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Phenotypic Spectrum of Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

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Abstract Glut1 deficiency syndrome (Glut1 DS) was originally described in 1991 as a developmental encephalopathy characterized by infantile onset refractory epilepsy, cognitive impairment, and mixed motor abnormalities including spasticity, ataxia, and dystonia. The clinical condition is caused by impaired glucose transport across the blood brain barrier. The past 5 years have seen a dramatic expansion in the range of clinical syndromes that are recognized to occur with Glut1 DS. In particular, there has been greater recognition of milder phenotypes. Absence epilepsy and other idiopathic generalized epilepsy syndromes may occur with seizure onset in childhood or adulthood. A number of patients present predominantly with movement disorders, sometimes without any accompanying seizures. In particular, paroxysmal exertional dyskinesia is now a well-documented clinical feature that occurs in individuals with Glut1 DS. A clue to the diagnosis in patients with paroxysmal symptoms may be the triggering of episodes during fasting or exercise. Intellectual impairment may range from severe to very mild. Awareness of the broad range of potential clinical phenotypes associated with Glut1 DS will facilitate earlier diagnosis of this treatable neurologic condition. The ketogenic diet is the mainstay of treatment and nourishes the starving symptomatic brain during development.

Keywords Seizures · Intellectual disability · Movement disorders · Hypoglycorrhachia · SLC2A1 mutations · Glucose transporter

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Introduction

Glucose, the principal fuel source for brain metabolism, needs to cross the luminal and abluminal membranes of the endothelial cell before entering the brain extracellular compartment. The glucose transporter, Glut1 (encoded by *SLC2A1*), is the fundamental vehicle that facilitates glucose entry into the brain and across the astrocyte membrane. It is also abundant in primate erythrocytes, in a form that is immunochemically identical to Glut1 in brain microvessels and astrocytes [1]. The cerebral metabolic rate for glucose is low during fetal development, increases linearly after birth, peaks around age 3 years, remains high through the first decade of life, and then declines gradually during the second decade of life to the rate of glucose utilization seen in early adulthood [2].

Glut1 DS is a disorder of brain energy metabolism characterized by impaired transport of glucose across the blood–brain barrier. The syndrome was originally described in 2 children with infantile-onset seizures refractory to anticonvulsant medications, acquired microcephaly, delayed development, spasticity, ataxia, and dystonia [3]. The laboratory hallmark of Glut1 DS is a low CSF glucose concentration (<60 mg/dL or 3.3 mmol/L in all cases reported to date; <40 mg/dL or 2.2 mmol/L in the majority of cases). Clinical symptoms arise as a result of Glut1 haploinsufficiency, due to mutations in the *SLC2A1* gene [4]. The majority of reported patients (~90 %) have a de novo heterozygous mutation in *SLC2A1*. About 10 % of affected individuals have an affected parent (autosomal dominant inheritance pattern). Autosomal recessive transmission has also been described in rare cases [5, 6••].

The phenotypic spectrum of Glut1 DS has expanded markedly over the past decade. We now recognize patients with milder forms of epilepsy, and patients with non-epileptic syndromes characterized by both persistent and paroxysmal movement disorders, and varying degrees of

cognitive impairment [7••, 8••]. The spectrum of severity is broad. Some patients have minimal clinical findings and appear relatively normal between symptomatic episodes. Others have severe, fixed neurologic deficits and never attain the ability to speak or walk independently.

Neurological features may be divided into 3 symptom domains: seizures, movement disorders, and cognitive/behavioral disturbances (Fig. 1). The classic Glut1 DS phenotype is characterized by persistent symptoms involving all 3 domains. In contrast, patients with milder phenotypes may experience symptoms in only 1 or 2 domains, and symptoms may be either intermittent or persistent.

Seizures

Approximately 90 % of patients diagnosed with Glut1 DS have clinical seizures. This high prevalence of seizures may well reflect an ascertainment bias, as infantile epilepsy has been widely considered to be a cardinal feature of the syndrome until recently.

Seizures usually present in early infancy and are refractory to conventional antiepileptic drug treatment [9, 10]. Clinical features may initially be subtle and brief, and include twitching of a limb, staring, abnormal eye movements, sudden pallor, limpness, and head nodding. These symptoms are not always immediately recognized as seizures.

Various seizures types have been described in patients with Glut1 DS. The most common are generalized tonic clonic, followed by absence, myoclonic, and partial onset seizures. Tonic seizures, infantile spasms, and epileptic spasms are observed rarely. Two-thirds of patients have more than one seizure type. In one large series, the average age of seizure onset was found to be around 8 months, while the average age at which a diagnosis of Glut1 DS was confirmed was 5 years, indicating a considerable lag in the time to diagnosis in many cases [11•].

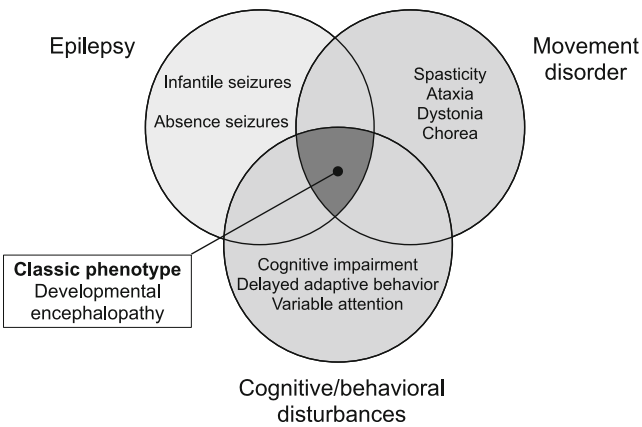

Fig. 1 Neurological symptoms in Glut1 DS fall into 3 domains: epilepsy, movement disorders, and cognitive/behavioral disturbances. The original, classic phenotype is a developmental encephalopathy encompassing all 3 domains. Milder phenotypes may not involve all domains, and symptoms may be intermittent rather than persistent

Absence Epilepsy

Recently, Glut1 DS has been recognized to cause milder forms of epilepsy and intellectual impairment than the infantile epileptic encephalopathy that was originally described. Early onset childhood absence epilepsy with mild intellectual disability is one such phenotype.

Among children with early onset childhood absence epilepsy (defined as seizure onset before age 4 years), Glut1 DS was diagnosed in 12 % (4/34 patients) [12]. Clinical response to anticonvulsant medication varied widely. Some children responded readily to anticonvulsant monotherapy, while others were refractory to medications. Intellectual function also varied, from normal to moderate intellectual impairment. Sometimes, mild motor symptoms including ataxia and paroxysmal exertional dyskinesia also were present [12].

Other Epilepsy Phenotypes

The detection of Glut1 DS in patients with early-onset absence epilepsy led to the subsequent recognition of a broad range of epilepsy phenotypes in the family members of 2 probands in a recent study by Mullen et al. [13••]. Many family members had absence seizures with onset from childhood to adulthood, clinically indistinguishable in individual cases from common forms of idiopathic generalized epilepsy (IGE). Several family members also had febrile seizures, myoclonic-astatic epilepsy, and focal seizures. About half of the individuals experienced mild paroxysmal exertional dyskinesia (see Movement Disorders, below), which was universally undiagnosed prior to the molecular genetic diagnosis being made. This study highlighted the importance of considering a diagnosis of Glut1 deficiency in the context of patients with familial IGE, particularly if there is a history of co-existent paroxysmal movement disorders. This finding has been further illustrated in 2 other families with IGE [14, 15], in which some individuals had mild generalized epilepsy with seizure onset in adolescence or adulthood. In one case, childhood absence epilepsy evolved into a syndrome of juvenile myoclonic epilepsy [15].

SLC2A1 mutations were recently detected in 5 % of patients (4/84) with myoclonic-astatic epilepsy [16]. These patients had early seizure onset (before age 2 years). The ketogenic diet led to resolution of seizures, and

subsequently a more favorable clinical outcome than other patients with myoclonic-astatic epilepsy.

Electroencephalography (EEG) Findings

The interictal background EEG in the fasting state typically demonstrates mild to moderate slowing. Generalized spike and wave discharges with a frequency of 2.5-4 Hz may be seen [10]. Background slowing and spike discharges improve following consumption of carbohydrates. Following ingestion of oral glucose, an improvement in EEG findings occurred within 30 minutes of glucose intake and persisted for approximately 4 hours [17]. Complete resolution of slowing, emergence of alpha activity, and a reduction in the frequency of epileptiform discharges were correlated with increases in serum glucose concentration. In addition, there was improvement in background EEG with resolution of focal slowing and emergence of alpha rhythm within the first 30 minutes following oral glucose intake [17].

Studies in humans and animals have shown that thalamus, occipital and parieto-occipital cortices are involved in the generation of the alpha rhythm [18–21]. The first clinical report describing fluorodeoxyglucose positron emission tomography (FDG-PET) imaging findings in Glut1 DS demonstrated widespread hypometabolism in neocortical regions and marked hypometabolism in the thalamus [22], suggesting impaired function of thalamo-cortical networks as a possible factor in epileptogenesis. The emergence of the alpha rhythm following oral glucose load strengthens our earlier contention that the transient clinical and laboratory improvement is centered regionally in thalamus and/or occipital cortex [19, 23]. Moreover, the improvement in attention noted during the oral glucose tolerance test may further support increased regional metabolic activity within thalamo-neocortical networks [17].

Treatment

Before a diagnosis of Glut1 deficiency is established, seizures are often treated with a number of antiepileptic medications. Phenobarbital, valproate, carbamazepine, lamotrigine, topiramate, and clonazepam are the most frequently used antiepileptic drugs. However, in the classic phenotype, seizures are typically refractory to medical treatment. Only 8 % of patients may reach seizure freedom with antiepileptic drug treatment alone [11•]. It should be kept in mind that in Glut1 DS, certain antiepileptic drugs have the potential to exacerbate seizures. For example, barbiturates can competitively inhibit the Glut1 transporter [24], and result in increased seizure frequency. Conversely, transient improvement in the seizures and EEG findings have been described during the post-prandial phase [25].

The ketogenic diet plays an indispensable role in the treatment of Glut1 DS. It provides ketone bodies, derived from the hepatic metabolism of fatty acids, as an alternative source of energy to meet the demands of the growing brain. Therefore, the ketogenic diet is essential not only for the treatment of seizures, but also for other clinical features of the syndrome (see Management, below).

Movement Disorders

Movement disorders are commonly observed in Glut1 DS. Patients experience a variety of persistent and paroxysmal motor symptoms. In a recent study, the authors evaluated videotaped examinations of 57 patients, the majority of whom had the classic Glut1 DS phenotype. Common motor disorders observed were an abnormal gait (89 %, typically ataxic or spastic-ataxic gait), dystonia (86 %), chorea (75 %), cerebellar intention tremor (70 %), and myoclonus (16 %) [26]. Most patients had more than one motor abnormality.

Glut1 DS is increasingly being diagnosed in patients who do not have seizures (8/55 patients, 15 %, in 1 recent large case series) [7••]. In these patients, movement disorders may be the most prominent feature. Following the report of a child with mental retardation, ataxia, dysarthria, and dystonia [27], other individual patients with Glut1 deficiency who presented with symptoms other than seizures have been described in recent years. Dysarthria, ataxia, and varying degrees of cognitive impairment were common features. Some patients additionally had either chorea and dystonia [28, 29] or spasticity [30]. Some patients experienced marked, intermittent worsening of their ataxia during exercise or fasting [29–32].

Paroxysmal Exertional Dyskinesia (PED)

Glut1 DS was recently established as a cause of PED. First described by Lance in a 3-generation family [33], PED is a movement disorder syndrome characterized by episodes of involuntary movements, typically 5 to 30 minutes in duration, that are triggered by sustained exercise. Episodes often begin during childhood, and both familial autosomal dominant [33, 34] and sporadic [35, 36] cases have been described. Lower limb dystonia precipitated by sustained walking or running is the most common manifestation [33, 34, 36]. However, other involuntary movements, including myoclonus, athetosis, chorea, and ballismus, may occur alone or in combination. Movements may affect the face, trunk or limbs, and episodes may be unilateral or bilateral.

In 2008, heterozygous missense mutations in *SLC2A1* were independently described in a total of 4 families with autosomal dominant PED, either with or without epilepsy [37, 38••]. The syndrome of PED due to a mutation in

SLC2A1 was subsequently designated DYT18 in the catalogue of genetic dystonia syndromes. Most affected individuals had normal interictal neurologic examinations [37, 38••], although some had mild learning disabilities [38••]. Movements during the episodes were described as sustained (dystonia), writhing (choreoathetosis) or jerky, leading in one family to characterization of the episodes as myoclonic seizures before they were recognized to be PED [37]. The authors of one study also reported a fifth family with similar clinical features and confirmed low CSF glucose concentration, but without a detectable mutation [38••]. *SLC2A1* mutations have subsequently been reported in familial [14] and sporadic [39] individual cases of PED and mild epilepsy, and in 2/10 patients with sporadic PED (one with epilepsy, one without) in one case series [40].

The syndrome of paroxysmal choreoathetosis/spasticity (DYT9) (originally described by Auburger et al.) [41] also has been reported to be allelic to Glut1 DS [42]. Individuals in 2 families had paroxysmal, mainly exercise-induced dyskinesia with onset between ages 1 and 15 years. Dyskinetic episodes in one family were characterized by painless stiffening, followed by chorea or ballismus. The frequency of episodes decreased later in life. Other associated findings included progressive spastic paraparesis with onset in early adulthood, mild ataxia, mild-to-moderate cognitive impairment, and seizures [42].

Paroxysmal Non-Epileptic Events

Paroxysmal non-epileptic events, including movement disorders, occur in patients across the spectrum of severity of Glut1 DS [7••, 26, 43]. Approximately 30 % of patients with the classic, early-onset epileptic phenotype have been reported to experience such episodes [7••, 26].

Individuals with Glut1 DS may experience a variety of episodic neurologic symptoms (Table 1). The onset of episodes may be acute or gradual. Episodes last from minutes to hours in most cases, but occasionally last days [26]. Movement disorders feature prominently, but other paroxysmal symptoms also occur. Some patients experience episodic monoparesis, hemiparesis, or total body paralysis. In one patient, the pattern of hemiplegic episodes and accompanying clinical features mimicked the syndrome of alternating hemiplegia of childhood [44]. Other paroxysmal symptoms include migraine headaches [45], vomiting [32, 46], and behavioral symptoms such as irritability, lethargy, and confusion [26, 32, 47].

Common triggers for episodic symptoms are fasting (upon waking, or before meals) and exercise. Other reported triggers include poor compliance with the ketogenic diet, fatigue, stress or excitement, and intercurrent febrile illness [26, 32, 46]. Sometimes, no trigger can be identified.

Table 1 Paroxysmal non-epileptic events in Glut1 DS

Movement disorders
Intermittent ataxia
Chorea
Dystonia
Parkinsonism
Myoclonus
Dyspraxia
Paroxysmal exertional dyskinesia (PED)
Paroxysmal non-kinesigenic dyskinesia (PNKD)
Other neurological symptoms
Confusion
Lethargy
Somnolence
Dysphoria, inconsolable crying
Migraine headaches
Vomiting
Sleep disturbance
Hemiparesis
Total body paralysis

More than one factor may contribute to the increasing recognition of paroxysmal symptoms, particularly movement disorders, in patients with Glut1 DS. First, a greater number of patients who have milder phenotypes, which consist of a movement disorder without seizures, have been diagnosed. Second, the increased awareness of paroxysmal motor symptoms also may lead to an increased identification of these episodes in patients with the classic, early-onset epileptic phenotype who may develop paroxysmal movement disorders in the second and later decades of life as their seizures become less prominent (authors' unpublished observations). This observation also suggests an age-dependent vulnerability to glucose deficiency in different brain circuits.

Cognitive and Behavioral Features

The majority of patients with Glut1 DS experience some degree of cognitive impairment, ranging from mild learning disability to severe intellectual impairment. Effects on general intellectual function, language development, adaptive behavior, and behavior have been examined.

General Intellectual Function

Most reported cases of individuals affected by Glut 1 DS list intellectual performance in the mental retardation range [7••, 17, 46, 48, 49]. Leen et al. reported that among 36 patients, all were mentally retarded with 36 % in the mild range,

44 % in the moderate range, and 17 % in the severe range [7••]. Among individuals in our sample, however, a wide range of intellectual performance has been found. Not all individuals score in the mentally retarded range. Data from 64 affected individuals shows intellectual performance is normally distributed but the mean is shifted down about 2 standard deviations from the general population, with about a quarter of the cases scoring within the average to low average range (De Vivo et al. manuscript in preparation).

Language Development

Language delays were noted in the first 2 described patients with Glut1 DS. The 2 27-month old infants each showed delayed language development; one had some single words while the other remained nonverbal [3]. Language skills have been noted to be extremely variable, ranging from no apparent deficits to absence of expressive speech, with the majority of affected individuals having reduced skills [48, 49]. Dysarthria is common, making understanding of the affected individual's speech difficult [46]. We described a patient's speech as halting, with pauses between syllables, having numerous articulation errors, and dropping the ending sounds of words [50]. Similar speech characteristics are observed across many, but not all, affected individuals and interfere with speech intelligibility. In addition, receptive language skills are disproportionately stronger than expressive skills for most affected individuals, although this may be confounded somewhat by the dysarthria (authors' unpublished observations).

Adaptive Behavior and Behavior

Adaptive behavior, or the measure of an individual's daily functions as reported by their parent or caretaker, is also adversely affected. As with other clinical manifestations of Glut 1 DS, there is wide variability across affected individuals, with a minority having normal adaptive behavior skills for their age and most having lower than expected adaptive skills. Indeed, in a sample of 13 cases, adaptive scores ranged from 23 (severely impaired) to 99 (normal function) [17]. We have seen this wide range across a larger sample of affected individuals as well, and have consistently noted that adaptive socialization skills are strengths for the group [49], (authors' unpublished observations). This finding is in agreement with general observations of the children's behavior that find them to be well related, socially outgoing, and friendly.

Sustained attention appears be an area of particular weakness for the people affected with Glut 1 DS, and this may be related, in part, to the availability of metabolic fuel in the CNS at any given moment. In a small group of children with Glut 1 DS, transient improvement in attention performance was found during the acute hyperglycemic phase following oral glucose ingestion [17]. Attention was described as improved as well in a group of children with Glut 1 DS who were treated with a modified Atkins diet [46]. Moreover, as attention is adversely affected during seizure, underlying brain electrical activity may well present as significant fluctuations in attention for affected individuals. Parents describe distinct periods when their child is "on" vs "off," and during the "off" periods children are inattentive and distractible and present with symptoms of Attention Deficit Disorder (authors' unpublished observations).

Extraneurologic Features

Hemolytic anemia was first described as a component of Glut1 DS in a family with PED and epilepsy [38••], The Glut1 transporter is expressed on the red blood cell membrane and conveys glucose into the red cell. The specific mutation in the family reported by Weber et al. (deletion of 4 amino acids, Q282-S285del) was found to induce a cation leak across the red blood cell membrane, leading to structural instability. A further 3 patients with hemolytic anemia associated with erythrocyte cation leak due to Glut1 DS have been recently reported [51, 52]. Two unrelated patients had the same 3-nucleotide deletion at the C-terminal (Ile435 or 436del) [51, 52], while the third had a point mutation adjacent to the putative glucose transport pathway (Gly286Asp) [51]. All 3 of these patients had a multisystem disorder characterized by hemolysis with hepatosplenomegaly, a neurologic syndrome (childhood onset seizures, mental retardation, motor abnormalities) and cataracts. The patient described by Bawazir et al. additionally had periventricular calcifications detected on brain imaging [52]. The precise pathophysiology of cataract formation remains to be elucidated. Glut1 deficiency has been demonstrated to cause defective development of ocular vasculature associated with exudation of blood cells on the lens in a zebrafish model, hinting at one possible mechanism [53].

Phenotypic Severity

A clinical scoring system, developed to classify phenotypic severity for mitochondrial diseases and Glut1 DS [54], has been used to correlate clinical severity with residual Glut1 activity, and with genotype [8••]. In a recent study, 53 affected individuals were stratified clinically according to the Columbia Neurological Score (CNS) into 4 groups: Minimal (CNS 70–76), Mild (CNS 60–69), Moderate (CNS 50–59), and Severe (CNS 40–49) [8••]. Patients with

the classic, early-onset epileptic phenotype fall into the moderate to severe range in this classification system.

Erythrocyte Glucose Uptake Assay

The erythrocyte glucose uptake assay is a functional surrogate measure of residual Glut1 transporter function [8••], currently performed on a research basis. Individuals with the classic Glut1 DS phenotype have on average 50 % residual glucose uptake, resulting from loss-of-function mutations that result in a 50 % reduction in Glut1 activity. A milder clinical phenotype with intermittent symptoms (epilepsy, movement disorders) may be expected with a 25 % reduction in Glut1 activity 6••, 55•]. These clinical observations are consistent with a mathematical model of glucose transport in the brain, which predicted that a 25 % reduction of Glut1 activity would cause only a modest reduction in glucose flux under conditions of normoglycemia, but erase the buffer which protects the brain from mild hypoglycemia [56]. The same model projected a 25 % decrease in Glut1 activity to cause a 50 % reduction in brain intracellular glucose concentration, while a 50 % reduction in Glut1 activity (similar to many patients with the classical Glut1 DS phenotype) would cause brain intracellular glucose concentration to fall to 10 % of normal [56]. Absence of Glut1 transporter expression is embryonic lethal [57, 58].

Genotype–Phenotype Correlations

Approximately 40 % of patients with Glut1 DS have a missense mutation in *SLC2A1*, and a range of other mutation types are observed in the other 60 % (Table 2). A relationship between clinical severity and the specific type of *SLC2A1* mutation has been noted recently [7••, 8••]. Missense mutations were detected predominantly in individuals with mild to moderate clinical syndromes. Splice site and nonsense mutations and insertions, deletions, and exonic deletions were associated with moderate to severe clinical syndromes. Complete gene deletions clustered in the severe clinical category [8••, 55•]. Despite these trends, there remains considerable clinical variability that is not explained by mutation type alone. For example, some patients with missense mutations have a severe phenotype, and among patients with the same mutation, clinical severity may vary considerably [7••].

Table 2 Type of *SLC2A1* mutation detected in 127 patients with Glut1 DS

	Leen 2010 [7••] no. (%) *n*=57	Yang 2011 [8••] no. (%) *n*=70	Total % *n*=127
Missense	23 (40)	29 (41)	41
Nonsense	7 (12)	5 (7)	9
Frameshift	15 (26)	20 (29)	28
Splice site	6 (11)	6 (9)	9
Multiple exon deletion	6 (11)	5 (7)	8
Complete gene deletion	–	5 (7)	5

Management

Ketogenic Diet

The ketogenic diet is the mainstay of therapy in Glut1 DS. The rationale for its use is to provide an alternative source of fuel for the brain. This serves 2 functions: (1) to support brain growth, which is particularly vital in the first decade of life; and (2) to support normal neuronal function, thereby controlling symptoms. We recommend early initiation of the ketogenic diet based on the assumption that early diagnosis and treatment improves the long term neurologic outcome.

The symptom domain in which the effect of the ketogenic diet has been most systematically assessed is control of seizures. The majority of patients with seizures experience an improvement in seizure control on initiation of the ketogenic diet, with half to two-thirds achieving complete seizure freedom on the diet alone [7••, 8••, 11•, 48]. The improvement is often rapid. In a recent retrospective study by Pong et al. [11•], two-thirds of the 41 patients who experienced a complete resolution of seizures (28/41) did so within one week of diet initiation.

The effect of the ketogenic diet on motor and cognitive symptoms is more variable, and has been characterized in less detail than the seizure response. A clear improvement in motor symptoms has been documented in individual patients with persistent movement disorders, including chorea, dystonia, and ataxia [28, 59]. However this benefit is not universally observed [7••]. Paroxysmal dyskinesias have also been reported to respond very well to the ketogenic diet [7••, 38••, 45]. Many parents notice an improvement in their child's attention and concentration upon starting the ketogenic diet. However, the effect on cognition in the long-term has been harder to quantify, and to distinguish from the benefit attributable to the control of refractory seizures.

To optimize treatment while patients are on the ketogenic diet, we recommend supplementation with carnitine 50 mg/kg/day (which is deficient in the diet, and essential for the metabolism of fats) [60], and alpha-lipoic acid, which has been shown to facilitate glucose transport into Glut4-dependent cultured skeletal muscle cells [61], although clinical efficacy has not yet been proven. Medications that should be avoided include phenobarbital (inhibits Glut1 activity) [24], valproic acid (inhibits Glut1 and may partially inhibit

fatty acid oxidation), and carbonic anhydrase inhibitors such as acetazolamide, zonisamide, and topiramate (which may potentiate metabolic acidosis and nephrocalcinosis).

Other Management Strategies

While the ketogenic diet is considered the current gold standard of treatment for Glut1 DS, it is a substantial challenge for many patients to sustain the diet for many years in the face of the extreme dietary restriction it demands. With this in mind, a recent study evaluated the effect of the less restrictive modified Atkins diet (which restricts carbohydrates to10 grams per day, and derives 65 % of daily calorie intake from fat) in 6 patients with Glut1 DS, who had presented with early-onset seizures [46]. Dysarthria, gait, and attention improved, as did paroxysmal symptoms such as vomiting, headache, and dyskinesias. The 5 patients with active seizures experienced a 90 % reduction in seizure frequency, albeit with concomitant anticonvulsant monotherapy. Seizure control, however, is not the ultimate treatment goal. It is more important to provide sufficient metabolic fuel to support optimal brain growth and development during infancy and childhood.

Medications remain an additional strategy for controlling symptoms in patients with milder syndromes. For example, infrequent seizures in adolescents and adults may be managed with anticonvulsant medications. Paroxysmal dyskinesias have been reported to respond extremely well to treatment with acetazolamide in 2 cases [59, 62]. However, medications do not correct inadequate nourishment necessary for brain growth and development, the central mechanism underlying the Glut 1 DS. Fuel availability remains central to the optimal long term outcome in this treatable clinical condition.

Conclusions

The original Glut1 DS phenotype, an infantile developmental encephalopathy with refractory seizures, developmental delay, acquired microcephaly, and a motor disorder, describes most patients diagnosed with Glut1 DS to date. The clinical manifestations associated with Glut1 DS are now recognized to be diverse. The recent recognition of milder clinical syndromes, including those in which patients may have few neurologic abnormalities between episodic symptoms such as seizures or movement disorders, suggest that, in time, an ever decreasing proportion of patients will fit the original phenotype. An awareness of the expanding clinical spectrum will alert physicians to consider the diagnosis of Glut1 DS, particularly if neurologic symptoms (of any type) worsen with fasting or exercise. Further investigations, including CSF glucose analysis and molecular genetic testing, should be carried out to determine if Glut1 DS is the diagnosis in such cases. Current treatment with a ketogenic diet, although burdensome, is effective. Future therapies hopefully will succeed in restoring glucose transport activity obviating the need for the restrictive dietary regimen.

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