**Brain Glucose Supply and the Syndrome of Infantile Neuroglycopenia**

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**Objective:** To describe neuroglycopenia as a specific syndrome caused by insufficient glucose availability during brain development.

**Design:** Neurologic examinations, neuropsychologic tests, biochemical methods, and functional imaging.

**Participants:** Patients afflicted by genetic mutation of the cerebral glucose transporter type 1 and a patient afflicted by persistent infantile hypoglycemia (hyperinsulinism) matched to her healthy twin.

**Results:** The hallmark of the phenotype is the combination of infantile epilepsy and cerebellar and pyramidal tract dysfunction, together with permanent neuropsychologic abnormalities and reduced thalamocortical glucose uptake despite subsequent supply of energetic substrate.

**Conclusions:** When neuroglycopenia—the lack of adequate glucose supply to the nervous system—occurs in the developing brain, thalamic and cortical metabolism mature aberrantly, causing epilepsy associated with other characteristic neurologic and behavioral disturbances, a pattern also reflected in functional images, as if there were a temporal window during which glucose were crucial for brain development. When maturation is complete, glucose merely serves as a fuel, and then, when deficient, it only causes unrelated disturbances.

*Arch Neurol.* 2007;64:507-513

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and exchange energy via the formation and breakdown of bonds found in certain compounds. Not all substances with the potential to restore high-energy bonds are efficient fuels, because only a few are recognized by cells. Thus, energy metabolism is inextricably dependent on molecular recognition. Most energetic compounds function as molecular signals in addition to fuels, because they regulate their own metabolism, acting directly on enzymes and genes. Therefore, disorders of energy metabolism cause secondary genetic dysregulation, similar to the way deficiencies of transcription or trophic factors alter gene expression. An additional mechanism, of not only metabolic disorders but of all genetic diseases, involves widespread effects exerted by a mutant gene on the rest of the genome at the pretranslational level, regardless of the function of the gene product. The effects of both substrate-mediated modulation and of mutation-induced intragenomic changes on the development of the nervous system are unknown in most neurometabolic diseases, partly because they need not act exclusively and partly because of oversimplified gene/protein function paradigms that do not describe metabolism accurately.

Brain energy serves 2 purposes: development and activity maintenance. After birth, brain metabolism relies predominantly on glycolysis, which is stimulated at an accelerated rate. During childhood, the cerebral uptake of glucose increases, exceeding that of the newborn by 3-fold and that of the adult by 2-fold. In the adult, the cerebral metabolic rate for glucose stabilizes and, at this time, can be assumed to mainly reflect maintenance consumption. The large difference between the highest (child) and lowest (neonate) glucose consumption includes expenditures in development.

Numerous energy-consuming processes are limited or preferentially circumscribed to infancy and childhood, but among them the formation and consolidation of neural circuits—which include

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the division and movement of neurons and precursors, and the generation and pruning of synapses—are associated with a high energetic demand. This energy must ultimately be derived from glucose. There are two instances where the cerebral access of glucose is compromised for a sufficiently prolonged period of time to impact development: one is mutation of the glucose transporter type 1 (GLUT1) of the blood-brain barrier, and the other is chronic congenital (or early infantile) hypoglycemia. Neither resembles acute hypoglycemia, which causes a different type of encephalopathy dominated by cellular injury.

The classic phenotype of GLUT1 deficiency is known, most patients who are GLUT1 deficient manifest encephalopathy dominated by hyperexcitability (epilepsy) and abnormalities of cognition and motor control that respond to a ketogenic diet to a varying degree. In particular, seizures are typically controllable with this diet, whereas other patients experience a transient improvement in neurologic performance after a carbohydrate load. Independent of these interventions, most patients exhibit a persistent, residual encephalopathy characterized by the constellation of motor and language dysfunction and mental retardation together with thalamocortical hypometabolism and accentuated basal ganglia metabolism as detected by $^{18}$F-2-deoxyglucose positron emission tomography (PET). This peculiar imaging pattern appears to be imprinted on the brain in infancy and remains essentially immutable, indicating that deficiency of GLUT1 causes an abnormal neural maturation and functional pattern during the earlier developmental interval.

We set out to elucidate whether this aberrant pattern was caused by the genetic deficit of GLUT1 (ie, by virtue of the mutation of the glucose carrier irrespective of its function as a transporter) or whether it was simply the consequence of diminished brain glucose availability during a specific developmental interval despite a normal GLUT1 gene. The clinical, neuropsychologic, and PET study of twins with normal GLUT1 expression, one of whom was afflicted by chronic congenital hypoglycemia, supported the latter mechanism, indicating that glucose, rather than GLUT1, is required for the development of normal excitability in certain cerebral regions during a critical developmental interval.

### METHODS

**PARTICIPANTS**

Informed consent conforming to the guidelines of the institutional review board of Columbia University and the Columbia Kreitchman PET Center was obtained from all research participants. Patients who are GLUT1 deficient (one of whom is subsequently described further), a congenital hypoglycemia patient, and the healthy twin sister of the latter were assessed for signs and symptoms of encephalopathy, erythrocyte glucose uptake (mediated by GLUT1), and sequence analysis of the GLUT1 gene if erythrocyte glucose uptake was abnormal.

Participant 1, a 23-year-old woman, experienced unrecognized hypoglycemia earlier in her life. Seizures were present since 3 months of age and were followed by a progressive epileptic encephalopathy that was refractory to anticonvulsants. From age 3 to 15 months, head circumference growth had decelerated from the 50th percentile to 2 cm below the third percentile, where she remained all of her life. Studies before the participant aged 15 months included a computed tomography scan of the head; electroencephalography; and examination of visual- and auditory-evoked potentials; urine oligosaccharides and amino acids; blood gases, pH, ammonia, lactate, pyruvate, amino acids, organic acids, lysosomal hydrolases; and cerebrospinal fluid lactate, pyruvate, and amino acids. All study results were normal. At age 15 months, a routine blood chemistry survey obtained while fasting during a hospital admission for further evaluation revealed a blood glucose of 15 mg/dL (0.83 mmol/L). Additional blood glucose determinations confirmed hypoglycemia. During a brief (6-hour) fast, blood glucose concentration fell from 92 to 32 mg/dL (5.1 to 1.8 mmol/L). At the end of the fast, a glucagon stimulation test resulted in a marked glycemia response peaking at 134 mg/dL (7.4 mmol/L), suggesting hyperinsulinism. Diazoxide and ephedrine failed to control glycemia and the patient ultimately necessitated a nasogastric glucose drip to prevent seizures associated with hypoglycemia. Several additional maneuvers also suggested hyperinsulinism: a ketogenic diet failed to generate ketone bodies despite decreasing glucose levels, and a leucine load failed to alter glycemia. Insulin levels were more often normal than elevated. A subtotal pancreatectomy (85%) revealed a pancreatic tail adenoma and islet cell material throughout the body of the organ, consistent with nesidioblastosis. On discharge several weeks later, the patient's neurologic performance was vastly improved with residual psychomotor abnormalities; language had not yet developed. Muscle tone and reflexes were increased, and plantar responses were flexor. Prominent ataxia limited standing to brief periods of time. Glycemic levels were normal or high normal (<130 mg/dL [<7.2 mmol/L]). Seizures all but ceased, and rare residual convulsions subsided during the next few years. Electroencephalography results were normal under normoglycemic conditions. At age 26 years, the patient's brain magnetic resonance imaging results were normal.

Participant 2, a 16-year-old adolescent boy, had GLUT1 deficiency. His early development was characterized by frequent generalized seizures that were refractory to anticonvulsants since age 18 months. Additional features were ataxia, dysarthria, and difficulties with limb action due to pyramidal tract dysfunction. Sitting was accomplished at 1 year of age and ambulation was achieved at 2 years. Head circumference growth decelerated and remained at the third percentile. Additional seizures consisting of loss of postural tone became prominent after 3 years of age and occurred routinely each morning within 20 minutes of waking. Brain magnetic resonance imaging and computed tomography results were normal at 15 years of age, as had been a variety of serial analytic investigations performed in blood and urine at different ages. He carried the mutation R126H in 1 GLUT1 allele, and his cerebrospinal fluid glucose concentration was 38 mg/dL (2.1 mmol/L).

Participant 3, the 23-year-old twin sister of participant 1, was healthy and served as a control. She was born just before her sister. Participant 4, aged 20 years, was an unrelated healthy man who also served as a control.

**PET SCANNING**

Participants fasted for at least 8 hours prior to injection of the radiopharmaceutical. Fasting glucose level was 79 to 100 mg/dL (4.4-5.6 mmol/L) in all cases. Intravenous access was obtained at least 15 minutes prior to the radiopharmaceutical administration. The participants were then injected with 0.14

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mCi of $^{18}$F-2-deoxyglucose per kilogram of body weight and scanned after a period of 30 minutes following injection. Studies were acquired on a Siemens RS ECAT EXACT HR+ (Siemens Medical Solutions, Malvern, Pa) with full-width half-maximum = 4 mm. Each study was acquired using a multiframe technique and autoattenuation correction in a dynamic scan mode (4 frames at 480 seconds per frame) with filter backprojection. Reconstruction with autoattenuation correction was achieved using a Hann filter (cutoff, 0.40 cycles per pixel). Postreconstruction transverse, oblique transverse, and coronal and sagittal plane images with a slice thickness of 0.50 cm were then produced and displayed using both an inverted gray-scale map and a rainbow (16-step) map. Images were interpreted visually on transverse brain image file (slice thickness, 2.54 mm). They were compared with a healthy control by a nuclear neurologist, who identified the main cerebral structures and evaluated uptake qualitatively. The images in the Figure were resliced at 1-cm thickness for illustration purposes.

ADDITIONAL CLINICAL STUDIES

Selected participants received standard electroencephalograms. Magnetic resonance imaging scans were performed using 1.5-T scanners. The following imaging sequences were obtained in the axial, coronal, and sagittal planes: T1-weighted axial and sagittal proton-density images; and T2-weighted axial, fluid-attenuated inversion recovery axial, and diffusion-weighted axial images.

GENETIC ANALYSIS

DNA was extracted from participants’ blood after consent for genetic testing had been obtained according to standard methods described elsewhere.1,9 Genomic DNA was purified and quantified, and samples were subjected to gel electrophoresis prior to polymerase chain reaction. Appropriate polymerase chain reaction primers were designed to yield DNA fragments spanning the entire GLUT1 coding region and intron-exon boundaries in chromosome 1. DNA was automatically sequenced and mutations were confirmed by sequencing both strands. All the patients with GLUT1 deficiency described herein, including participant 2 and our prior series of patients studied by PET,11 carried 1 mutation in 1 allele.

ERYTHROCYTE UPTAKE ASSAY

Function of GLUT1 was assessed in erythrocytes. Blood samples were collected in sodium-heparin or citrate-phosphate-dextrose solution, and uptake of 0.5 mmol of $^{14}$C-labeled 3-O-methyl-D-glucose (stock activity 1 mCi/mL) per liter of blood into erythrocytes was measured at 4°C and a pH of 7.4. 3-O-methyl-D-glucose influx was terminated at 5-second intervals; washed cells were lysed, and uptake was quantitated by liquid scintillation counting. Data were expressed as the natural logarithm of the ratio of intracellular radioactivity at various times and at equilibrium vs time; 3-O-methyl-D-glucose uptake was expressed as the slope of the resulting curve.11

NEUROPSYCHOLOGIC STUDY

Participants 1, 2, and 3 were given a battery of neuropsychologic tests, including measures of intelligence (the Wechsler Adult Intelligence Scale, Third Edition), vocabulary (the Peabody Picture Vocabulary Test, Third Edition), and visual construction (the Developmental Test of Visual-Motor Integration). The object assembly subtest of the Developmental Test of Visual-Motor Integration was not administered. The mothers of participants 1, 2, and 3 completed a measure of adaptive function (the Vineland Adaptive Behavior Scales).

NEUROLOGIC FUNCTION

Participant 1 was afflicted by a residual encephalopathy at 23 years of age when her PET scan was performed. She was receiving special education. Her neurologic examination results were abnormal, showing hypertonicity, ataxia, dystarthria, hyperreflexia with ankle clonus, and Babinski signs. Participant 2 had residual epileptic encephalopathy at age 16 years when he underwent PET scanning. He was receiving special education and was employed part-time. His neurologic examination was dominated by spasticity, ataxia, dystarthria, hyperreflexia with ankle clonus, and Babinski signs. Later in his life, inter-
Table 1. Syndromes of Diminished Brain Glucose

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cause</th>
<th>Course</th>
<th>Manifestation</th>
<th>Key Analyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroglycopenia</td>
<td>GLUT1 deficiency syndrome</td>
<td>Static</td>
<td>Epilepsy</td>
<td>CSF glucose (&lt;40 mg/dL [2.2 mmol/L])</td>
</tr>
<tr>
<td></td>
<td>Chronic congenital hypoglycemia</td>
<td></td>
<td>Spasticity</td>
<td></td>
</tr>
<tr>
<td>Acute hypoglycemia</td>
<td>Various</td>
<td>Reversible</td>
<td>Microcephaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Movement disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Behavioral abnormalities</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizures</td>
<td>Blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hemiparesis</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Coma</td>
<td></td>
</tr>
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</table>

Abbreviations: CSF, cerebrospinal fluid; GLUT1, glucose transporter type 1.

Table 2. Neuropsychologic Assessment of Neuroglycopenia

<table>
<thead>
<tr>
<th>Test</th>
<th>Participant 1</th>
<th>Participant 2</th>
<th>Participant 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler subtest</td>
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<td></td>
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<tr>
<td>WAIS-III</td>
<td>Standard Score*</td>
<td>Standard Score*</td>
<td>Standard Score*</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>62</td>
<td>60</td>
<td>97</td>
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<tr>
<td>Performance IQ</td>
<td>73</td>
<td>46</td>
<td>113</td>
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<tr>
<td>Full-scale IQ</td>
<td>64</td>
<td>49</td>
<td>104</td>
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<tr>
<td>WISC-III</td>
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<tr>
<td>Scaled Score†</td>
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</tr>
<tr>
<td>Vocabulary</td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Digit/symbol coding</td>
<td>5</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Similarities</td>
<td>5</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Block design</td>
<td>7</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>3</td>
<td>6</td>
<td>11</td>
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<tr>
<td>Matrix reasoning</td>
<td>4</td>
<td>NA</td>
<td>14</td>
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<tr>
<td>Digit span</td>
<td>4</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Information</td>
<td>6</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Comprehension</td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Letter/number sequencing</td>
<td>3</td>
<td>NA</td>
<td>12</td>
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<tr>
<td>Other tests</td>
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<td></td>
<td></td>
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<tr>
<td>PPVT-IV</td>
<td>Standard Score*</td>
<td>Standard Score*</td>
<td>Standard Score*</td>
</tr>
<tr>
<td>VMI</td>
<td>66</td>
<td>47</td>
<td>105</td>
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<tr>
<td>VABS composite</td>
<td>61</td>
<td>55</td>
<td>65</td>
</tr>
</tbody>
</table>

*Standard scores have a population mean ± SD of 100 ± 15.
†Scaled scores have a population mean ± SD of 10 ± 3.

PET SCANS

The functional images of participants 1 and 2 were almost identical (Figure). They were qualitatively analyzed by a nuclear neuroradiologist unaware of genotype or clinical manifestations. Mild to moderate hypometabolic activity was noted in the parietal regions bilaterally. More marked hypometabolism was identified in the temporal regions bilaterally and especially medially. Hypometabolic activity was identified in the thalamus. This overall hypometabolic pattern contrasted with a relative enhancement of uptake displayed by the basal ganglia. These results are typical of GLUT1 deficiency. Participants 3 and 4 had normal PET-scan results and were used as similar age controls.

NEUROPSYCHOLoGIC PERFORMANCE

Participants 1 and 3 were simultaneously assessed for intelligence (the Wechsler Adult Intelligence Scale), vocabulary (the Peabody Picture Vocabulary Test), and visual construction (the Developmental Test of Visual-Motor Integration). Their mother completed the Vineland Adaptive Behavior Scales as a means of determining each participant’s adaptive capabilities. Both individuals applied themselves to the testing, differing in their demeanor. Participant 3 was serious, answered questions thoroughly, spoke articulately, and worked quickly through the tests. Participant 1 was friendly and laughed easily. Her speech was indistinct because of poor articulation (substitutions of w sounds for r sounds) and prosody, with each word being uniformly stressed without inflection. Additionally, she displayed semantic paraphasia; for example, she described the “bodies of the face” instead of the “parts of the face,” and the “bristle of the knife” instead of the “point of the knife.” Participant 3 had a full-scale IQ score of 104 (61st percentile, in the average range) while the full-scale IQ score for participant 1 was 64 (first percentile, in the very low range) (Table 2). Participant 3 performed within normal limits while participant 1 demonstrated an impaired performance across all subtest and composite scores on the Wechsler Adult Intelligence Scale. Both twins showed relative strength on the nonverbal items; participant 3 scored in the high average range, while her sister scored within the borderline range (participant 3, performance IQ = 113
living skills, whereas participant 1 was more self-pronounced. Further, participant 2 had deficient daily prosody. In general, participant 2 was more impaired, responding. Both also had unusual speech characteristics. According to their mother, both women had good adaptive behavior skills, with participant 3 scoring in the high average range and participant 1 scoring in the low average range (Vineland Adaptive Behavior Scales composite scores = 119 [90th percentile] and 83 [13th percentile], respectively).

Participant 2 was tested when he was aged 16 years. He was tested with the Wechsler Intelligence Scales for Children, Third Edition, as well as the Peabody Picture Vocabulary Test, and the Developmental Test of Visual-Motor Integration; his mother completed the Vineland Adaptive Behavior Scales. His manner during the evaluation was cheerful and friendly. He was attentive and persevered even when the material became difficult for him. His speech was notably difficult to understand; he spoke haltingly, pausing between syllables, and made numerous articulation errors. For example, he pronounced r sounds as w sounds (eg, saying “twee” for “tree”) and frequently simplified syllabic complexity at the end of words (eg, “toothbuw” for “toothbrush”). His performance across all the measures was significantly impaired (Table 2). His full-scale IQ and his performance IQ scores were both 49 (0.1 percentile, in the extremely low range). His verbal IQ score was also impaired (verbal IQ = 60; 0.4 percentile, in the extremely low range).

On both the drawing test and the test of receptive vocabulary, the participant had marked difficulty and also scored in the extremely low range. According to his mother’s responses on the Vineland Adaptive Behavior Scales, his adaptive behavior skills were also impaired (Vineland Adaptive Behavior Scales composite score = 49; 0.03 percentile, in the extremely low range).

In summary, participants 1 and 2 had similarly, significantly impaired cognitive skills across all the test measures, especially when compared with participant 3. Both had full-scale IQ scores in the extremely low range. Participant 1 scored somewhat better than participant 2 on visuospatial items (such as those constituting the performance IQ score), yet their scores on verbal tests were comparable. Both had extremely limited receptive vocabularies and verbal skills. Both spoke in complete sentences, yet the construction of the sentences was very simple, and when asked to answer complex questions, both had difficulty responding. Both also had unusual speech characteristics, including poor articulation and restricted prosody. In general, participant 2 was more impaired, and his speech difficulties were considerably more pronounced. Further, participant 2 had deficient daily living skills, whereas participant 1 was more self-sufficient, with adaptive skills within the normal range. Both individuals exhibited a friendly demeanor, and each attempted the test items in a playful manner, a feature characteristic of GLUT1 deficiency.

The combination of infantile epilepsy, mental retardation, and abnormal movement coordination and tone, together with a pattern of cerebral–gray matter abnormalities detectable by PET scanning—all due to a persistent decrease in glucose access to the developing brain—constitutes the syndrome of neuroglycopenia. This disorder can be caused by 2 mechanisms: persistent hypoglycemia and molecular deficits in the GLUT1 gene. Both are eminently recognizable and treatable diseases. In infancy, the fundamental manifestation of neuroglycopenia is epilepsy that is refractory to medications and deceleration of head growth. Abnormalities of ocular movement resembling opsoclonus (which can be particularly prominent in GLUT1 deficiency), alterations of muscle tone, articulatory language dysfunction, and movement disorders (including ataxia and dystonia) are commonly associated. After childhood, the residual clinical pattern is dominated by spasticity, ataxia, and language difficulties, with or without epilepsy. In GLUT1 deficiency, these clinical features are often associated with generalized 2.5-3-5 Hz spike-wave electroencephalographic discharges and with normal brain structure as assessed by magnetic resonance imaging. Measures of neuropsychologic performance are invariably abnormal.

A subset of patients with GLUT1 deficiency are able to overcome a variety of milder developmental and learning disabilities, and these patients give rise to the familial transmission of the disease in an autosomal-dominant fashion. These patients with a milder phenotype generally suffer from isolated dyslexia, mental retardation, ataxia, or dystonia and constitute an increasingly recognized group, as the practice of performing a lumbar puncture (documenting hypoglycorrachia) for the study of these neurologic abnormalities is receiving increased consideration. Thus, our observation of epilepsy in all cases of GLUT1 deficiency as originally reported constituted an ascertainment bias arising from the initial recognition of the most severely affected patients.

Because glucose transport appears to be rate limiting for brain metabolism, chronic congenital hypoglycemia is more likely to produce a severe neuroglycopenia phenotype, as reflected by the study of participant 1. Despite interprandial normoglycemia, a subsequent (and probably consistent) preprandial and postprandial decrease in glucose concentration caused encephalopathy as severe as that experienced by some hemizygous patients with GLUT1 deficiency or as that caused by mutations that effectively abolish the function of 1 GLUT1 allele. As an autosomal-dominant condition, GLUT1 deficiency is associated with a normal residual GLUT1 allele, supplying at least 50% of transport capacity in the context of normoglycemia.

Acute hypoglycemia, a related entity, is characterized by divergent pathologic and clinical features. The fundamental difference from neuroglycopenia is a tem-
A PERSISTENT PATTERN OF ABNORMALITIES

Both the clinical and PET imaging features of neuroglycopenia leave an indelible mark on the brain; neurobehavioral difficulties persist and thalamocortical glucose uptake remains decreased. In this abnormal background, the basal ganglia signal appears enhanced. It is not known whether the basal ganglia metabolic rate is absolutely increased or whether it is also decreased but appears higher than the contrasting surrounding structures. Nevertheless, these PET findings are stereotyped regardless of disease severity, or type and duration of therapy, and persist into adulthood. For example, a minimally symptomatic patient with GLUT1 deficiency, the 39-year-old father of a 7-year-old patient with genetically transmitted severe epileptic encephalopathy, was only afflicted by dyslexia. His PET scan was indistinguishable from all other patients with GLUT1 deficiency, despite his advancing age and mild disease severity (J.M.P., unpublished data, 2003). In contrast, the time of appearance of the imaging abnormalities is not known. Neuroglycopenia presents clinically only in infancy or later, when the phenotype is one of mild developmental and learning disabilities. Two explanations are possible. The prenatal and neonatal blood-brain barrier is immature and allows the penetration of substances (either directly or by specialized mechanisms) that are later excluded. According to this view, molecules such as glucose might circumvent the blood-brain barrier during the first weeks of postnatal life as other small molecules do until the blood-brain barrier matures. This interpretation is unlikely because the cerebral metabolic rate of glucose is low perinatally, which is in good correlation with both the low rate of glucose transport across the blood-brain barrier after birth and the diminished GLUT1 density typical of that developmental period. Only later, when GLUT1 expression increases, the metabolic rate for glucose is stimulated and the brain becomes a predominantly glucose-consuming organ. Alternatively (and more likely), the manifestations of neuroglycopenia may not appear evident until the corticothalamic unit is functionally active and capable of influencing behavior. More studies of an animal model of GLUT1 deficiency will be necessary to address this question.

GLUCOSE AS A DEVELOPMENTAL SIGNAL

The syndrome of neuroglycopenia is characterized by a partial and persistent deprivation of substrate while the brain develops. Our view, in light of the current results, considers two possible mechanisms by which decreased brain glucose can cause neurologic disturbance: one is decreased fuel (energy), and the other is abnormal thalamocortical maturation (development). Both are expanded upon herein, recognizing that these are simplified hypotheses and that additional alternatives may be feasible.

Several considerations underlie our current view of glucose as an energetic substrate. Of all cellular and extracellular compartments, the interstitial fluid is the least likely to contain glucose and carbohydrates in GLUT1 deficiency. Most likely, there is reduced availability of interstitial medium glucose to both astrocytes and neurons, the former of which rely on GLUT1 for their glucose uptake, while glucose transporter type 3, the high-affinity neuronal transporter, may remain fully active, effectively capturing all available glucose into the neuron. If the calculations of Barros et al and the experimental observations of Magistretti and colleagues are correct, the astrocyte, which probably is not a significant barrier to plasma-interstitium glucose flux, would be deprived of glucose, which in turn could result in a decrease in the amount of lactate produced for subsequent delivery to the neuron. From this perspective, both GLUT1 deficiency and hypoglycemia would primarily impair astrocytic lactate production, resulting in downstream neuronal dysfunction manifested (for reasons that are still unclear) as seizures, the immediately observable phenomena hallmark to these conditions.

From a developmental perspective, additional observations may be relevant. In carnivores, developing thalamocortical axons first approach their appropriate cortical regions and then wait in the subplate region before invading the cortex. They then progress tangentially toward the cingulate, changing direction. The waiting period that these axons experience as well as the change of direction that they undergo suggest that the subplate contains important signals for thalamocortical circuit development, including glycosaminoglycans, which can serve as axonal guidance cues. We hypothesize that accumulation of cerebral glycosaminoglycans may be impaired in GLUT1 deficiency. During maturation, collateral projections of thalamocortical and corticothalamic fibers enter the reticular nucleus of the thalamus, which occupies a central place in the synchronization of networks of neurons. The activity of the reticular nucleus on thalamic relay cells results in mode switching from tonic to repetitive burst firing that is propagated to and from the cortex, inducing resonance. This form of synchronization may constitute the basis of approximately 3-Hz spike-wave epilepsy in neuroglycopenia.
Neuroglycopenia, a syndrome associated with selective neural deficits, can result from GLUT1 deficiency or early hypoglycemia, which phenocopy one another. In infancy, the state of neuroglycopenia predominantly causes hyperexcitability and is accompanied and followed by residual encephalopathy with marked pyramidal and cerebellar dysfunction. While the mechanisms of neuroglycopenic brain development and function remain to be elucidated, glucose may act in a dual capacity, both as fuel and as a signaling molecule, causing a more selective spectrum of abnormalities than those due to global unavailability of energetic substrate.

Accepted for Publication: October 19, 2006.
Published Online: February 12, 2007 (doi:10.1001/archneur.64.4.noc06165).

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Financial Disclosure: None reported.

Funding/Support: This work was supported by grants NS037949 (Pascual, Wang, and De Vivo) and NS001698 (Pascual and Wang) from the National Institute of Neurological Disorders and Stroke.

Acknowledgment: We appreciate the assistance of the Giblin and Will Foundations. We also thank Hong Yang, MD, Dalina Stiner, MS, and Carolina Regus, BS, at the Colleen Giblin Laboratories at Columbia University and John Kim, BS, at the Columbia Kretchman PET Center. We also thank Felipe Barros, MD, PhD, for his insightful discussions.

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