Objectives: To expand the spectrum of glucose transporter type 1 deficiency syndromes with a novel clinical and radiological phenotype not associated with microcephaly.

Design: Case report.

Setting: Two academic medical centers.

Patient: A 7-year-old patient followed up for 4 years.

Results: The patient exhibited a predominant syndrome of chorea and mental retardation associated with a combination of paroxysmal ataxia, dysarthria, dystonia and aggravated intellectual disability induced by fasting or exertion. She harbored a sporadic, heterozygous amino acid insertion in the GLUT1 transporter (insY292) that, in all likelihood, impaired blood-brain glucose flux. Her brain configuration appeared hypotrophic via magnetic resonance imaging, particularly over the occipital lobes. A ketogenic diet resulted in brain growth that accompanied a favorable symptomatic outcome.

Conclusions: To date, glucose transporter type 1 deficiency syndrome includes several epileptic and movement disorder phenotypes caused by the clinical expressivity of the prominent cortical, basal ganglia, and cerebellar abnormalities found in the disease, but hypomorphic or novel variants are probably yet to be discovered.


In the brain, structure and function are intimately interrelated such that a change in structure necessarily implies a noticeable change in function. The converse relationship remains unproven, or, at least, not as easily observable via current neurological methods, but there is no reason why it should not be assumed to be valid. The study of brain energy utilization disorders offers an exceptional window into a curious group of bifunctional compounds that support both the structure and the function of the nervous system. On one hand, brain fuels supply most of the carbon and all the energy that the brain needs to function (for example, to maintain electrical excitation-inhibition balance at synapses and cell bodies), while on the other hand, brain fuels become brain matter in the form of cell membranes, myelin, and other structures. Rare brain-fuel–utilization mutants support the hypothesis that brain growth and excitability are always coupled, probably since the time of neurogenesis, such that energy failure is commonly associated with epilepsy at any and all stages of life. What remains to be determined is whether the brain retains the capacity to utilize fuel for architectonic (structural) purposes once most of the neurogenetic forces subside (ie, after infancy). In practice, in the context of serious diagnostic challenges (energetic compounds are notoriously elusive from an analytic point of view), the implications of late energy-metabolism—defect detection and treatment would seem minimal or, at best, only palliative if the brain had already exhausted its growth potential earlier in life. In contrast with this contention, a variety of available and potential alternate fuel treatments would be worth administering should the brain retain the capacity to grow at later developmental stages.

When the principal brain glucose transporter (GLUT1, the main gateway to brain fuel) mutates, patients often experience epilepsy and deceleration of head growth (an indicator of brain stagnation). It is thought that epilepsy further aggravates energy deficits by increasing metabolic demands. Ketones, which are energetically equivalent to glucose, rapidly restore brain excitability and prevent epilepsy, but
whether ketones can also contribute to brain growth after infancy, when the brain relies primarily on glycolysis, is not known. Of note, ketones are also an effective treatment for epilepsy owing to pyruvate dehydrogenase deficiency, a brain dysgenetic syndrome that limits acetyl coenzyme A production. In the common form of the disease, the brain bears the functional consequences of aberrant neuronal migration and connectivity in the context of elevated lactate concentrations.7

We set out to uncover nonconvulsive forms of GLUT1 deficiency (GD) to investigate whether brain growth is feasible after infancy by observing patients with a treatable encephalopathy not associated with dysgenesis, epilepsy, or systemic metabolic disturbance that could skew energy utilization and growth potential. We reasoned that, with rare exceptions, the identification of most patients with GD known to date has relied on the presence of epilepsy and that our understanding of the disease may be skewed because of this ascertainment bias.4,8 A novel GD syndrome that consists of chorea and mental retardation in the context of cerebral hypotrophy, an unusual syndromic association, was identified in a child who carried a sporadic insertion in the GLUT1 transporter. Brain fuel replacement via a ketogenic diet at 5 years of age resulted in almost full suppression of extrapyramidal symptoms and in brain growth, despite the demonstration of the persistent inability of the brain to take up glucose in healthy fashion, which suggests that ketones had become brain matter. The results are indicative of a dormant cerebral developmental potential that can be harnessed by circumvention of the obstruction to acetyl coenzyme A synthesis that probably underlies the manifestations of the disease.

REPORT OF A CASE

A 5-year-old, white, developmentally delayed girl experienced an abrupt neurological decompensation that consisted of flaccidity and loss of ambulation without impairment of consciousness. She was the second child born to healthy, nonconsanguineous parents. Her brother, 8 years old, had hemiparesis owing to perinatal middle cerebral artery occlusion. The proband had been born at term after an uneventful pregnancy. Apgar scores were normal, as were her appearance, anthropometric dimensions, and newborn screening results. Alternating converging strabismus was noted and unsuccessfully treated surgically and later by chemodenervation in the first months of life. Ambulation was delayed until 22 months of age and then impaired by unsteadiness and frequent falls. First-language acquisition was also delayed until the second year of life. At presentation (age 5 years), she became spontaneously prostrate and flaccid for several minutes. Recovery ensued without intervention. Comprehensive blood, urine, and cerebrospinal fluid (CSF) metabolic indicators (such as folate and neurotransmitter metabolites) which are typically assayed when inborn errors of metabolism are suspected, disclosed no abnormalities, except that CSF glucose was not reported. Brain magnetic resonance imaging at 1.5T illustrated moderately severe supratentorial cortico-subcortical atrophy with a predilection for the occipital lobes and ventricular enlargement. Hemispheric myelination was normal, as was cerebellar morphology. Electroencephalography revealed mild diffuse slowing of the electrocerebral rhythm, especially over the posterior brain. One year later, the patient had entered a mainstream school under a modified curriculum and special pedagogic support. Her motor performance remained stable except for recurrent, brief episodes of slowed psychomotor ability, dysarthria, and gait ataxia accompanied by orolingual and hand dyskinesia. These episodes occurred twice per week and were induced by fasting or fatigue.

She was engaging and well formed, but had incessant limb movements that denoted chorea. Her head circumference measurements had always progressed along the 85th percentile. She had convergent strabismus and dysarthria. Her muscle tone was globally decreased and her reflexes hyperactive. The choreic movements were present at rest and consisted of proximal jerks that affected both the upper and lower limbs; she tried to incorporate those jerks into healthy limb action. Action hand tremor, upper limb dystymia, truncal ataxia, a broad-based gait, and lower limb incoordination when not bearing weight were associated but minor features. Blood glucose and lactate were reexamined and found to be at normal levels, but CSF glucose and lactate concentrations were diminished (1.9 mM [34.2 mg/dL; range 2.2-3.4 mM] and 0.68 mM [0.075 mg/dL; range 1.2-2.2 mM], respectively). The rest of the CSF investigations (ie, protein, cells, amino acids, pterins and neurotransmitter metabolites) were normal. Direct DNA sequencing of 22 amplicons that comprised both strands, including the entire coding region and all intron splice sites and introns (except intron 1) of the SLC2A1 gene (which encodes GLUT1), revealed 5 known polymorphic variants and a heterozygous amino acid insertion coding for tyrosine (Y) between amino acid residues 291 to 292 (insY292) that were absent from all her first-degree relatives and other healthy individuals (NM_006516.2). The insertion is located at the extracellular boundary of the seventh transmembrane domain of the transporter, in the vicinity of threonine 295, a residue that, when mutated, causes the common GD phenotype by the alteration of transport kinetics through the impediment of substrate release from the extracellularly bound transporter.9-12

A ketogenic diet was initiated and indefinitely maintained, with persistent ketosis (blood β-hydroxybutyric acid levels routinely exceeded 4 mM). Mild early blood carnitine depletion was restored with oral L-carnitine supplementation (50 mg/kg/d). Implementation of the diet was followed by considerable clinical improvement, including the cessation of both chorea and paroxysmal episodes (except one occurrence) and the reduction of limb ataxia, which allowed the girl to learn to run. In the opinion of all caregivers, her neuropsychological performance was unmodified by the diet. Measures of her executive function, linguistic ability, memory, matrix solving ability, and intellectual quotient remained below the fifth percentile for age, in the context of an unusually robust motivation and a cooperative demeanor, a striking feature of GD. Magnetic resonance imaging at 7 years...
of age revealed significant brain growth, as manifested by a reduction of the subarachnoid space and the cerebral ventricular volume relative to the previous studies. At the same age, $[^{18}F]$ fluoro-2-deoxy-D-glucose positron emission scanning revealed persistently decreased glucose uptake ability in the cerebral cortex, cerebellum, and thalamus with relatively prominent basal ganglia uptake in a pattern typical of GD14 (Figure 1).

The case described illustrates several principles: first, unsuspected GD phenotypes are likely to remain unidentified until genotyping replaces the ascertainment bias introduced by diagnostic criteria currently in use. At the same age, $[^{18}F]$ fluoro-2-deoxy-D-glucose positron emission scanning revealed persistently decreased glucose uptake ability in the cerebral cortex, cerebellum, and thalamus with relatively prominent basal ganglia uptake in a pattern typical of GD14 (Figure 1).

Second, genotype-phenotype correlations in GD seem implausible from the analysis of the approximately 125 patients that have been described in the literature.9,15-20 While it is not feasible to predict the structural disruption induced by the insertion mutant described in this report, neighboring mutations alter the cellular expression, targeting, and function of GLUT1 in unpredictable ways when considered against the transporter primary and proposed tertiary structures.9 Third, the clinical semiology of GD states includes static neurological impairments (often manifested as mental retardation, spasticity, dysarthria, ataxia, and dystonia, either together or in various syndromic combinations18,21) in conjunction with paroxysmal events such as epilepsy, flaccidity, dyskinesia, or opsoclonus. Often, but not invariably, these states manifest in the context of small fluctuations in blood glucose concentration, such as those achieved by fasting or nourishing individuals with otherwise unimpaired carbohydrate metabolism.4 Except for rare exceptions such as the case presented here and another case that involved delayed cerebral myelination,22 the neurological substrate
has appeared uninformative from a structural point of view (to our knowledge, no pathological analysis of GD has yet been undertaken), while cerebral glucose uptake has proven remarkably and uniformly altered over select brain regions.14 In fact, even transient hypoglycemia during infancy has been associated with a clinical-metabolic imaging phenotype similar to GD.8 Therefore, the phenotype is not accounted for by brain structure or brain glucose uptake, although, to our knowledge, quantification of glycolysis has not yet been attempted in GD. Of the 4 fundamental derivatives of brain fuels (brain matter, adenosine triphosphate, and the neurotransmitters glutamate and γ-aminobutyric acid), only the first has been investigated (and proven abnormal) in mice23,24 and human patients,8 both of which can have microcephaly. Therefore, fluctuations in adenosine triphosphate levels or neurotransmitter action across different cerebral networks may account for the pleomorphic phenotypes of GD syndromes. The results invite further considerations: only select features of neuroglycopenia (including that caused by GD) may be treatable. In other words, all the paroxysmal manifestations of the disease, and perhaps brain growth, can be significantly ameliorated, whereas the impairment of intelligence and thalamocortical metabolism persists,8 which underscores the developmental role of glucose on cerebral maturation and serves as the defining feature of GD.

Accepted for Publication: March 31, 2009.

Correspondence: Juan M. Pascual, MD, PhD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Mail Code 8813, Dallas, TX 75390-8813 (Juan.Pascual@UTSouthwestern.edu).

Author Contributions: Study concept and design: Pérez-Dueñas, Prior, and Pascual. Acquisition of data: Pérez-Dueñas, Prior, Ma, Fernández-Alvarez, Setoain, Artuch,
and Pascual. Analysis and interpretation of data: Pérez-Dueñas, Prior, Ma, Fernández-Álvarez, Setoain, Artuch, and Pascual. Drafting of the manuscript: Pérez-Dueñas, Prior, Artuch, and Pascual. Critical revision of the manuscript for important intellectual content: Pérez-Dueñas, Prior, Ma, Fernández-Álvarez, Setoain, Artuch, and Pascual. Obtained funding: Pascual. Administrative, technical, and material support: Pérez-Dueñas, Prior, Ma, and Fernández-Álvarez. Study supervision: Pérez-Dueñas and Artuch.

Financial Disclosure: None reported.

Funding/Support: This work was supported by grant number 5UL1RR024982-02 from the National Institutes of Health, and by a grant from the Fondo de Investigación Sanitaria (P1070348). The Centro de Investigación Biomédica en Red: Enfermedades Raras is an initiative of the Instituto de Salud Carlos III.