GLUT1 deficiency
A glut of epilepsy phenotypes

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The genetic generalized epilepsies (GGEs), previously called the idiopathic generalized epilepsies, account for one-quarter of all epilepsies and have a genetic basis. Clinical genetic insights, drawing on the high heritability shown in family aggregation and twin studies, suggest that the common syndromes, such as childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME), follow complex inheritance. Complex inheritance means the likely involvement of multiple genes, possibly with an environmental contribution. It is not clear, however, whether this means that a person will require a few genes of major effect or many genes of minor effect or possibly a combination of both to express a GGE.

The search for susceptibility alleles underlying complex inheritance for the GGEs has yielded only a handful of convincing variants, including recurrent microdeletions, particularly the 15q13.3 microdeletion, that contribute to these complex disorders. In this context of complex inheritance, it is somewhat surprising to see the emergence of a monogenic cause in a clinically significant proportion of the GGEs.

Glucose transporter 1 (GLUT1) deficiency was first recognized as a rare encephalopathy with progressive intellectual disability, epilepsy, motor disorders, and acquired microcephaly. The diagnostic test for this metabolic disorder was hypoglycorrhachia on lumbar puncture with fasting CSF glucose <2.2 mmol/L (<40 mg/dL) or a fasting CSF/plasma glucose ratio <45%. De novo dominant mutations of SLC2A1 (solute carrier family 2 [facilitated glucose transporter], member 1) encoding GLUT1 are causative. GLUT1 is the major transporter of glucose across the blood-brain barrier and into glia. GLUT1 deficiency is treated with the ketogenic diet, which bypasses the metabolic deficit by delivering an alternative energy source to the brain. In children with GLUT1 encephalopathy, the ketogenic diet is used to control seizures and improve cognitive development.

Subsequently, large autosomal dominant families were reported with a movement disorder, exercise-induced dystonia (PED), in which brief or long-lasting dystonic or dyskinetic episodes occurred after 15–60 minutes of exertion. In these families, a few members had GGE or intellectual disability.

The epilepsy spectrum of GLUT1 deficiency has expanded considerably in the last 2 years, revealing a far broader range of phenotypes than previously entertained. For many of the phenotypes, intellectual disability is not a feature. We found that early-onset absence epilepsy beginning at less than 4 years of age was due to GLUT1 deficiency in 10% of children. More recently, we found that GLUT1 deficiency was responsible for 5% of cases of epilepsy with myoclonic-astatic seizures (previously called myoclonic-astatic epilepsy or Doose syndrome). In both studies, de novo and inherited mutations were observed. Given the relatively high frequency and the implications for treatment with the ketogenic diet, SLC2A1 mutational analysis should become a routine investigation in both these patient groups.

Family studies of probands with GLUT1 deficiency have further extended our understanding of the GLUT1 phenotypic spectrum. Family members of probands with early-onset absence epilepsies had absence epilepsies beginning from childhood to early adult life. Their epilepsies were often easily treated and self-limited. In addition, multifocal epilepsies were seen. The biggest clue to GLUT1 deficiency was the presence of PED, which was generally neither volunteered nor known about by relatives and dismissed as nonspecific cramps by physicians. Often individuals simply modified their lifestyle to avoid this symptom.

In this issue of Neurology®, Striano et al. investigated 95 probands with familial GGE and found that one family segregated a missense mutation with functional effect. They confirmed that absence epilepsies of variable age at onset were observed, including early-onset CAE, JAE, CAE evolving to JME, and adult-onset patterns. A critical question is what underlies the phenotypic variability observed in this

See page 557
family and the epilepsy, movement disorder, and cognitive phenotypes in other reported families, given an underlying dominant SCL2A1 mutation.\textsuperscript{2,3,6} Striano et al. showed that GLUT1 is a rare but important cause of familial GGE.

The phenotypic spectrum of GLUT1 deficiency has recently widened to include progressive spastic paraparesis and even autosomal recessive presentations including autosomal recessive intellectual disability.\textsuperscript{8–10} Functional studies suggest that haploinsufficiency, the situation in which a gene mutation results in only one copy of the gene being fully functional, underlies these disorders. Phenotype-genotype correlation shows that more severe mutations correlate with more severe phenotypes. Functional studies should now be poised to reveal underlying pathophysiological mechanisms that may include astrocytic dysfunction and should permit a deeper understanding of how GLUT1 deficiency triggers the spectrum of observed phenotypes and potentially how other genetic and environmental factors influence severity.

Where do we go in the future? It is already time to test routinely in early-onset absence epilepsies and epilepsy with myoclonic-atonic seizures. Families with a dominant pattern of absence epilepsies should be screened. PED is a red flag that should suggest GLUT1 deficiency until proven otherwise. It is quite likely, but yet to be proven, that early treatment with the ketogenic diet may improve cognitive outcome. How relevant GLUT1 is to the large group of sporadic GGEs is an important question that remains to be answered.

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Prof. Scheffer has served on scientific advisory boards for UCB and Jansen-Cilag EMEA; serves on the editorial boards of the \textit{Annals of Neurology} and \textit{Epileptic Disorders}; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria and funding for travel from Athena Diagnostics, UCB, Jansen-Cilag EMEA, and Biocodex; and receives/has received research support from the National Health and Medical Research Council of Australia, National Institutes of Health, Health Research Council of New Zealand, The University of Melbourne, American Epilepsy Society, the Jack Brockhoff Foundation, the Shepherd Foundation, and the Perpetual Charitable Trustees.

REFERENCES