Glucose transporter type 1 deficiency: a study of two cases with video-EEG

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Abstract Glucose transporter type 1 (GLUT1) deficiency is an inborn error of glucose transport. Clinical manifestations are presumed secondary to reduced glucose transport across the blood brain barrier, and include seizures, abnormal tone, developmental delay and hypoglycorrhachia. A high index of suspicion is important as GLUT1 deficiency is a potentially treatable cause of mental retardation. We studied two affected children by continuous video-EEG in order to better understand the cause of the clinical manifestations and improvement on a ketogenic diet. The EEG was characterized by generalized paroxysmal 2–2.5 Hz spike-wave discharges, although normal EEGs were also obtained. Atypical absence seizures were the most prominent clinical seizure. Epileptiform activity and clinical seizures occurred in both children while acutely ketotic and non-ketotic, but were markedly more frequent in one child when non-ketotic. Discharges were not associated with a reduction in substrate for brain metabolism in the blood at that time.

Conclusion Atypical absence seizures are common in glucose transporter type 1 deficiency and should alert the clinician to the possibility of this treatable disorder when present in a young child with developmental delay. Our data suggest that the therapeutic mechanism of the ketogenic diet in this disorder is more complicated than simply delivering ketones as an alternative substrate for brain metabolism.

Key words Glucose transport · Absence seizures · Video-EEG · Ketogenic diet · Blood-brain barrier

Abbreviation GLUT1 glucose transporter type 1
Introduction

Glucose is an essential substrate for a wide variety of biosynthetic pathways, as well as an important fuel for many tissues, especially brain. A family of six facilitative glucose transporters has been identified which aid the movement of this hydrophilic substrate across membranes [5]. Glucose transporter type 1 (GLUT1) is the sole glucose transporter on the surface of brain endothelium, where it is found at a density of about 10 times greater than that in any other tissues except erythrocytes [4, 7]. Curiously, GLUT1 is also the sole glucose transporter on human erythrocytes [5, 7], and this provides an easily accessible tissue for assessing GLUT1 transporter activity.

GLUT1 deficiency was first described by De Vivo et al. in two children with seizures, developmental delay and persistent hypoglycorrhachia [4]. A total of 18 cases currently are known to the authors, including 8 cases briefly described by De Vivo et al. [1, 2]. However, only the original two cases have been published in detail [4]. Neurological symptoms, including seizures and developmental delay, have been present in all cases, presumably due to a decreased supply of glucose to the brain. All cases reported have had the onset of symptoms in the 1st year of life. Phenotypic severity has ranged from generalized seizures starting on the 2nd day after birth with subsequent microcephaly, severe hypotonia, and profound developmental delay in the worst cases, to normal early development and frequent absence seizures. Both large deletions and point mutations in the GLUT1 gene have been described with molecular data suggesting autosomal dominant [10] and autosomal recessive [8, 9] inheritance in different families. However, all cases reported to date have been sporadic.

The ketogenic diet has been suggested as the treatment of choice in GLUT1 deficiency as chronic ketosis presumably provides an alternate source of fuel for the brain [4]. The response to the diet has been varied, although some benefit has been appreciated in many cases, including improved seizure control and accelerated developmental gains [1, 2, 4 and the present authors’ observations]. However, seizures are not completely eliminated and adherence to the diet is difficult. Intractable epilepsy, unresponsive to anticonvulsant therapy, has been central to the phenotype in the majority of untreated cases, however, only brief summaries of the EEG in a few cases have been published [2, 4]. Moreover, the influence of the ketogenic diet, as well as acute deviations from the diet, on brain electrophysiologic activity has not been well characterized.

To further elucidate the clinical spectrum of this disorder, we present two additional cases with GLUT1 deficiency. Both cases exhibited tonic-clonic seizures under excellent control on anticonvulsants, but continued to have symptoms associated with atypical absence seizures. In order to better understand the cause of the clinical manifestations and improvement on a ketogenic diet, we performed continuous video-EEG monitoring while on the ketogenic diet and also following a nonketogenic challenge meal.

Case reports

Case 1

This child was a 3220 g male of Italian/Norwegian ancestry born after 36 weeks gestation. Developmental milestones were moderately delayed, with walking and first words at age 2 years. Eye rolling started at age 3 months. He had one generalized tonic-clonic seizure at age 2 years and was treated with phenytoin. EEG showed generalized irregular spike activity and localized right sided discharges without clinical accompaniment. Because of persistent absence seizures the anticonvulsant was changed to valproic acid, which was discontinued at 4.5 years of age following a normal EEG. Monthly “episodes” of lethargy and ataxia started at age 4 years. By age 5 years, episodes occurred twice weekly and included hypotonia, slurred speech, and emotional lability. These episodes lasted minutes to hours, often appearing after high protein meals and upon awakening in the morning. By age 5.5 years these episodes occurred almost daily and the child rarely attended school. The parents summarized these episodes by stating that their child appeared “drunk”. A vegetarian diet (1.0 g protein/kg/d) was associated with a decrease both in the frequency and duration of the episodes.

Physical examination showed decreased distal musculature, mild ataxia, mild diffuse hypotonia and slight dystonic posturing of the distal lower extremities. Several episodes were witnessed by three of the present authors and represented a significant deterioration in function from baseline. Of specific note were frequent 1–2 s intervals of staring without loss of tone. At age 5 years, weight was at the 3rd percentile, height was at the 25th percentile and head circumference was at the 50th percentile. A Kaufman Assessment Battery for children performed at age 5.0 years revealed a scattering of sub tests scores ranging from below 2.6 to 6.9 years; performance was worst on motor coordination and visual motor integration tests, and best on auditory input and sequential memory tests.

Laboratory results are detailed in Table 1. CSF glucose was low on two occasions while CSF lactate was normal. Persistent mild hyperammonemia (50–80 μM/L, normal < 35) occurred on an unrestricted diet for at least a year following the discontinuation of valproic acid. Plasma ammonia remained normal while on the low protein diet. GLUT1 deficiency was diagnosed at age 5.5 years by a low initial erythrocyte uptake of 3-O-methyl glucose (Table 1) and decreased specific D-glucose inhibitable binding of 3H-cytochalasin B to erythrocyte ghosts.

A ketogenic diet with 70% of calories from fat was started and within 1 month the episodes essentially resolved. Fine motor coordination and attention span markedly improved in the next few months, and the child returned to school with rare absences. At present, he is in the 6th grade at age 12 years and is performing at grade level. Neurological sequelae are limited to mild difficulty in motor skills and speech articulation. Epileptic seizures occur rarely and are usually associated with excess carbohydrate intake. Interestingly, on the ketogenic diet protein intake up to 2–3 g/kg per day are well tolerated without inducing symptoms or hyperammonemia.

Case 2

This child was a 2630 g term male product born to unrelated Guatemalan parents. Family history was noncontributory. At 2 months of age he had inconstant crying and frequent tonic-clonic and atypical absence seizures. Phenobarbital and valproic acid controlled the tonic-clonic seizures, although brief staring spells