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Review

GLUT1 deficiency syndrome 2013: Current state of the art

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ABSTRACT

Glucose transporter type 1 deficiency syndrome (GLUT1DS) is the result of impaired glucose transport into the brain. The "classic" GLUT1DS patient presents with infantile seizures (resistant to traditional seizure medications), developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia. However, over the years, other clinical manifestations have been described, such as paroxysmal exertion-induced dystonia with or without seizures, choreoathetosis, alternating hemiplegia, and other paroxysmal events, such as intermittent ataxia, dystonia, and migraine.

At the current state of the art in understanding of GLUT1DS, classifying the disease phenotype as "classical" or "non-classical" seems to be of limited clinical utility. It seems more appropriate to think in terms of a broad clinical spectrum in which we can observe intellectual impairment, acquired microcephaly, epilepsy, and movement disorders characterized by different clinical manifestations and degrees of severity.

Lumbar puncture, a simple investigation, should be considered the first diagnostic step that, moreover, is feasible worldwide. Thereafter, 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).

Early diagnosis is critical because it allows prompt initiation of treatment with a ketogenic diet (KD). Childhood is the critical period for treatment of GLUT1DS: early diagnosis is crucial for an effective etiological therapy. KD treatment can be useful in adulthood too. Compliance has been found to be much better in GLUT1DS than in the other conditions for which KD treatment is indicated.

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1. Introduction

Glucose is the essential substrate for brain energy metabolism. In the resting state, the adult brain can consume up to 25% of the body's total glucose supply,[1] while in infants and children it can use as much as 80%.[2]

The diffusion of this essential fuel across the blood–brain barrier is facilitated by glucose transporter type 1 (GLUT1). In the brain, GLUT1 interacts with other specific GLUT isoforms mediating glucose transport into astrocytes and neurons.[3]

GLUT1 deficiency syndrome (GLUT1DS) results from impaired glucose transport into the brain.[4]

The classic GLUT1DS patient presents with infantile seizures (often resistant to traditional seizure medications), developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia.[5]

Recently the clinical spectrum of GLUT1DS has been broadened to include developmental delay, epilepsy and/or movement disorders,[6] as well as familial and sporadic paroxysmal exercise-induced dyskinesia with or without epilepsy.[7] There are also varying degrees of cognitive impairment associated with dysarthria, dysfluency, and expressive language deficits. In most patients, the cerebrospinal fluid (CSF)-to-blood glucose ratio is below 0.50, and CSF lactate is low to normal.

A diagnosis of GLUT1DS can be confirmed by molecular analysis of the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene, while analysis of glucose uptake into erythrocytes can confirm the impaired GLUT1 function. Early diagnosis is critical because it allows prompt initiation of treatment with a ketogenic diet (KD), which is a high-fat, low-carbohydrate diet that mimics the metabolic state of fasting. Since ketones use another transporter to enter the central nervous system, they can provide the brain with an alternative source of fuel, thereby effectively correcting the impaired brain energy metabolism[8] and reducing the frequency of the seizures and the severity of the dystonic movement disorder.

The normal rate of cerebral oxygen consumption is low during the fetal and perinatal periods; it then increases in a linear fashion

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to peak at the age 3 of years, thereafter remaining high until adolescence when it shows a gradual decline.[9] Therefore, childhood is the critical period for treatment of GLUT1DS: early diagnosis is crucial for effective KD treatment.

2. Molecular basis

GLUT1 is a member of the GLUT family of facilitative glucose transporters, which comprises 13 proteins (gene symbol SLC2A, protein symbol GLUT). Cloned and sequenced in 1985, GLUT1/SLC2A1 (OMIM 138140) was the first gene of this family to be identified.[10] Located on the short arm of chromosome 1 (1p34.2), this gene is 35 kb long and consists of 10 exons.

GLUT1 is constitutively expressed in most tissues and selectively expressed in erythrocytes, brain microvessels and astroglia.[3] It exists in two molecular weight forms (45 and 55 kDa), which differ only in the extent of glycosylation of the protein.[11] The 45 kDa form is detected in most cells including astrocytes and may be responsible for basal glucose uptake by cells. The 55 kDa form is found predominantly in the endothelial cells of brain microvessels and erythrocytes, where it is the principal glucose transporter.[6] If there is a deficiency of GLUT1, the quantity of glucose passing from the blood into the brain can be reduced, and this causes a dysfunction in the central nervous system.

Human and animal data suggest that there is only a narrow safety margin for glucose transport across the blood–brain barrier to meet the needs of brain metabolism and cerebral function. A milder clinical phenotype with intermittent symptoms (epilepsy, dyskinesias, ataxia) may be predicted in the presence of a 25–35% reduction in GLUT1 transporter function,[12] while a more severe phenotype is likely to result from reductions in the order of 40–75%.[13]

Most detected SCL2A1 mutations are de novo; in familial cases the condition is inherited as an autosomal dominant trait with complete penetrance. A case of autosomal recessive transmission has also recently been described.[14] All detected mutations are heterozygous; indeed, homozygous GLUT1 mutations are presumably lethal in utero.[15]

Patients with missense mutations generally present with moderate to mild symptoms, but no clear-cut phenotype–genotype correlations have been established. Indeed, patients sharing identical mutations often do not have identical clinical manifestations, which suggests that there are additional mechanisms at work, such as disease-modifying genes and proteins that alter phenotype and potentially contribute to the pathophysiology of this complex entity.[16] Leen et al.[8] studied 57 patients, trying to identify a specific relationship between genotype and phenotype. They found that mild mental retardation was more often present in patients with a missense mutation (Type A), and movement disorders than in those with translation initiation mutations (Type B) or multiple exon deletions (Type C). However, severe mental retardation was found to be present in a few Type A patients and mild mental retardation in some Type B or C patients. Additionally, patients with the same mutation displayed phenotypic heterogeneity, in terms of range of clinical expression and severity. It is possible that other secondary genes or other proteins are involved in glucose transport, which might explain the phenotypic diversity of this disease.[17]

GLUT1 deficiency syndrome may also occur as a part of broader genetic syndromes, as seen in microdeletion syndromes involving the SLC2A1 gene.[18]

3. Clinical phenotypes

3.1. Classical phenotype

GLUT1 deficiency syndrome was first described in 1991 as an early-onset childhood epileptic encephalopathy.[19] This phenotype, now defined "classical", was rapidly expanded to include epileptic encephalopathy with different seizure types, developmental delay, acquired microcephaly, complex movement disorders (variable combinations of ataxia, dystonia and spasticity), and paroxysmal events. Seizures were initially described as brief, subtle myoclonic limb jerking with alternating staring and eye-rolling, unresponsiveness, hypotonia and head bobbing. Now, also generalized seizures of all types (absences, generalized tonic-clonic, myoclonic, atonic, etc.) are considered features of the classical phenotype. The movement disorders presented differ from patient to patient, but most frequently consist of ataxia and spasticity. Paroxysmal events of possibly non-epileptic origin include intermittent ataxia, periodic confusion, periodic weakness, periodic limb paralysis, recurrent headaches, and intermittent sleep disturbances.

The clinical severity of the classical phenotype varies, ranging from mild motor and cognitive dysfunction between epileptic attacks to severe neurological disability, with some patients never achieving the ability to speak or walk unsupported.[6] In most patients with the classical phenotype neurological symptoms are not influenced by fasting or food intake,[20] even though there are isolated reports of paroxysmal worsening of symptoms (mainly movement disorders) with prolonged fasting.[8]

3.2. Non-classical phenotypes

Several clinical variants of GLUT1DS have been reported over the two decades since the first description of the classical phenotype. Brockmann's classification is the one most cited in the literature,[6] and it classifies patients into the following groups on the basis of their symptoms: (i) carbohydrate-responsive symptoms, characterized by a correlation between fasting and neurological deterioration including seizure frequency; (ii) predominant ataxia or dystonia, but without seizures, and (iii) paroxysmal exertion-induced dyskinesia and seizures.

However, over the years numerous atypical clinical manifestations have been described, such as paroxysmal exertion-induced dystonia (PED) with[21] or without seizures,[7,22,23] choreoathetosis,[24] alternating hemiplegia[25] and other paroxysmal events,[26] such as intermittent ataxia, dystonia, and migraine.

At the current state of the art in understanding of GLUT1DS, classifying the disease phenotype as "classical" or "non-classical" seems to be of limited clinical utility. It seems more appropriate to think in terms of a broad clinical spectrum in which we can observe:

3.2.1. Intellectual impairment

Intellectual impairment in patients with GLUT1DS varies widely and may include: language delay, expressive language difficulties possibly associated with dysarthria, learning difficulties, and mild, moderate or severe cognitive delay, but without a significant neuropsychological profile. In our experience, cognitive impairment is often proportional to the severity of other symptoms; indeed intelligence quotient (IQ) is usually normal in patients with minimal symptoms.

Leen et al., in their sample[8] of 57 patients, found mental retardation (from mild to severe) in almost all the patients with a severe phenotype (46 out of 48), in half of those with a mild phenotype (4 out of 8), and in neither of the two patients with minimal symptoms.

Other psychiatric symptoms, such as behavioral difficulties, depression, and attention deficit hyperactivity disorder, are only sporadically described.[28]

3.2.2. Acquired microcephaly

This is a frequent but not essential component of the clinical spectrum.

Acquired microcephaly was mainly observed in classical phenotype patients.[28] Adult cases with "minimal symptoms" do not present microcephaly, whereas it can be found in around 40% of patients with mild phenotypes and in around 50% of those with a severe phenotype (classical De Vivo syndrome).[8]

3.2.3. Epilepsy

GLUT1 deficiency syndrome should be considered in the differential diagnosis of any form of intractable epilepsy.[29] Patients usually develop seizures in infancy and early childhood.

In infants, seizures are described as brief, subtle myoclonic limb jerks with alternating staring and eye-rolling, sudden-onset pallor, a dazed expression, horizontal roving eye movements, unresponsiveness, hypotonia and head bobbing. The EEG usually shows multifocal spike discharges.

Pong et al.[30] recently reviewed 87 patients with GLUT1DS and noticed that 78 (90%) had epilepsy with a mean age at onset of 8 months. Seizures were a mixture of different types: generalized tonic-clonic (53%), absence (49%), complex partial (37%), myoclonic (27%), drop (26%), tonic (12%), simple partial (3%), and spasms (3%) (these authors described the first two cases of spasms in GLUT1DS).

In childhood, seizures are frequently myoclonic and generalized;[28] myoclonic astatic epilepsy (MAE) is a commonly reported form.[31,32] This finding could be linked to brain maturation; indeed, as the brain matures, seizures become synchronized and manifest clinically as generalized events associated with 3–4 Hz spike-and-wave discharges.

Some authors have described forms of epilepsy that are particularly responsive to carbohydrate intake.[6]

However, it is important to stress that forms described as MAE and caused by SLC2A1 mutations cannot be considered "typical": GLUT1DS was present in only four out of 84 MAE probands (5%) investigated by Mullen et al.[31] and it is important to underline that two of these patients also presented PED in childhood; another presented ataxia, dysarthric speech and deceleration of head growth.

Idiopathic generalized epilepsies (IGEs), not usually drug-responsive, have also previously been described. More than 10% of early-onset[33,34] or myoclonic[35] absence epilepsies are caused by mutations of the SLC2A1 gene.

Recently, a very interesting article by Arsov et al.[36] showed that mutations of SLC2A1 are responsible for approximately 1% of all IGEs. The authors analyzed a total of 504 probands with IGEs (juvenile myoclonic epilepsy – 32%, juvenile absence epilepsy – 21%, childhood absence epilepsy – 31%, generalized tonic-clonic seizures – 13%, and unspecified forms of IGE – 2%) and 470 controls. In total, seven of the 504 probands and none of the 470 controls had mutations demonstrating a functional effect on the protein product. The cases described had a history of IGEs, with seizures responding well to antiepileptic drugs (AEDs), and normal intellectual outcome, although closer analysis of the patients' clinical records revealed cases with atypical forms of juvenile myoclonic epilepsy who became seizure-free on oxcarbazepine, and cases with associated exercise-induced movement disorders.

Prior to this study, a GLUT1DS family with PED and IGEs had already been described.[37] This family showed onset of epilepsy in adolescence/childhood but, oddly and atypically, clear and definite EEG focus. Tzadok et al.[27] recently reported a series of eight patients with supposed IGEs but quite atypical features, namely: absence epilepsy without myoclonias but with 3/sec spike-and-wave discharges interspersed with polyspike waves, myoclonic absences associated with ataxia and mild mental retardation, and aspecific seizures with PED. A quarter of these patients with epilepsy were found to have IGEs and the authors showed GLUT1 deficiency to be an important cause of IGEs.

At present, GLUT1 deficiency should be considered the most common known monogenic cause of atypical IGEs, and this raises the question of whether abnormalities in glucose delivery form part of a general, shared mechanism in IGEs.

GLUT1 deficiency syndrome should not really be regarded as a clinical feature of known epileptic syndromes (myoclonus-astatic epilepsy, absences epilepsy, etc.); rather GLUT1DS is a broad, complex syndrome that includes seizures with specific semiology possibly linked to known epileptic syndromes.

3.2.4. Movement disorders

Subjects with GLUT1DS commonly present complex movement disorders, which can be characterized by ataxia, dystonia, and chorea. These disorders can be continuous and/or paroxysmal

false-negative results in patients carrying pathogenic mutations.[20] Furthermore, these investigations are not commercially available and are demanding in terms of protocol, time, sample size and sample quality.[29]

4.3. Molecular analysis

Approximately 70–80% of patients carry SLC2A1 mutations.[15] Genetic testing is commercially available worldwide. It should include polymerase chain reaction (PCR) sequencing of all 10 exons, splice site, and the promoter region.[7] If it is negative, deletions/duplications within the SCL2A1 gene can be detected by multiplex ligation-dependent probe amplification (MLPA).[8]

In SCL2A1-negative patients, GLUT1DS can be diagnosed only in the presence of clear hypoglycorrhachia. In such cases it is, indeed, reasonable to suspect GLUT1DS and to initiate KD treatment. An immediate response to the diet will support the diagnosis.[29]

These patients constitute a particularly interesting subset as they might carry defects in GLUT1 assembly, three-dimensional GLUT1 folding, GLUT1 trafficking to the cell, or GLUT1 activation.[5]

5. EEG findings

No characteristic electroencephalography (EEG) pattern in GLUT1DS has yet been identified, and patients can actually show a normal interictal EEG.[6,30]

Infants with GLUT1DS can present with multifocal spike discharges on EEG, underlying infantile focal seizures (non-generalized) that may include eye movements, cyanotic spells, etc.[46] Subsequently, as the brain matures, these seizures become synchronized and clinically manifest themselves as generalized events associated with 3–4 Hz spike-and-wave discharges.

Tzadoket al.[27] maintain that the presence of polyspike wave discharges in the context of absence epilepsy without myoclonus or prominent aggravation of generalized polyspike wave discharges during sleep – which they did not usually observe in IGE patients – could be characteristic signs.

However, on the basis of our personal experience, we suggest that the above-mentioned features can also be present in "simple" forms of IGE. In our sample of GLUT1DS patients (article in press), we found that many "unusual" signs can be detected in idiopathic forms, such as the presence of atypical spike-and-wave discharges. In our view, these findings cannot be taken as characteristic signs.

On the contrary, some authors have reported improvement in the EEG findings post-prandially or after intravenous administration of glucose.[47] These EEG recordings could offer a simple screening test for GLUT1DS, even though, on their own, they cannot be considered diagnostic.

Marin-Valencia et al.[48] recently demonstrated in a mouse model of GLUT1DS that thalamocortical hypersynchronization is an important mechanism in GLUT1DS epileptogenesis due to impaired glucose uptake. Intrinsic cortical hyperexcitability arises from failure of internal thalamic inhibition, which causes propagation of excitation to the cortex; this could explain the frequent clinical presentation of absence epilepsy in patients with GLUT1DS. Moreover, because brain cells derive most of their energy from glucose, GLUT1 deficiency also impairs the synthesis of key molecules involved in energy production and neurotransmission, such as acetyl-CoA, tricarboxylic acid cycle intermediates and other derivatives.

6. Brain imaging

Neuroimaging findings in patients with GLUT1DS are not significant. Magnetic resonance imaging (MRI) scans of patients with GLUT1DS mostly show either normal findings[6] or occasionally mild enlargement of inner and outer CSF spaces.[5,49]

Cerebral fluorodeoxyglucose positron emission tomography (PET) in 14 patients with the classical GLUT1DS phenotype revealed a global decrease in glucose uptake in the cortex, more severe in the mesial temporal regions and thalami, and less marked in the basal ganglia.[22] The distinctive PET signature appears in early infancy and persists into adulthood regardless of disease severity or KD therapy. Although PET is readily available in clinical practice, the sensitivity and specificity of PET in the diagnosis of GLUT1DS have not yet been established.[50]

7. Treatments

7.1. Ketogenic diet

In the fasting state, brain glycogen storage is exhausted within minutes. The brain cannot utilize amino acids and fat to produce energy and, in the absence of glycogen, switches to ketones as an alternative fuel to maintain function. Ketones are generated in the liver from fatty acid degradation and enter the brain via facilitated diffusion mediated by the monocarboxylate transporter 1 (MCT1 transporter). This mechanism is particularly effective in infants and young children in whom ketone extraction and utilization is three-to-four-fold higher than in adults.[2]

The KD is a high-fat, carbohydrate-restricted diet that mimics the metabolic state of fasting. It has been used safely and effectively for decades in intractable childhood epilepsy.[1] The classic KD, as developed by the Johns Hopkins University, uses long-chain triglycerides and consists of 4 g of fat to every 1 g of carbohydrate and protein combined (4:1 ratio) with supplemental vitamins and minerals. The spectrum of the KD has now increased considerably[51] and includes several alternative diets such as the classic KD with a 3:1 ratio, medium-chain triglycerides (MCTs), the modified Atkins diet (MAD) (which provides 10 g carbohydrates/day in children and 15 g/day in adults), and the low glycemic index treatment (LGIT), which restricts the consumption of certain types of carbohydrate-containing foods.

Novel indications for KD include disorders of brain energy metabolism such as pyruvate dehydrogenase deficiency (PDHP) and GLUT1DS.[52]

Although, in epilepsy, the mechanism of action underlying the effectiveness of the KD is not yet clear,[53] in GLUT1DS it essentially provides an alternative fuel source. The effectiveness of the KD in GLUT1DS might be enhanced by its anticonvulsant action. The vast majority of GLUT1DS patients obtain seizure freedom with the classical 4:1 or 3:1 formula, allowing anticonvulsant therapy to be withdrawn.[5] There are a few reports in which the KD was not fully effective and anticonvulsants were not completely eliminated.[54,55]

The KD also has a positive effect on movement disorders such as hypotonia, ataxia, dystonia, and PED.[24,56]

The impact of KD treatment on developmental delay appears less prominent.[6] However, several authors have reported a marked increase in alertness and activity in patients on the KD.

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. The literature contains numerous reports of improved psychomotor impairment, but these are hard to verify in case–control studies.

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.[57]

It remains unclear whether a rigorous KD is essential in GLUT1DS. 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. The MAD 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 of MCT therapy and therefore cannot express an opinion on this option. We feel that MCTs could be integrated into

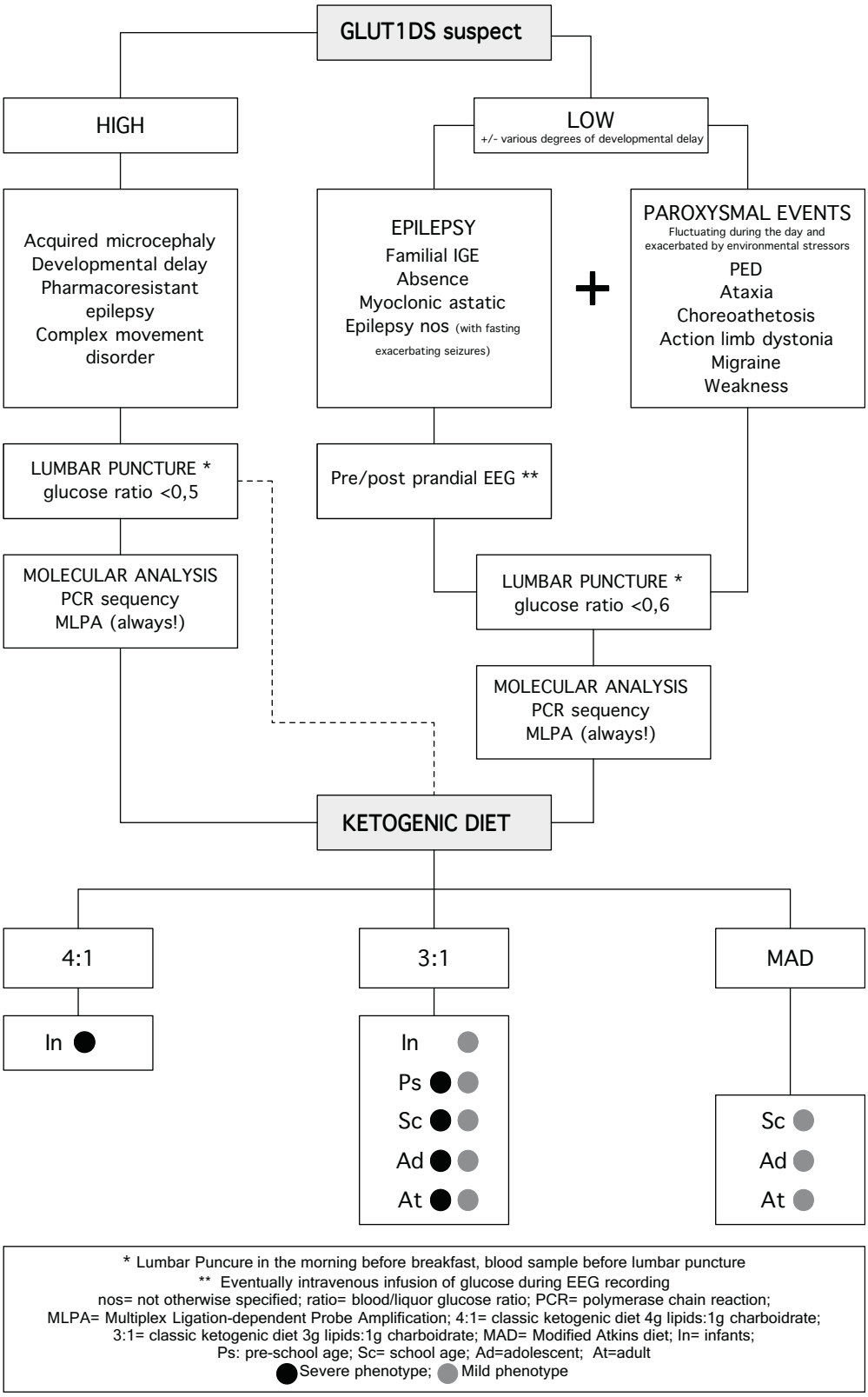

Fig. 1.

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.

Fig. 1 details, in addition to the diagnostic procedure, our clinical practice as regards the use of the KD in GLUT1DS patients at different ages and in different classes of severity.

There remain various challenges to be addressed. These include determination of the most efficient ratio and composition of the diets, and the development of treatment strategies in GLUT1DS adults.

The KD approach has advanced considerably over the past years, to the point that it is now considered a first-line therapy in infantile spasms, MAE, Dravet syndrome, and status epilepticus [including febrile infection-related epilepsy syndrome]. KDs are also now being increasingly studied for neurological conditions other than epilepsy, including Alzheimer's disease and cancer.[53] Further research could shed light on the mechanisms that may make metabolism-based therapy particularly helpful in terms of anticonvulsant and possibly neuroprotective effects.

7.2. Additional measures

Treatment with a KD should be complemented by additional measures: pharmacological agents known to impair GLUT1 function, e.g. caffeine, phenobarbital, diazepam, chloral hydrate and tricyclic antidepressants, should be avoided.[49]

There are also reports of the use of alternative compounds for the treatment of 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. Alpha lipoic acid 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;[20,30] however, to date there are no published data in humans to demonstrate its effectiveness.

Acetazolamide was reported to be beneficial for paroxysmal dyskinesias in a single patient with GLUT1DS.[58]

Triheptanoin is a triglyceride that has been used as an anaplerotic substrate in humans to treat inherited metabolic diseases such as pyruvate carboxylase deficiency and carnitine palmitoiyltransferase II deficiency.[59] It is metabolized into five carbon compounds 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. Although promising in theory, there are currently no clinical data to support the use of this compound in GLUT1DS.

8. Follow-up and outcome

Regular follow-up visits are needed after a diagnosis of GLUT1DS in order to monitor the patient's clinical evolution.

Patients starting KD treatment should be monitored particularly closely.

In accordance with the 2011 Italian consensus statement on KD therapy,[39] we recommend that follow-up of GLUT1DS children/adults include regular dietary and neurological evaluations and EEG, performed at least five times in the first year of treatment (after 1, 3, 6, 9, and 12 months). Annual cognitive and developmental assessments are also recommended, as are regular blood and metabolic evaluations.

In contrast to intractable childhood epilepsy patients, individuals affected by GLUT1DS should continue the diet into adolescence to meet the increased energy demands of the developing brain.[52] In our opinion, KD treatment can be useful in adulthood, too, because even though epilepsy seems to disappear in adulthood, the movement disorder can persist unchanged and there are, as yet, no reliable data confirming a stable cognitive outcome in adult patients with GLUT1DS. More important, 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.[60] Furthermore, in GLUT1DS patients, KD therapy could be beneficial to organs expressing GLUT1 at high levels such as the retina, colon, ovaries and testicles.[1]

For these reasons, if there are no serious side effects, we recommend lifelong KD treatment in GLUT1DS patients, even if symptom control is not complete. It is necessary to compensate for the deficit caused by the failure of glucose to cross the blood–brain barrier in order to reduce the long-term risks associated with the disease.

In our experience, compliance is much better in GLUT1DS than in the other conditions for which KD treatment is indicated. According to the literature there is a good level of satisfaction: up to 75% of patients consider the diet effective and 50% tolerate and accept it.[55]

The question of when to discontinue AEDs in patients with GLUT1DS is not really debated in the literature. According to our protocol, if seizures and non-epileptic paroxysmal events have disappeared, gradual reduction of AEDs can start from the first year after the introduction of the KD. If the diet does not completely control the symptoms, AEDs are continued at the most effective and best tolerated dose.

No information is available on the long-term efficacy and tolerability of the treatment in GLUT1DS patients, but non-GLUT1DS seizure-free epileptic patients on the diet for >10 years have been reported.[61]

9. Conclusions

GLUT1 deficiency syndrome results from impaired glucose transport into the brain. Recently the clinical spectrum of GLUT1DS has been broadened and it is becoming less meaningful to consider the disease in terms of "classical" and "non-classical" phenotypes.

On the basis of current knowledge, this disease should be suspected (Fig. 1) and a CSF investigation (with determination of the CSF-to-blood glucose ratio) strongly recommended in the presence of:

- any seizures that are refractory and/or influenced by fasting, especially if associated with mild neurological (pyramidal or extra-pyramidal) signs and/or mental impairment and/or atypical EEG features and/or a family history of epilepsy or movement disorder.
- any history of unexplained paroxysmal events – especially if PED – associated with previous self-limited seizures and/or mental impairment and/or a family history of epilepsy or movement disorder.

Other signs such as microcephaly, mental retardation, and dysarthria are frequently observed in GLUT1DS patients, however our experience shows that they are not hallmarks.

An extra-neurological sign we frequently observed in our GLUT1DS cases was prognathism: this could be a gestalt sign worth remembering.

The question of whether or not to perform lumbar puncture has been extensively debated in the literature. Even today, most patients presenting with epilepsy or a movement disorder do not have a diagnostic lumbar puncture.

In accordance with De Vivo and Wang,[45] we emphasize the continuing value of the lumbar puncture as the classical approach to the neurological patient with an unexplained condition. This procedure has withstood the test of time and remains cost-efficient. It is true that gene sequencing is an increasingly available, non-invasive test with a pretest probability of 1% for IGEs,[36] rising to 10% for early-onset absence epilepsy.[31] However, we do not consider it useful to perform mutational analysis of the SLC2A1 gene in all patients with early-onset absence epilepsies or epilepsy with myoclonic-atonic seizures,[62] believing, instead, that the analysis should be reserved for patients with highly suggestive clinical findings and low CSF glucose or borderline clinical findings and CSF glucose who require genetic testing to confirm the diagnosis prior to starting a KD. This approach is certainly less expensive than wider genetic screening, and also feasible worldwide.

At present, it seems most interesting to focus on those patients who have a clinical picture highly suggestive of GLUT1DS, a low glycorrhachia value, and possibly a good response to the KD, but who are negative on gene SLC2A1 sequencing and MLPA. In these *SLC2A1*-negative GLUT1DS patients other potential disease mechanisms could be at work.[63]

This is why sequencing of the entire exome should be performed in an attempt to identify other genes possibly implicated in GLUT1 protein assembly, three-dimensional folding, trafficking to the cell, or activation.

It is essential diagnose this entity as early as possible to allow prompt compensation, through the KD, for the brain's lack of fuel. Early identification of children with GLUT1DS is important in order to avoid submitting them to possibly ineffective or potentially detrimental treatments with anticonvulsants, and to ensure that their brains are provided with an alternative energy source during a time of increased cerebral metabolism.

On the basis of current knowledge, it is not possible to say with absolute certainty that the condition of GLUT1DS patients never deteriorates. The hallmark deficiency of glucose in the CNS, if allowed to persist for many years, could be responsible for brain atrophy, which could be observed on the MRI scans of these patients, and for a moderate but steady reduction of IQ, as well as for the maintenance of more or less drug-resistant epilepsy and a disabling movement disorder. The few GLUT1DS adult patients identified to date do not provide sufficient evidence to clarify our doubts in this regard.

Ongoing research to discover pathogenic mechanisms underlying different phenotypes, the availability of new animal models of GLUT1DS, growing patient numbers, and the diffusion of knowledge of this relatively "new" disease could help us to provide answers to some of the many still open questions about GLUT1DS. Moreover exomewide sequencing in a small number of patients with a similar phenotype could disclose other genes implicated in GLUT1DS.

Ethical approval

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

None of the authors has any conflict of interest to disclose

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