Since the beginning of the 21st century, there has been an explosion in our knowledge of single-gene causes of epilepsy, leading to a better understanding of the pathophysiologic mechanisms by which epilepsy occurs and opening the door for development of targeted treatments.\(^1,2\) Whereas each of these gene variants may be rare in the population overall, the proportion of epilepsy cases explained by genetic etiologies is increasing, generating the demand for more tailored treatments.

Glucose transporter type 1 deficiency syndrome (GLUT1-DS), which causes impaired glucose transport to the brain, is characterized by early-onset epilepsy, paroxysmal and other movement disorders, and developmental delay.\(^3\) GLUT1-DS is a rare but treatable genetic cause for epilepsy. We describe the history and features of GLUT1-DS; the diagnosis, genetics, and pathophysiology of the disease; and the tailored treatment that is particularly effective for this disorder.

Clinical Features

GLUT1-DS was first described by De Vivo et al\(^4\) in 1991 in 2 individuals with seizures, developmental delay, and hypoglycemia, treated with the ketogenic diet (KD). Subsequent studies have demonstrated a widening spectrum of clinical symptomatology with a variable but age-dependent pattern beginning with paroxysmal head-eye movements and early-onset seizures, followed by developmental delay and microcephaly, and with persistent paroxysmal movement disorders as the principal manifestations in adolescence and adulthood (Figure 1).

Movement disorders can be the earliest expression of GLUT1-DS. Head-eye movements are seen as early as age 1 month, with brief saccadic shifts of gaze accompanied by head movements in the same direction.\(^5,6\) Ataxia, chorea, tremor, and dystonia occur later in infancy and can impair gait. The hallmark movement disorder in GLUT1-DS is paroxysmal exercise-induced dyskinesia, which consists of episodic choreoathetotic, dyskinetic, dystonic, or ballistic movements that can last for 10 to 15 minutes, often arising in the legs and following exercise. Other paroxysmal movement disorders associated with GLUT1-DS include episodic ataxia, writer’s dystonia, alternating hemiplegia, and chorea. Movements can be triggered by fasting, anxiety, or other stressors, and can improve with carbohydrate intake. More persistent features, such as ataxia, tremor, epileptic or nonepileptic myoclonus, choreathetosis and spasticity, including spastic hemiparesis, can be seen in children and adults.\(^7-9\)

GLUT1-DS accounts for up to 1% of genetic generalized epilepsies.\(^10\) Seizures can present early, often in the first 6 months of life, and frequently are refractory to antiseizure medications. Although almost all seizure types have been seen in GLUT1-DS, generalized tonic-clonic seizures are most frequently reported. GLUT1-DS is diagnosed in 12% of cases of early-onset (before age 4 y) absence epilepsy and 5% of cases of epilepsy with myoclonic–atonic seizures.\(^11,12\)

Additional paroxysmal nonmotor events described with GLUT1-DS include confusional episodes, migraine, stroke-like events, and hemiplegic migraine.\(^8,13\) Other nonparox-
ysmal clinical features of GLUT1-DS reflect an inadequate supply of energy for the developing brain, including acquired microcephaly, developmental delay, dysarthria, speech and language disorders, and dyspraxia.\(^9,14\)

**Pathophysiology**

Most people with GLUT1-DS possess a heterozygous de novo sequence variation of the \(SLC2A1\) gene, which encodes for the glucose transporter protein (GLUT1). Although homozygous loss-of-function variants are lethal in animal models, both autosomal-dominant and autosomal-recessive inheritance patterns have been identified in individuals with GLUT1-DS.\(^{15,16}\) Other proposed etiologies for the more than 10% of individuals with clinical GLUT1-DS who do not have identified \(SLC2A1\) sequence variations include posttranscriptional or splice-site modifications, disruption in the assembly or trafficking of the transporter, or following insult to the transporter by means of traumatic or metabolic disruptions.\(^9,16\) The diversity of the GLUT1-DS phenotype among individuals suggests that other genetic modifiers of GLUT1 expression exist as well.\(^{17}\)

The clinical manifestations seen in GLUT1-DS derive from insufficient delivery of glucose across the blood–brain barrier. GLUT1 is a glycoprotein bound to the membranes of erythrocytes and the endothelial and glial cells of the brain, and is the exclusive transporter of glucose across the blood–brain barrier. Disruption in GLUT1 protein structure, expression, or trafficking compromises the availability of the brain’s principal energy supply. Because serum glucose levels are normal in GLUT1-DS, there is no physiologic trigger for the production of ketone bodies—an alternate energy supply for the brain—to compensate for the brain’s low supply of glucose. This chronic energy deficiency in the central nervous system leads to the clinical phenotype of GLUT1-DS.

**Diagnosis**

In a 2020 international consensus statement,\(^9\) experts identified 3 criteria for diagnosing GLUT1-DS: clinical features, hypoglycorrhachia, and pathogenic \(SLC2A1\) sequence variations (Figure 2). Definitive diagnosis requires all 3 criteria; however, a probable diagnosis can be achieved with either clinical features or a pathogenic \(SLC2A1\) variant when there is concurrent hypoglycorrhachia. The diagnosis is considered possible with a pathogenic variant or hypoglycorrhachia alone, particularly if paired with a positive family history.\(^9\)

1. Clinical features of early-onset epilepsy, movement disorder, or developmental delay, or a combination
2. Hypoglycorrhachia consisting of cerebrospinal fluid (CSF) glucose levels <52 mg/dL and CSF:serum glucose ratio of 19% to 59%\(^7,18\)
3. Pathogenic variant in the \(SLC2A1\) gene; variants of uncertain significance and negative studies should be assessed in the proper clinical setting.

Consensus guidelines recommend eliminating potential
confounders when performing CSF glucose studies, such as postprandial or stress-induced elevations of serum glucose. Lumbar puncture should be performed in a fasting state of at least 4 to 6 hours and a serum glucose level should be obtained immediately before the procedure.9

Molecular genetic testing includes single-gene sequencing of SLC2A1, gene panels, and genomic testing. GLUT1-DS results from a loss of function genetic change, which has been described with pathogenic missense variants, protein truncating variants, or deletions that include this gene. Due to phenotypic overlap between GLUT1-DS and other genetic etiologies, gene panels and genomic testing are preferred over single gene testing when feasible. Other studies are often obtained to evaluate for GLUT1-DS. CSF lactate levels can be useful to obtain, because low to normal lactate is seen in GLUT1-DS, and these data can exclude mitochondrial or other metabolic pathologies, subarachnoid hemorrhage, and acute infection.9 A novel assay of GLUT1 expression on erythrocytes recently has been validated as a blood test to screen for GLUT1-DS without performing a lumbar puncture, and may provide additional screening options for GLUT1-DS in the near future.19,20

Neuroimaging may identify nonspecific abnormalities on MRI of the brain, but no clear structural malformations are associated with the decrease in glucose availability. EEG regularly shows normal interictal patterns in GLUT1-DS, but, uniquely, abnormalities can be provoked by fasting. Generalized 2.5- to 4-Hz spike-wave discharges are common (41%), followed by generalized slowing (34%), which are seen in older children (ages 2 to 8). Additional findings include focal epileptiform discharges, more commonly in children younger than 2 years.21 Comparison of preprandial and postprandial studies demonstrates improvement in the EEG background with reductions in multifocal and generalized epileptiform discharges and slowing.7,22

TREATMENT

As presented in the initial description of GLUT1-DS,4 dietary therapies have proven to be a true form of precision medicine for this genetic epilepsy, informed by the mechanism of the genetic mutation. In GLUT1-DS, impairment of the glucose transporter at the blood–brain barrier prevents adequate supply of glucose to the brain and causes a state of chronic energy depletion in the central nervous system. Dietary therapies such as KD or modified Atkins diet induce the production of ketone bodies—an alternative energy source for the brain not reliant on the GLUT1 protein for transport—that instead crosses the blood–brain barrier using the monocarboxylic acid transporter. Thus, the use of dietary therapies for GLUT1-DS represents a rationally designed treatment for bypassing the genetic defect and restoring brain function.

Good seizure control with KD monotherapy has been described in up to 64% of individuals. Greater than 90% seizure reduction was seen in 80% of individuals, with better outcomes noted with earlier initiation of treatment.23 In older individuals, the modified Atkins diet is an accepted alternative with demonstrable efficacy and improved tolerance.24 Additional research is ongoing to identify other alternate sources of fuel for the brain (for example, by supplementing with ketoesters or triheptanoin) but has not yielded evidence to support any alternate precision therapy. When additional antiseizure medications are required for epilepsy despite the initiation of dietary therapies, the use of levetiracetam, valproic acid, or lamotrigine is common.9 However, there is insufficient evidence to recommend any particular antiseizure medication as being most effective in GLUT1-DS when dietary therapy alone is insufficient.

In addition to preventing seizures, KD is effective in improving movement disorder symptoms and cognitive impairment, with a retrospective study showing better cognitive outcomes with earlier initiation.9,25 Given the efficacy of this precision therapy for GLUT1-DS, the consensus opinion is that KD should be started as early as possible in individuals with GLUT1-DS and continued as long as the individual tolerates it.

Conclusions

GLUT1-DS is a rare cause of genetic epilepsy with precision therapy based on the understanding of the pathophysiology of the genetic defect. Clinicians should have a high index of suspicion for GLUT1-DS in individuals with early-onset absence or other early-onset epilepsies, movement disorders,
or other paroxysmal events. Diagnosis can be supported in the setting of clinical concerns by the presence of hypoglycorrhachia in CSF analysis, a pathogenic SLC2A1 sequence variation, or family history. Early initiation of KD—the precision treatment of choice in GLUT1-DS—bypasses the genetic defect in energy supply to the central nervous system, can accomplish seizure freedom in otherwise intractable epilepsy, and can improve neurodevelopmental outcomes when initiated early.

Outcomes are best when individuals are identified and treated early, and some individuals may have mild symptoms that can be overlooked if genetic or CSF testing is not performed. As additional genetic causes of epilepsy are uncovered, other neurogenetic disorders may also prove amenable to precision therapies that can modify the course of the disease. As in GLUT1-DS, the outcomes with these therapies may be best when individuals are identified early, when symptoms may be mild and therefore may not prompt genetic evaluation. The example of GLUT1-DS underscores the need for early evaluation for underlying genetic etiologies in children with epilepsy to maximize the chance for the best outcome.

Disclosures
Dr. Armstrong reports no disclosures. Dr. Fong is a consultant for Nutricia.