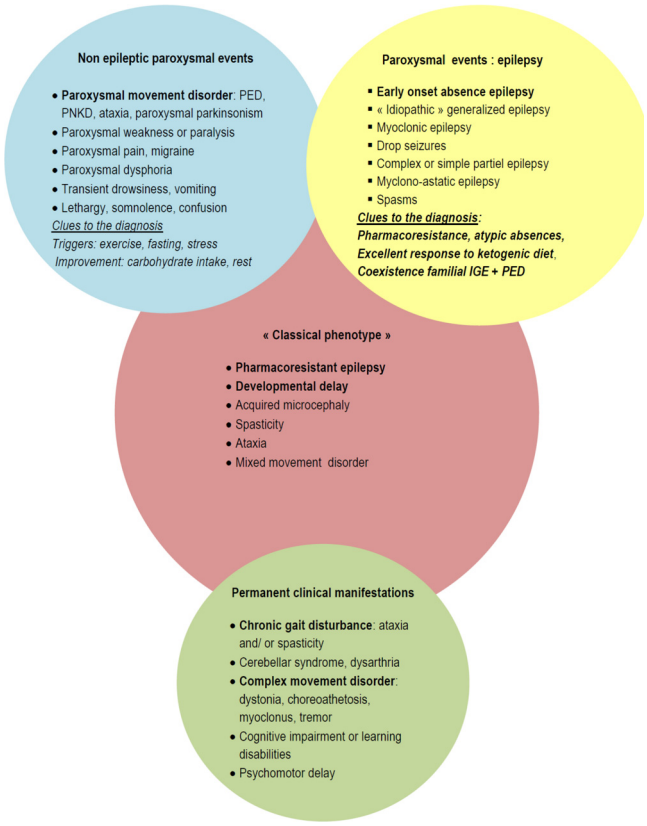


Fig. 1 – The broad clinical spectrum of glucose transporter GLUT1 deficiency. PED: paroxysmal exercise-induced dyskinesia; PNKD: paroxysmal non-kinesigenic dyskinesia; IGE: "idiopathic" generalized epilepsy.

onset is occasionally observed and tends to be associated with milder mental retardation (Leen et al., 2010). About 15% of the patients have mental retardation with movement disorders, but without epilepsy (Brockmann, 2009; Leen et al., 2010). In some patients with mild forms of the disease, paroxysmal episodes, usually paroxysmal dyskinesia, epilepsy or both, may be the main or the sole manifestations (Afawi et al., 2010; Anheim et al., 2011; Arsov et al., 2012a, 2012b; Bovi et al., 2011; Pons et al., 2010; Schneider et al., 2009; Striano et al., 2012; Suls et al., 2008, 2009; Weber et al., 2008; Zorzi et al., 2008). It is noteworthy that this purely paroxysmal phenotype can also be observed in early childhood, in the absence of psychomotor retardation (personal observation). Mutations in *SLC2A1* account for 12% (11/89) of the early-onset childhood absence epilepsy (Arsov et al., 2012a; Suls et al., 2009) and for about 1% (7/504) of patients with various typical "idiopathic" generalized epilepsy, including absence epilepsy but also generalized tonic-clonic epilepsy and myoclonic epilepsy (Arsov et al., 2012b). Myoclonic astatic epilepsy can also be due to *SLC2A1* in 5% (4/84) of patients and is then often associated with psychomotor retardation and sometimes with paroxysmal movement disorders (Mullen et al., 2011). *SCLC2A1* is also a major culprit gene for paroxysmal exercise-induced dyskinesia or mixed syndromes with non-kinesigenic and exercise-induced paroxysmal dyskinesia, in both familial (Suls et al., 2008) and sporadic cases of the disease (Anheim et al., 2011; Schneider et al., 2009). Fig. 1 summarizes the clinical phenotypes that should prompt the clinician to consider the diagnosis of GLUT1-DS and Fig. 2 illustrates the link between the phenotype and the age at onset.

2.2. *Permanent clinical manifestations*

Permanent clinical manifestations may include mental retardation, cerebellar syndrome, spasticity (with or without paraparesis) and complex movement disorders resulting in gait disturbances and dysarthria. The motor manifestations are sometimes increasing when fasting or improving with carbohydrate intakes but they fluctuate unpredictably in most patients with the classical phenotype (De Vivo et al., 2002).

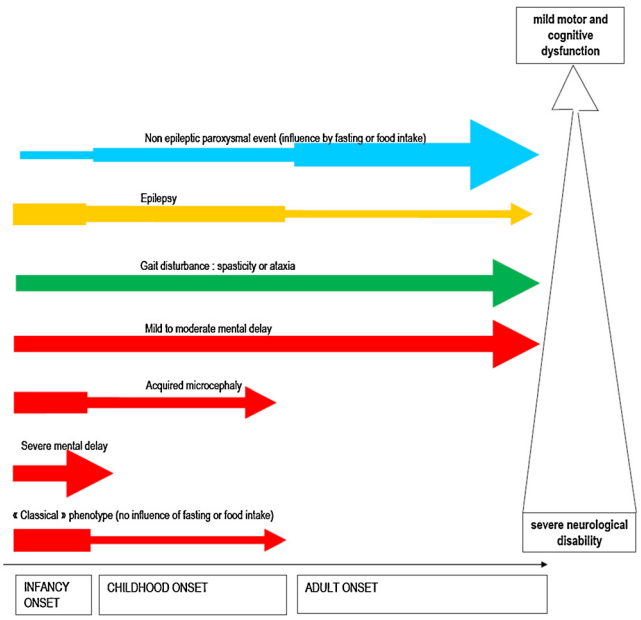


Fig. 2 – Clinical phenotype and severity depending on the age of onset.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

The cognitive status of GLUT1-DS patients varies from normal to severe mental retardation. Psychomotor retardation is observed in 80 to 98% of the patients but is often mild (Leen et al., 2010; Pons et al., 2010). It is usually associated with a postnatal deceleration of head growth resulting in a progressive microcephaly. Severe mental retardation is more frequent in the early-onset classical phenotype (Leen et al., 2010). Beside psychomotor retardation, fluctuating attention deficit and behavioral disorders are frequently observed (Pearson et al., 2013 and personal observation). Children with normal psychomotor development and adults with normal cognitive function have rarely been reported (Brockmann et al., 2001; Leen et al., 2010; Pons et al., 2010).

About 90% of patients with GLUT1-DS have gait disturbances. Typically, the gait disorder consists in an ataxic or a spastic gait or both (Pons et al., 2010). Ataxia is generally mild and can fluctuate. Patients with a more spastic gait tend to be more severely disabled, with some patients unable to walk independently. Speech disorder is frequent, mostly in the form of mixed dysarthria, which may include features of spastic, ataxic and hyperkinetic dysarthria, and may interfere with speech intelligibility (personal observation).

Complex movement disorders may include variable combinations of dystonia, choreoathetosis, myoclonus, tremor, tics and stereotypies. Dystonia is the most frequent movement disorder in GLUT1-DS with a distal predominance. It is often exacerbated when walking and running (Pons et al., 2010). Mild chorea involving the face and the upper limbs is found in 75% of the patients (Pons et al., 2010). Tremor is observed in 70% of the patients (mostly limb tremor) and is often a dystonic tremor or a tremor related to the cerebellar dysfunction (Pons et al., 2010; Roubergue et al., 2011).

2.3. *Paroxysmal clinical manifestations*

A wide range of paroxysmal manifestations can be encountered in GLUT1-DS, either isolated or associated with permanent neurological disorders (Pons et al., 2010). The typical precipitating factors for paroxysmal episodes are exercise and fasting. Psychological stress, intercurrent illness, tiredness and sleep deprivation are occasional triggers (Weber et al., 2011). However, the episodes can also occur spontaneously. Carbohydrates eating and rest are alleviating factors.

Epilepsy is a core feature of the disease, affecting 80–90% of the patients (Leen et al., 2010; Pearson et al., 2013; Pong et al., 2012; Pons et al., 2010). Seizures usually start in the first year of life, although onset in adulthood is rarely observed (Afawi et al., 2010; Pong et al., 2012; Striano et al., 2012). In a retrospective review of 87 patients, the average age for seizure onset was 8 months (Pong et al., 2012). Likewise, early neonatal epilepsy is not suggestive of GLUT1-DS, which is likely due to the preferential use of ketone bodies by the neonatal brain. About 70% of the patients have mixed types of seizures, generalized tonic-clonic seizures and absence seizures being the most common (Pong et al., 2012). Other seizure types observed in GLUT1-DS are complex partial seizures, drop seizures and tonic seizures; rarely, simple partial seizures or spasms (Pong et al., 2012). The EEG findings are highly variable and there is no typical EEG pattern (Pong et al., 2012). Importantly, any epilepsy with an early-onset (a few months old) and/or an atypical phenomenology (variable seizure types and EEG findings) should prompt the physician to consider the possibility of GLUT1-DS, regardless of the associated phenotype. A poor response to antiepileptic drugs and/or a dramatic response to a ketogenic diet are highly suggestive of the diagnosis.

Non-epileptic paroxysmal manifestations occur in about 30% of the patients and comprise paroxysmal movement disorders – paroxysmal exercise-induced dyskinesia, paroxysmal non-kinesigenic dyskinesia, episodic ataxia, paroxysmal parkinsonism –, paroxysmal weakness, paroxysmal pain (including paroxysmal headache), transient drowsiness, vomiting, and paroxysmal dysphoria (Brockmann, 2009; Koy et al., 2011; Leen et al., 2012; Liu et al., 2012; Pearson et al., 2013; Pons et al., 2010; Rotstein et al., 2009; Weber et al., 2011). The presence, frequency and severity of non-epileptic paroxysmal disorders are not linked to the extent and severity of the permanent neurological deficits. Episodes usually last from minutes to hours and their frequency ranges from several per day to a few per year. Importantly, paroxysmal dyskinesias occuring after at least two hours of continuous exercise may be the sole manifestations of the disease (personal observation). Paroxysmal disorders are very good clues to the diagnosis of GLUT1-DS, particularly when a patient has various types of paroxysmal events or complex episodes with multiple paroxysmal manifestations occurring simultaneously or sequentially.

2.4. *Differential diagnosis*

The classical severe phenotype with mental delay, epilepsy and microcephaly shares commonalities with Rett syndrome (*MECP2* mutations). In case of familial forms of GLUT1-DS, other genes involved in autosomal dominant epilepsies may be considered. Non-epileptic paroxysmal events are also the main symptoms of paroxysmal kinesigenic dyskinesia (*PRRT2* mutations) and channelopathies (*EA2* mutations). Of note, in disorders of intermediary metabolism (e.g., respiratory chain disorders, pyruvate dehydrogenase deficiency or maple syrup urine disease), paroxysmal symptoms (seizures or movement disorders) can be precipitated by fasting like in GLUT1-DS.

2.5. *Rare non-neurological manifestations*

Few cases of GLUT1-DS with hemolytic anemia are reported (Bawazir et al., 2012; Flatt et al., 2011; Weber et al., 2008). One possible explanation is that GLUT1 is the primary glucose transporter in red blood cells. In GLUT1-DS, the amount of GLUT1 in the erythrocyte membrane is reduced to 60% normal and the protein displays little glucose transport activity (Flatt et al., 2011). One case of GLUT1-DS associated with growth failure due to severe growth hormone defect is reported (Nakagama et al., 2012). However, the effect of GLUT1 malfunction on the endocrine system is not well investigated. Whether this association is causal or incidental remains unexplained.

3. Diagnosis

The key points to make the diagnosis of GLUT1-DS are shown in Fig. 3. The diagnosis is based on CSF analysis and molecular

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

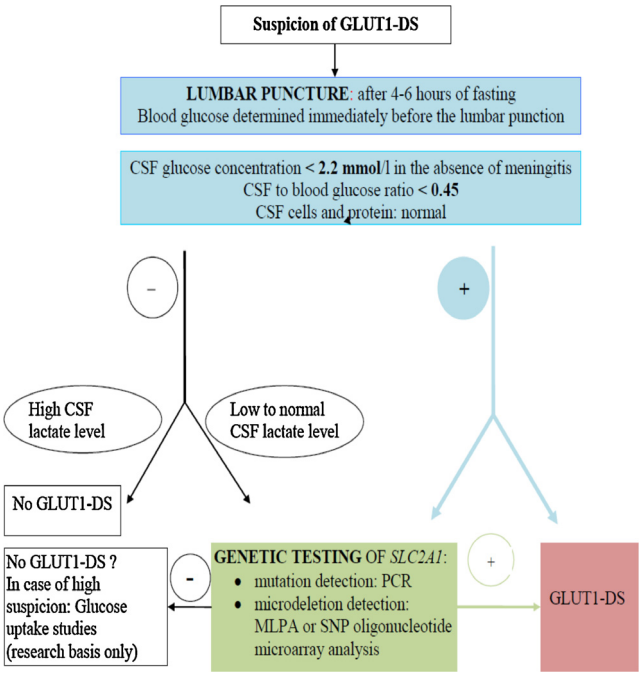


Fig. 3 – Key points to make the diagnosis of GLUT1-DS.

analysis of the *SLC2A1* gene. Low CSF glucose with low CSF to blood glucose ratio is the best biochemical clue to the diagnosis. Importantly, to ensure the reliability of the results:

- lumbar puncture should be performed after at least 4–6 h of fasting to achieve a glucose steady state within the CSF compartment (ideally in the morning before breakfast);
- and blood glucose should be determined immediately before the lumbar puncture to avoid stress-related hyperglycemia.

The diagnosis is confirmed:

- when CSF glucose concentration is < 2.2 mmol/L in the absence of meningitis;
- and/or when the CSF to blood glucose ratio is < 0.45 (Klepper, 2012).

Low CSF lactate levels also support the diagnosis, particularly in the presence of hypoglycorrhachia, since lactate is an important energy substrate for astrocytes (Allaman et al., 2011). Of note, increased lactate CSF concentrations are usually associated with hypoglycorrhachia due to other causes, reflecting anaerobic glycolysis in the CNS. In three reviews of more than 50 patients, the mean CSF glucose values were respectively 1.7 mmol/L (range 0.9–2.7) – mean ratio 0.35 (range 0.19–0.49) (Klepper and Leiendecker, 2007) –, 1.8 (range 0.9–2.4 mmol/L) – mean ratio 0.37 (range 0.19–0.52) (Leen et al., 2010) – and 1.8 mmol/L (range 1.3–2.2) – mean ratio 0.36 (range 0.21–0.49) (Pons et al., 2010). It is now clear that patients with a mild form of the disease may have CSF glucose levels and CSF to blood glucose ratio within the low normal range (Mullen et al., 2010; Suls et al., 2008; Weber et al., 2008). In these latter patients, only molecular analyses of *SLC2A1* can ascertain the diagnosis of GLUT1-DS. It is noteworthy that brain MRI and interictal EEG are normal in most cases or show non-specific abnormalities and are thus not helpful for diagnosis.

4. Genetics and pathophysiology

The brain is a highly energy-requiring 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 25% of total body glucose utilization. Nevertheless, it seems that the brain contains little energy storage capacities like glycogen, which implies a continuous glucose supply, or alternative energy substrates like ketone bodies, to ensure optimal functions. 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 (Vannucci et al., 1997). The gene associated with GLUT1-DS is *SLC2A1*, located on chromosome 1 (1p34.2). Mutations or deletions in this gene result in a loss of function with altered glucose transport to the brain. Insufficient glucose availability leads to cerebral energy deficiency that is likely deleterious for brain development and impairs brain functions. Most GLUT1-DS patients have heterozygous private *de novo* mutations resulting in sporadic cases, although familial forms can occur with an autosomal dominant mode of inheritance. Bi-allelic *SLC2A1* mutations are thought to be lethal in almost all cases (Wang et al., 2005, 2006), although autosomal recessive transmission has been reported, likely linked to mutations with less deleterious functional effects on glucose transport (Rotstein et al., 2010). Around 100 different mutations have been described in the *SLC2A1* gene (Leen et al., 2010) including large-scale deletions, missense, nonsense, frameshift and splice-site mutations, all resulting in a loss of function. A comprehensive genetic testing consists in:

- mutation detection by PCR sequencing of all 10 exons, splice-sites and the promoter region;
- microdeletion detection by multiplex ligation-dependent probe amplification or SNP oligonucleotide microarray analysis (Leen et al., 2010; Levy et al., 2010).

There is no definite genotype-phenotype correlation with high inter-individual phenotypic variability, even within the same family. However, missense mutations resulting in 50–75% residual function of GLUT1 are often associated with mild to moderate forms of the disease whereas the early-onset severe form is most likely associated with hemizygosity – microdeletions, nonsense mutations, frameshift mutations and splice-sites mutations resulting in 50% loss of GLUT1 (Leen et al., 2010; Wang et al., 2005). The modulation of:

- glucose transport to the brain by other genetic, epigenetic or environmental factors;
- and/or alternative sources of natural substrates for the brain like ketone bodies may participate to the phenotypic variability.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

5. Treatment

5.1. *Therapeutic strategy*

A thorough clinical evaluation is the starting point when defining the therapeutic strategy. It is crucial to determine the type and severity of the epilepsy and to evaluate the cognitive dysfunctions that are major determinants of patients' quality of life. Physical examination should be focused on the topography, type and severity of the motor manifestations, as well as the nature and degree of the functional impairment in daily life. The therapeutic strategy and the related constraints should be discussed in details with the patient (adult), or the child and the family. Ketogenic diet is the cornerstone of the treatment and implicates a close monitoring by a multidisciplinary team including trained dieticians. 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 (Cano et al., 2008; Pong et al., 2012) and acetazolamide may be the first choice to treat paroxysmal movement disorders (Anheim et al., 2011; Chambon et al., 2013). Drugs potentially altering GLUT1 function should be avoided, including caffeine, phenobarbital, diazepam, valproate and tricyclic antidepressants (Brockmann, 2011; Cano et al., 2008). 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.

5.2. *Ketogenic diet*

Ketogenic diet is the gold standard treatment for GLUT1-DS. When the glucose supply is insufficient, ketones bodies are the only relevant alternative fuel source for brain metabolism. Ketogenic diet is a high-fat, carbohydrate-restricted diet that mimics the metabolic state of starvation, in which glucose metabolism is switched to ketones bodies metabolism. The diet forces the body to burn fats rather than carbohydrates, thereby producing ketones bodies that penetrate the blood-brain barrier and serve as an alternative fuel for the brain metabolism. 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. This is achieved by excluding high-carbohydrate foods, while increasing the consumption of high-fat foods. An example of a typical daily menu for an adult is shown in Figs. 4 and 5.

The discipline needed to maintain the ketogenic diet is often challenging for patients and the compliance to the diet is difficult to obtain. The diet is a genuine medical nutrition therapy and should be initiated in a hospital under close supervision. Patients, families and caregivers should be trained to calculate and apply the diet. The support from a team of experienced physicians and dieticians is also essential. A 3:1 diet is usually sufficient for adequate ketosis and therapeutic effects. Thus, it is recommended to provide adequate amounts of protein, particularly in growing children. Supplements are necessary to counteract the resulting dietary deficiencies including vitamins, L-carnitine and minerals. Long-term side effects may include constipation, proatherogenic lipoprotein profile and raised cholesterol levels, nephrolithiasis and growth retardation. They usually do not require the discontinuation of the diet and are manageable in most patients. The modified Atkins diet is less restrictive and may be an interesting alternative when the compliance to classical ketogenic diet is low or when the patients are reluctant to start classical ketogenic diet, particularly in school-age children and adolescents. The modified Atkins restricts carbohydrates to 10 g/day in children (15 g/day in adults), while encouraging high-fat foods, thereby providing 65% of the calories from fat sources. This diet does not restrict protein and calories intake. It mimics a 0.9:1 ketogenic ratio.

Because of the high-energy demand of the developing brain, ketogenic diet should be started as early as possible and maintained at least until adolescence. Ketogenic diet seems to be beneficial even when started in late childhood (Gramer et al., 2012). Whether adults with GLUT1-DS will benefit from a

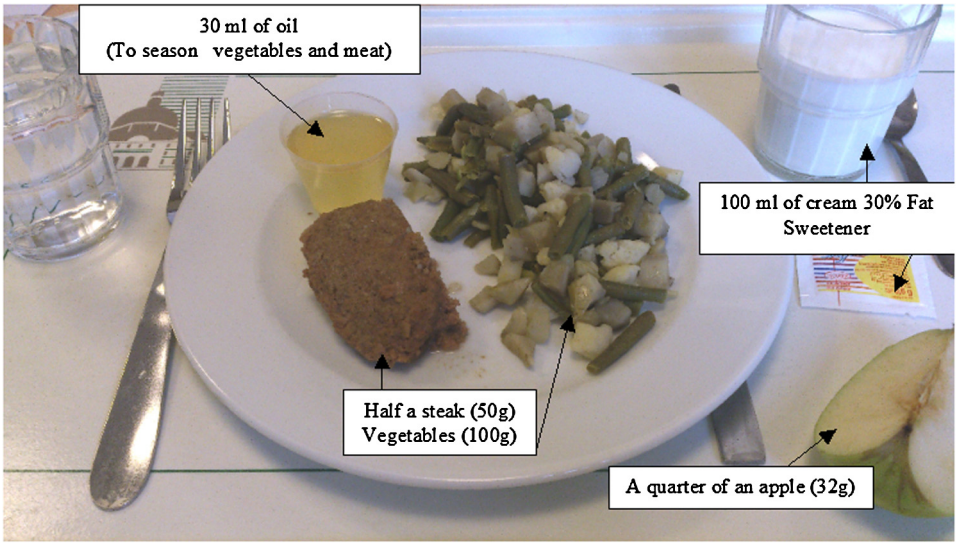


Fig. 4 – Practical clues to ketogenic diet. Example of a ketogenic meal.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

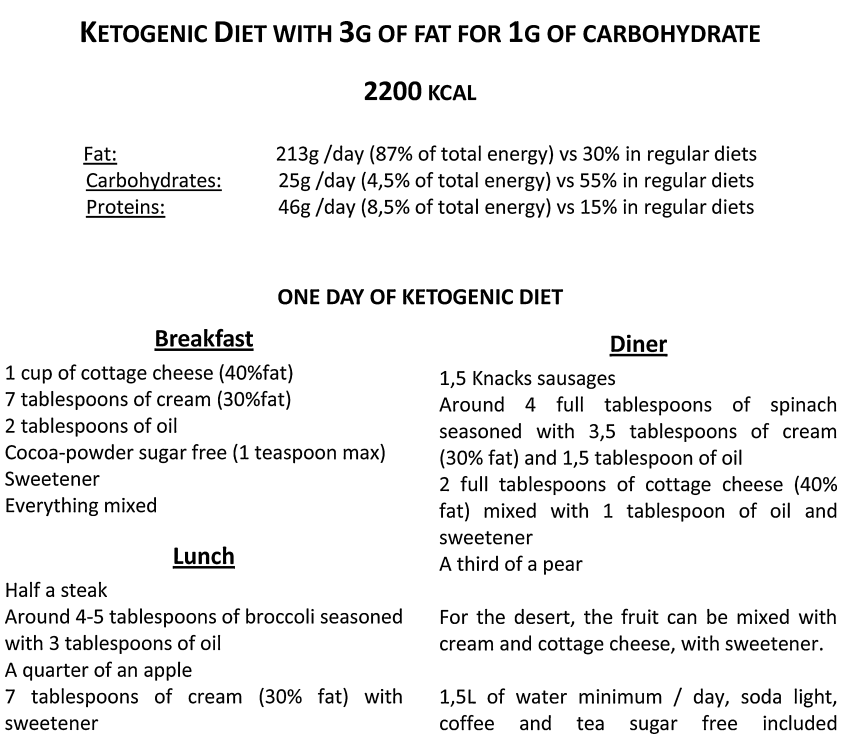


Fig. 5 – Practical clues to ketogenic diet. Typical day of ketogenic diet.

life-long ketogenic diet needs to be investigated. Changes in ketone bodies, fatty acids, and limited glucose might work in concert to stabilize synaptic function and limit neuronal hyperexcitability (Bough and Rho, 2007). In addition, the ketogenic diet might exert neuroprotective effects by limiting reactive oxygen species generation and by up-regulating mitochondrial biogenesis and boosting energy production (Klepper, 2008; Klepper and Leiendecker, 2013). Seizures freedom, or at least seizure reduction, is obtained in most GLUT1-DS patients on a ketogenic diet (Klepper and Leiendecker, 2007). In case of good response to the ketogenic diet, seizures resolve within a week to a month after diet initiation (Pong et al., 2012). Similarly, other paroxysmal disorders are often rapidly responsive to ketogenic diet, at least partially (Brockmann, 2009; Klepper and Leiendecker, 2007; Leen et al., 2010; Suls et al., 2008). Interictal motor disorders tend to improve more slowly within weeks to months (Gramer et al., 2012). Except in anecdotal reports, there is no clear evidence of possible beneficial effects of ketogenic diets on neurodevelopment and cognitive functions, and standardized quantitative longitudinal studies are lacking to properly address this issue (Brockmann, 2009; Koy et al., 2011). Preliminary data suggest a good efficacy of the modified Atkins diet (Ito et al., 2011) but its effect has not been systematically compared with that of classical ketogenic diet in a large series of GLUT1-DS patients.

5.3. *Treatment perspectives*

Alpha-lipoic acid and triheptanoin are discussed as a potential treatment of GLUT1-DS (Klepper, 2012).

Alpha-lipoic acid is an antioxidant that serves as a coenzyme in energy metabolism. It neutralizes free radicals and improves cellular glucose uptake by stimulating the insulin signal cascade. In particular, it was found to improve glucose transport in muscle cells via mobilization of the GLUT1 and GLUT4 transporters from intracellular pools (Estrada et al., 1996). However, there is no convincing experimental evidence that this supplementation will have similar effects on the GLUT1 transporter through the blood-brain barrier.

Triheptanoin is a triglyceride made of an odd number of carbons, therefore providing not only acetyl-CoA but, more importantly, propionyl-CoA, an anaplerotic intermediate and precursor of oxaloacetate in the Krebs cycle. Through the hepatic synthesis of C5 ketone bodies and their transport to the CNS, triheptanoin is likely to provide energetic substrates to brain energy metabolism when glucose metabolism is impaired as shown in pyruvate carboxylase deficiency (Mochel et al., 2005). Through its anaplerotic effect, triheptanoin may be an interesting alternative to ketogenic diets, which only produce acetyl-CoA. Preliminary studies in GLUT1 mice support this hypothesis (Marin-Valencia et al., 2013). Since triheptanoin usually represents 35% of total calories intake, compared to about 80% calories from fat required for the traditional ketogenic diet, triheptanoin may offer a better compliance and safety profile. However, its efficacy in GLUT1-DS remains to be determined.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

REFERENCES

Afawi Z, Suls A, Ekstein D, Kivity S, Neufeld MY, Oliver K, et al. Mild adolescent/adult onset epilepsy and paroxysmal exercise-induced dyskinesia due to GLUT1 deficiency. Epilepsia 2010;51(12):2466–9.

Allaman I, Belanger M, Magistretti PJ. Astrocyte-neuron metabolic relationships: for better and for worse. Trends Neurosci 2011;34(2):76–87.

Anheim M, Maillart E, Vuillaumier-Barrot S, Flamand-Rouviere C, Pineau F, Ewenczyk C, et al. Excellent response to acetazolamide in a case of paroxysmal dyskinesias due to GLUT1 deficiency. J Neurol 2011;258(2):316–7.

Arsov T, Mullen SA, Damiano JA, Lawrence KM, Huh LL, Nolan M, et al. Early-onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency. Epilepsia 2012a;53(12):e204–7.

Arsov T, Mullen SA, Rogers S, Phillips AM, Lawrence KM, Damiano JA, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. Ann Neurol 2012b;72(5):807–15.

Bawazir WM, Gevers EF, Flatt JF, Ang AL, Jacobs B, Oren C, et al. An infant with pseudohyperkalemia, hemolysis, and seizures: cation-leaky GLUT1 deficiency syndrome due to a SLC2A1 mutation. J Clin Endocrinol Metab 2012;97(6):E987–93.

Bough KJ, Rho JM. Anticonvulsant mechanisms of the ketogenic diet. Epilepsia 2007;48(1):43–58.

Bovi T, Fasano A, Juergenson I, Gellera C, Castellotti B, Fontana E, et al. Paroxysmal exercise-induced dyskinesia with self-limiting partial epilepsy: a novel GLUT1 mutation with benign phenotype. Parkinsonism Relat Disord 2011;17(6):479–81.

Brockmann K, Wang D, Korenke CG, von Moers A, Ho YY, Pascual JM, et al. Autosomal dominant GLUT1 deficiency syndrome and familial epilepsy. Ann Neurol 2001;50(4):476–85.

Brockmann K. The expanding phenotype of GLUT1 deficiency syndrome. Brain Dev 2009;31(7):545–52.

Brockmann K. Towards a more palatable treatment for GLUT1 deficiency syndrome. Dev Med Child Neurol 2011;53(7):580–1.

Cano A, Ticus I, Chabrol B. [Glucose transporter type 1 (GLUT1) deficiency]. Rev Neurol (Paris) 2008;164(11):896–901.

Chambon R, Vuillaumier-Barrot S, Seta N, Wagner S, Sarret C. Partial effectiveness of acetazolamide in a mild form of GLUT1 deficiency: a pediatric observation. Mov Disord 2013;28(12):1749–51.

De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Arik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med 1991;325(10):703–9.

De Vivo DC, Leary L, Wang D. Glucose transporter 1 deficiency syndrome and other glycolytic defects. J Child Neurol 2002;17(Suppl. 3):3S15–23S [discussion 3S4–5].

Estrada DE, Ewart HS, Tsakiridis T, Volchuk A, Ramlal T, Tritschler H, et al. Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. Diabetes 1996;45(12):1798–804.

Flatt JF, Guizouarn H, Burton NM, Borgese F, Tomlinson RJ, Forsyth RJ, et al. Stomatin-deficient cryohydrocytosis results from mutations in SLC2A1: a novel form of GLUT1 deficiency syndrome. Blood 2011;118(19):5267–77.

Graham Jr JM. GLUT1 deficiency syndrome as a cause of encephalopathy that includes cognitive disability, treatment-resistant infantile epilepsy and a complex movement disorder. Eur J Med Genet 2012;55(5):332–4.

Gramer G, Wolf NI, Vater D, Bast T, Santer R, Kamsteeg EJ, et al. Glucose transporter-1 (GLUT1) deficiency syndrome: diagnosis and treatment in late childhood. Neuropediatrics 2012;43(3):168–71.

Ito Y, Oguni H, Ito S, Oguni M, Osawa M. A modified Atkins diet is promising as a treatment for glucose transporter type 1 deficiency syndrome. Dev Med Child Neurol 2011;53(7):658–63.

Klepper J, Leiendecker B. GLUT1 deficiency syndrome: 2007 update. Dev Med Child Neurol 2007;49(9):707–16.

Klepper J. Glucose transporter deficiency syndrome (GLUT1-DS) and the ketogenic diet. Epilepsia 2008;49(Suppl. 8):46–9.

Klepper J. GLUT1 deficiency syndrome in clinical practice. Epilepsy Res 2012;100(3):272–7.

Klepper J, Leiendecker B. GLUT1 deficiency syndrome and novel ketogenic diets. J Child Neurol 2013;28(8):1045–8.

Koy A, Assmann B, Klepper J, Mayatepek E. Glucose transporter type 1 deficiency syndrome with carbohydrate-responsive symptoms but without epilepsy. Dev Med Child Neurol 2011;53(12):1154–6.

Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010;133(Pt 3):655–70.

Leen WG, Willemsen MA, Wevers RA, Verbeek MM. Cerebrospinal fluid glucose and lactate: age-specific reference values and implications for clinical practice. PLoS One 2012;7(8):e42745.

Levy B, Wang D, Ullner PM, Engelstad K, Yang H, Nahum O, et al. Uncovering microdeletions in patients with severe GLUT1 deficiency syndrome using SNP oligonucleotide microarray analysis. Mol Genet Metab 2010;100(2):129–35.

Liu Y, Bao X, Wang D, Fu N, Zhang X, Cao G, et al. Allelic variations of GLUT1 deficiency syndrome: the Chinese experience. Pediatr Neurol 2012;47(1):30–4.

Marin-Valencia I, Good LB, Ma Q, Malloy CR, Pascual JM. Heptanoate as a neural fuel: energetic and neurotransmitter precursors in normal and glucose transporter I-deficient (G1D) brain. J Cereb Blood Flow Metab 2013;33(2):175–82.

Mochel F, DeLonlay P, Touati G, Brunengraber H, Kinman RP, Rabier D, et al. Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. Mol Genet Metab 2005;84(4):305–12.

Mullen SA, Suls A, De Jonghe P, Berkovic SF, Scheffer IE. Absence epilepsies with widely variable onset are a key feature of familial GLUT1 deficiency. Neurology 2010;75(5):432–40.

Mullen SA, Marini C, Suls A, Mei D, Della Giustina E, Buti D, et al. Glucose transporter 1 deficiency as a treatable cause of myoclonic astatic epilepsy. Arch Neurol 2011;68(9):1152–5.

Nakagama Y, Isojima T, Mizuno Y, Takahashi N, Kitanaka S, Igarashi T. Growth hormone deficiency: a possible complication of glucose transporter 1 deficiency? Acta Paediatr 2012;101(6):e259–62.

Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (GLUT1-DS). Curr Neurol Neurosci Rep 2013;13(4):342.

Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 2012;53(9):1503–10.

Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in GLUT1 deficiency. Mov Disord 2010;25(3):275–81.

Ramm-Pettersen A, Nakken KO, Skogseid IM, Randby H, Skei EB, Bindoff LA, et al. Good outcome in patients with early dietary treatment of GLUT1 deficiency syndrome: results from a retrospective Norwegian study. Dev Med Child Neurol 2013;55(5):440–7.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)

Rotstein M, Doran J, Yang H, Ullner PM, Engelstad K, De Vivo DC. GLUT1 deficiency and alternating hemiplegia of childhood. Neurology 2009;73(23):2042–4.

Rotstein M, Engelstad K, Yang H, Wang D, Levy B, Chung WK, et al. GLUT1 deficiency: inheritance pattern determined by haploinsufficiency. Ann Neurol 2010;68(6):955–8.

Roubergue A, Apartis E, Mesnage V, Doummar D, Trocello JM, Roze E, et al. Dystonic tremor caused by mutation of the glucose transporter gene GLUT1. J Inherit Metab Dis 2011;34(2):483–8.

Schneider SA, Paisan-Ruiz C, Garcia-Gorostiaga I, Quinn NP, Weber YG, Lerche H, et al. GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias. Mov Disord 2009;24(11):1684–8.

Striano P, Weber YG, Toliat MR, Schubert J, Leu C, Chaimana R, et al. GLUT1 mutations are a rare cause of familial idiopathic generalized epilepsy. Neurology 2012;78(8):557–62.

Suls A, Dedeken P, Goffin K, Van Esch H, Dupont P, Cassiman D, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in SLC2A1, encoding the glucose transporter GLUT1. Brain 2008;131(Pt 7): 1831–44.

Suls A, Mullen SA, Weber YG, Verhaert K, Ceulemans B, Guerrini R, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. Ann Neurol 2009;66(3):415–9.

Vannucci SJ, Gibbs EM, Simpson IA. Glucose utilization and glucose transporter proteins GLUT1 and GLUT3 in brains of diabetic (db/db) mice. Am J Physiol 1997;272(2 Pt 1):E267–74.

Wang D, Pascual JM, Yang H, Engelstad K, Jhung S, Sun RP, et al. GLUT1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann Neurol 2005;57(1):111–8.

Wang D, Pascual JM, Yang H, Engelstad K, Mao X, Cheng J, et al. A mouse model for GLUT1 haploinsufficiency. Hum Mol Genet 2006;15(7):1169–79.

Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Maljevic S, et al. GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. J Clin Invest 2008;118(6):2157–68.

Weber YG, Kamm C, Suls A, Kempfle J, Kotschet K, Schule R, et al. Paroxysmal choreoathetosis/spasticity (DYT9) is caused by a GLUT1 defect. Neurology 2011;77(10):959–64.

Zorzi G, Castellotti B, Zibordi F, Gellera C, Nardocci N. Paroxysmal movement disorders in GLUT1 deficiency syndrome. Neurology 2008;71(2):146–8.

© 2015 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 30/01/2015 par UNIVERSITE PARIS VI - BIBLIOTHEQUE - (15258)