INHERITED METABOLIC EPILEPSIES
Second Edition
PHILLIP L. PEARL

Praise for the Previous Edition:
“This book fills an important and unique niche in pediatric neurology, and will be a frequently referenced textbook for all clinicians caring for children with epilepsy. It is well-organized and readable, and provides essential and up-to-date clinical data on these individually rare, but collectively more common, disorders.”
-Susanne Wirrell, MD, Neurology

“Specialists in pediatric neurology, epilepsy, and biochemical genetics will find this volume to be indispensable for their daily practice. The organized approach to an incredibly complex set of disorders will also benefit trainees trying to make sense of the complex field and develop their own clinical approach, as knowledge about metabolic epilepsies continues to grow.”
-Carl E. Stafstrom, MD, PhD, Journal of Pediatric Epilepsy

The continued explosion of information in neurogenetics and metabolism mandates increasing awareness of current diagnostic and therapeutic strategies in disease settings where prompt identification and intervention is crucial for a positive outcome. This thoroughly revised and greatly expanded new edition of the first book to bridge clinical epilepsy with inherited metabolic diseases brings together leading authorities to present state-of-the-art clinical reviews covering the science, recognition, and treatment of the inherited metabolic epilepsies and related disorders.

Inherited Metabolic Epilepsies, Second Edition, contains 15 new chapters, and all existing chapters have been updated to reflect the latest science and clinical advances in this fast-moving field. New sections on basic and clinical science—covering energetics, metabolomics, pathways, the use of novel investigations like transcranial magnetic stimulation, neuropathology, and genomic technologies—supplement the disease-focused sections. Dedicated chapters focus on recently recognized disorders having novel therapeutic implications: pyridoxal-5-phosphate dependency, Menkes’ disease, and thiamine transporter deficiency. The book also includes new clinical applications of genomics and advanced generation gene sequencing in the diagnosis of inherited metabolic epilepsies. This readable, well-illustrated reference concludes with an updated clinical algorithm to aid physicians in screening and identifying suspect metabolic disorders and a collection of resources for families.

Features
- Synthesizes cutting-edge diagnostic, clinical, and scientific information on epilepsy and inborn errors of metabolism
- Completely updated and expanded second edition contains the latest knowledge and 15 entirely new chapters
- Authored and edited by international experts in neurology, metabolic disorders, and genetics
- A readable and well-illustrated reference for clinician
- Essential coverage of the new generation of genetic tests, which were not widely available or utilized when the first edition was published
- New chapter on inherited metabolic epilepsies in adults

Recommended Shelving Category:
Neurology
Inherited Metabolic Epilepsies
This book is dedicated to my wife, Maria Tartaglia Pearl, MD, whose sacrifices for my work are fortunately outmatched by our mutual love for medicine.
Contents

Contributors xi
Preface xvii
Acknowledgments xix

PART I. GENERAL PRINCIPLES

1. Recognition, Scope, and Implications of Inherited Metabolic Epilepsies 2
   Phillip L. Pearl
2. Overview of Inherited Metabolic Disease 16
   Lance H. Rodan and Gerard T. Berry
3. Treatable Inherited Metabolic Epilepsies: Diagnoses Not to Miss 40
   Phillip L. Pearl and Mohammed Almuqbil

PART II. BASIC SCIENCE IN METABOLIC EPILEPSIES

4. Metabolic Epilepsies: Principles and Mechanisms 56
   Carl E. Stafstrom and Jong M. Rho
5. Metabolic Energetics in Epilepsy 74
   Ashwini Sri Hari and Manisha Patel
6. Pathways: Dysregulation of mTOR and Epilepsy 86
   Darius Ebrahimi-Fakhari, Jonathan Lipton, and Mustafa Sahin
7. Protein Anchoring as an Important Mechanism in Early Onset Epilepsy: Glycosylphosphatidylinositol (GPI) Deficiency Syndromes 98
   Gali Heimer, Bruria Ben-Zeev, and Yair Anikster

PART III. CLINICAL SCIENCE IN METABOLIC EPILEPSIES

8. Neuroimaging in the Metabolic Epilepsies 110
   Robert A. Zimmerman and Zarir P. Khademian
9. Advances in MR Spectroscopy for Inherited Epilepsies 125
   Andrew Breeden, Morgan J. Prust, Stanley T. Fricke, Matthew Whitehead, and Andrea L. Gropman
10. Neuropathology of Metabolic Epilepsies: Novel Aspects in Children and the Diagnostic Role of Skin Biopsy 135
    Harvey B. Sarnat
11. Electroencephalography in the Metabolic Epilepsies 149
    Samata Singhi, Mona Alduligan, and Phillip L. Pearl

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12. Genomic Technologies in Clinical Practice 187
   Christina Y. Hung and Olaf A. Bodamer

13. Measures of Cortical Excitability by Transcranial Magnetic Stimulation 201
   Alexander Rotenberg

14. Ketogenic Diet in Metabolic Epilepsies 207
   Susan L. Fong and Eric H. Kossoff

PART IV. SMALL MOLECULE DISEASES

15. Amino and Organic Acid Disorders and Epilepsy 218
   Kimberly A. Chapman and Jamie L. Fraser

16. Fatty Acid Oxidation Disorders and Epilepsy 237
   Dimitar Gavrilov and Dietrich Matern

17. Urea Cycle Disorders and Epilepsy 257
   Debra S. Regier, Brendan Lanpher, and Marshall L. Summar

18. Mitochondrial Diseases and Epilepsy 267
   Sumit Parikh, Lynne A. Wolfe, and Andrea L. Gropman

19. Pyridoxine-Dependent Epilepsy 275
   Sidney M. Gospe, Jr.

20. Pyridoxamine 5’-Phosphate Oxidase (PNPO) Deficiency 287
    Barbara Plecko-Startinig

21. Tetrahydrobiopterin Deficiencies and Epilepsy 293
    Nenad Blau and Thomas Opladen

22. Disorders of GABA Metabolism and Epilepsy 301
    Phillip L. Pearl, Kara Vogel, and K. Michael Gibson

23. Glucose Transporter Type 1 Deficiency Syndrome 313
    Cigdem I. Akman and Darryl C. De Vivo

24. Thiamine Transporter Deficiency and Epilepsy 326
    Brahim Tabarki

25. DEND Syndrome: Developmental Delay, Epilepsy, and Neonatal Diabetes, a Potassium Channelopathy 333
    Carolina Lahnmann and Frances Ashcroft

26. Hyperammonemia/Hyperinsulinism Syndrome and Epilepsy 345
    Nicholas S. Abend and Andrea Kelly

27. Glycine Encephalopathy and Epilepsy 353
    Julia B. Hemmermann, Johan L. K. Van Hove, and Curtis R. Coughlin II

28. Serine Synthesis Disorders and Epilepsy 364
    T. J. de Koning

29. Lesch–Nyhan Disease and Epilepsy 371
    Beth A. Leeman-Markowski and Hyder A. Jinnah

30. Sulfite Oxidase Deficiency/Molybdenum Cofactor Deficiency and Epilepsy 394
    Jörn Oliver Sass and Barbara Plecko-Startinig

31. Creatine Disorders and Epilepsy 401
    Ton de Grauw
32. Cerebral Folate Deficiency and Epilepsy 407
   Robert Steinfeld

33. Menkes’ Disease and Infantile Epilepsy 415
   Asuri N. Prasad

PART V. LARGE MOLECULE DISEASES

34. Congenital Disorders of Glycosylation and Epilepsy 428
   Susan E. Sparks

35. Lysosomal Storage Diseases and Epilepsy 445
   Pranoot Tanpaiboon and Grisel Lopez

36. Peroxisomal Diseases and Epilepsy 473
   Parastoo Jangouk, Kristin W. Barañano, and Gerald V. Raymond

37. Leukodystrophies and Epilepsy 483
   Davide Tonduti and Adeline Vanderver

PART VI. CONCLUSIONS

38. Diagnostic Approaches to Genetic Epilepsies 490
   Erika Takle Axen, Christelle El Achkar, and Annapurna Poduri

39. Therapeutic Approaches to Inherited Metabolic Epilepsies 497
   Brandy Verhalen and Berge A. Minassian

40. Inherited Metabolic Epilepsies in Adults 503
   Phillip L. Pearl

41. Genetic Counseling in Metabolic Epilepsies 508
   Jodie M. Vento

42. Support and Resources for Patients and Families With Inherited Metabolic Epilepsies 518
   Christopher Ryan and Jennifer Jeffs

43. Clinical Approach to Inherited Metabolic Epilepsies 525
   Scott Demarest, Anna Lecticia Pinto, and Phillip L. Pearl

Index 529
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Preface

This edition of *Inherited Metabolic Epilepsies* is a greatly expanded and updated version of the first. Following a rousing response to the first edition far beyond any anticipated measure, it was clear that a reexamination of the material, taking into account many helpful suggestions that I received from readers far and wide, was in order. Despite my own misgivings that books are no longer fashionable and are largely replaced by journals and online sources that lend themselves to periodic, if not continual, updating, there remains an appetite and clamor for books that accomplish what I had hoped to do originally and aim to achieve to a greater extent in this edition: to encapsulate a burgeoning field sufficiently that a student, practitioner, or investigator can turn to the source with confidence that the necessary background as well as detail will be available to reward the search for information and also move the field forward.

The first edition of this monograph was born following the organization of the Pediatric State-of-the-Art Symposium on Treatable Metabolic Epilepsies presented at the annual meeting of the American Epilepsy Society in Boston in 2009. At the time of proposing the topic, I was wrestling with a chasmic gap between the fascinating disorders being discussed at the genetic–metabolic meetings and the advancing wave in epilepsy classification, diagnosis, and treatment occupying the meetings attended by members of the societies associated with neurology and epilepsy. At that time, a storybook series of investigations elucidated not only the surprising antiquitin defect in pyridoxine-dependent epilepsy, but also the highly charged requirement that physicians consider a pivotal role for folic acid and pyridoxal-5-phosphate in patients with virtually the same clinical presentation. I also perceived a relative lack of awareness of disorders such as glucose transporter 1 deficiency; serine synthetic defects; developmental delay, epilepsy, and neonatal diabetes (DEND); and hyperinsulinism–hyperammonemia (HI–HA) that had very specific therapeutic implications with potential for dramatically improving outcome, but with an even greater likelihood that they were escaping diagnosis.

Overall, the inherited metabolic epilepsies represent a group of disorders that is rare individually, but in aggregate represents a substantial clinical burden as well as a vexing area for physicians, investigators, and students to master. The sheer amount and complexity of information are overwhelming and require the physician to synthesize key concepts in neurology, genetics, and epilepsy. As a pediatric epileptologist and medical educator, I have found this area among the most challenging and rewarding in practice and research. The first edition organized the disorders in a traditional approach under the roof of metabolism by dividing them into small- and large-molecule disorders. In the Preface to that edition, there was an explanation of various ways of organizing these disorders, some more user friendly to the neurologist than the small- versus large-molecule divide, but this was an opportunity to present that way of thinking to the neurologist, which brings this clinical specialty closer to that of genetics metabolism.

In this second edition, there is an expansion from four sections (General Principles, Small Molecule Diseases, Large Molecule Diseases, and Conclusions) to six sections, with the addition of chapters in basic science and clinical science of the metabolic epilepsies. The book has been expanded from 28 to 43 chapters, with new chapters including overviews of metabolic disease and the basic science of metabolic epilepsy, plus new topics such as metabolic energetics and implications of vital pathways. A full chapter is devoted to the mechanistic target of rapamycin (mTOR) pathway that regulates cell replication and so much of homeostasis and new pathophysiologic mechanisms such as protein anchoring disorders. There are new chapters on neurotransmitter transmission measurement using transcranial magnetic stimulation, genomic technologies, and approaches to diagnosis and therapy referable to this group of disorders. The clinical science section now includes a marvelous and reflective chapter on neuropathology by Harvey B. Sarnat. There are new chapters devoted to specific disorders such as pyridoxal-5-phosphate dependency and Menkes’ disease. There are chapters with completely new vantage points, from community and family resources to an emphasis on adult patients, the latter being the most commonly requested area to cover that I receive after giving talks on the subject. In addition, the prior chapters from the first edition have been revised and updated.
Hence, what began as a quest to increase awareness of treatable metabolic epilepsies first became a monograph to give some form to this arena and has now been enlarged and updated to a second edition. It is hoped that this will provide a resource to, in some way, lead the field and carry it forward. It is truly hoped that this book will educate, if not enlighten, physicians, particularly specialists and trainees in pediatric and adult neurology, neurodevelopmental disabilities, epilepsy, and genetics, while caring for patients with inherited metabolic epilepsies, as well as spur further research into basic mechanisms and clinical trials in this group of maladies.

Phillip L. Pearl, MD
Acknowledgments

This book was first suggested to me by Beth Barry from Demos Medical Publishers following my organization of the Pediatric State-of-the-Art Symposium on Treatable Metabolic Epilepsies presented at the American Epilepsy Society 2009 meeting. Beth was a driving force for the creation of this second edition, and she and Young Kim at Demos, now aligned with Springer, are gratefully acknowledged for unmatched hard work and perseverance in seeing this through to completion.

My education in child neurology and epilepsy is grounded by great mentors, including Ralph D. Feigin, MD, in pediatrics and Marvin A. Fishman, MD, in pediatric neurology of Baylor College of Medicine in Houston, and Gregory L. Holmes, MD, in epilepsy and clinical neurophysiology, then at Children’s Hospital, Harvard Medical School in Boston. I wish to take this opportunity to acknowledge these teachers of mine.

My foray into metabolic disorders has been made possible by the always helpful, brilliant, and steadfast work of Mike Gibson, PhD, whose collaboration in the area of gamma-amino butyric acid (GABA) disorders, specifically succinic-semialdehyde dehydrogenase (SSADH) deficiency, has been a constant source of intellectual nourishment and encouragement. My career during the two editions of this book has now spanned two great children’s hospitals, Children’s National and Boston Children’s, and the insight and support of colleagues at both institutions have been fundamental to this work. Ongoing collaborations with Mike Gibson as well as William H. Theodore, MD, chief of the Clinical Epilepsy Section at the NINDS, have been critical to the ongoing investigative work on metabolic epilepsies.

I thank each of the contributors to the first edition of this book for revising and updating their chapters and each of the authors of the new chapters, resulting in a significant expansion. The outstanding assistance of Alisa Marino is gratefully acknowledged given the enormous complexity of the project and the organizational skills needed to accomplish this and a myriad of other tasks. As a group, I thank the many patients and families, as well as students, residents, and fellows, who inspire our work. I thank my own family who, as with all of us, shoulder the largest burden of personal sacrifice and inspire us the most.

Phillip L. Pearl, MD
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Inherited Metabolic Epilepsies, Second Edition
Brain energy metabolism in the nonfasting state is dependent primarily on a continuous supply of glucose. Glucose transport across the blood–brain barrier is uniquely facilitated by the glucose transporter type 1 (GLUT1) (1). GLUT1 is highly expressed in the luminal and abluminal membranes of the endothelial cells that comprise the brain microvasculature. Additionally, the GLUT1 transporter facilitates the diffusion of glucose from the brain interstitial compartment across the plasma membranes of astrocytes, oligodendrocytes, and other glial cells (2).

The metabolic demand of the child’s developing brain during the first decade of life far exceeds that of the newborn infant brain and the mature brain; hence, a disproportionately large amount (80%) of total body glucose utilization is consumed by the developing brain. This high demand for glucose by the developing brain correlates with the high synaptic density in early life, before pruning occurs, during the sculpting and specialization of brain connections and circuits. It also correlates with the fact that much of brain energy metabolism is dedicated to synaptic activation, balancing the relative influences of the excitatory and inhibitory neuronal populations, and preventing epileptic activity (2).

GLUT1 deficiency was discovered in 1991 when De Vivo and colleagues reported two infants with this condition (OMIM 138140) (3). Both children presented with infantile onset refractory seizures, delayed neurological development, acquired microcephaly, and ataxia. The unusual findings of low cerebrospinal fluid (CSF) glucose in the setting of a normal blood glucose coupled with a low to low-normal CSF lactate led De Vivo et al. to postulate a disturbance in the transport of glucose from blood to brain. Seven years later, this investigative team identified disease-causing mutations in the GLUT1 (SCL2A1) gene to confirm initial speculation (4). De Vivo and colleagues proposed to treat the children with the ketogenic diet (KD), thereby providing the only alternate fuel source for brain energy metabolism. The high-fat diet remains the standard of care for these patients and is very effective in controlling the seizure disorder. Also, the investigative team realized that the GLUT1 transporter in the erythrocytes was chemically and immunologically identical to the GLUT1 protein located in the brain cells. They developed the radiometric RBC glucose uptake assay and demonstrated a decreased uptake in the first patient. It has proven to be a diagnostic gold standard for this condition, correlating well with phenotypic severity, haploinsufficiency, and the presence of disease-causing mutations in the GLUT1 gene (5). Both parents typically are used as assay controls because the majority of patients have de novo monoallelic mutations.

**EPIDEMIOLOGY**

Confirmed cases of GLUT1 deficiency syndrome (DS) now span the globe, having been reported in North and South America, Australia, China, Japan, and Europe. Collectively, these cases usually recapitulate the originally described classic phenotype with infantile-onset seizures described as brief, subtle myoclonic limb jerking, staring and eye–head movements, pallor, decreased responsiveness, disturbed body tone, and head bobbing (6–11). The eye movements have been called opsinclonus by many authors including ourselves until recently. We studied these movements, now termed by us as aberrant gaze saccades, and distinguished them from opsinclonus by the presence of associated head movements and intermovement visual fixation. We believe these movements are distinctive, and possibly diagnostic of GLUT1 DS (12). The early presentation of GLUT1 DS is paroxysmal in the young infant who otherwise appears to be developing normally. Delayed neurological development then becomes increasingly apparent later in infancy. Unfortunately, symptomatic treatment...
with phenobarbital and other anti-seizure drugs is often pursued without a careful search for a cause, and precious time elapses between clinical presentation in infancy and correct diagnosis of GLUT1 DS in childhood. Although awareness of this syndrome has gradually increased in the medical community, the true birth incidence and prevalence of GLUT1 DS are yet to be determined. Two studies have estimated the birth incidence to be around 1:80,000 to 1:90,000, in all likelihood a conservative underestimate (13,14). If accurate, this incidence would suggest about 50 new cases per year in the United States and a prevalence of about 3,000 to 4,000 cases. The worldwide prevalence, then, would be approximately 100,000 cases or less.

A study in 34 patients diagnosed with early onset absence epilepsy identified SLC2A1 mutations in 12% of the patients (15). Childhood onset epilepsy accounts for approximately 2% to 8% of people with epilepsy. Seizure onset is usually between ages 3 and 11 years, and most often between ages 5 and 8 years. Considering the prevalence of epilepsy as affecting 10.5 million children worldwide, we suspect that GLUT1 DS is significantly underdiagnosed among the children presenting with childhood onset epilepsy. Part of this likely underdiagnosis is related to the reluctance to perform appropriate diagnostic studies, including a lumbar puncture, when the patient first presents with seizures or other paroxysmal symptoms.

There are a number of barriers to making a GLUT1 DS diagnosis proactively. First is the lack of newborn screening which exists for other treatable metabolic conditions of infancy, such as phenylketonuria. Development of a newborn screen relies on the presence of a high throughput screening test that can be developed from the routine blood spot. Currently, this test does not exist for GLUT1 DS. The promise of molecular genetic screening is complicated by the number of reported disease-causing mutations in this condition, and further limited by the current cost of technology.

Second, the main diagnostic procedure, the lumbar puncture, is often delayed, deferred, or inaccurately interpreted. Low CSF glucose values are often dismissed as a laboratory error or as clinically unimportant. Simultaneous measures of blood and CSF glucose and lactate values are an important part of the evaluation. CSF lactate values are expected to be low or low-normal (< 1.3 mM). In our experience, timely performance of the diagnostic lumbar puncture and associated blood studies are the main impediments to early diagnosis and treatment with a KD. As a result, the developing brain is deprived of sufficient nutrients to sustain growth and development. Recent studies also document a developmental arrest in cerebral angiogenesis, likely leading to chronic hypoperfusion of the developed brain (68).

GENETICS

The genetic defect causing GLUT1 DS involves the SLC2A1 gene, located on chromosome 1p34.2. The genomic DNA spans 35 kilobases and contains 10 exons (MIM 138140). By the year 2010, there were over 100 reported pathogenic mutations, including missense, nonsense, deletion, insertion, and splice site mutations (6,16,17). All reported mutations cause loss of function. Most cases result from de novo mutations accounting for the fact that the majority of patients represent single cases within families. When transmitted from one generation to the next, it behaves as an autosomal dominant trait and the phenotype generally is milder, often resulting from a missense mutation. Rare examples of clinically asymptomatic parents with genetic mosaicism have been described. Two families have been described with a pattern of autosomal recessive inheritance (16,18). One of these families was consanguineous.

Recent work by our group has demonstrated that the pattern of inheritance is determined by the degree of haploinsufficiency and the pathogenicity of the mutation (19). Compound heterozygotes, for example, may inherit a recessive mutation from a clinically unaffected parent, and suffer a de novo dominant mutation in the other allele, resulting in a severe phenotype (19). The erythrocyte 3-O-methyl-D-glucose uptake assay is a functional measure that correlates with phenotypic severity and is a surrogate for the degree of GLUT1 haploinsufficiency.

GLUT1 DS model mice have recapitulated the human phenotype with acquired microcephaly, seizures, and disturbed motor function (20). GLUT1 mutations have been shown to account for a monogenic form of dystonia and paroxysmal exertion-induced dyskinesia (PED, DYT18) with or without epilepsy (21). GLUT1 missense mutations, associated with decreased glucose uptake in functional assays, also have been identified in family members who suffer from a slowly progressive spastic paraparesis combined with PED (paroxysmal choreoathetosis/spasticity, DYT9) (22–24).

DIAGNOSTIC GENETIC TESTING

Diagnostic genetic testing for an individual presenting with epilepsy, movement disorders, or delayed neurological development in the setting of hypoglycorrhachia is offered on a commercial basis in the United States. GLUT1 DS represents one scenario in which identification of a genetic mutation in an epilepsy condition has important and direct impact on treatment choice, and ultimately on prognosis. With early diagnosis and institution of the KD, the progressive symptoms of acquired microcephaly/
brain hypotrophy, refractory epilepsy, ataxia, and developmental regression may be mitigated (23,25).

Approximately one third of patients with a clinical phenotype consistent with GLUT1 DS and a confirmatory CSF biomarker profile will have negative genetic testing for a GLUT1 disease-causing mutation. In general, these patients will also have a normal RBC glucose uptake assay, suggesting that some other molecular mechanism is responsible. Some of these patients also will respond to the KD because this treatment is effective for epilepsy regardless of genetic etiology. The key take-home message is that the CSF biomarker profile is necessary, but not sufficient, for the diagnosis of GLUT1 DS. The yield of confirmatory testing will likely increase as newer molecular genetic diagnostics are developed (26). There is, as mentioned earlier, no currently available newborn screening method for GLUT1 DS. For the moment, the diagnostic acumen of the physician, at the time of the first clinical event in infancy, remains critical and is essential to prognosis. With increased surveillance, earlier testing, and improved treatment outcomes, genetic counseling provides an important intervention for affected individuals as they mature to reproductive ages (27).

CLINICAL DIAGNOSIS

The diagnosis of GLUT1 DS currently depends on clinical acumen. Confirmatory genetic testing is available commercially and on a research basis. The clinical hallmarks are early onset epilepsy that is refractory to standard anti-seizure medications. Diagnosis is facilitated by assessment of cerebrospinal fluid, classically showing hypoglycorrhachia (<40 mg/dL) and low-normal or low CSF lactate values (<1.3 mM) in the setting of normoglycemia (~70–110 mg/dL). The KD should be started immediately after documenting these clinical and laboratory findings, and further confirmatory studies should follow as discussed previously. Left untreated, patients will develop acquired microcephaly, motor and cognitive impairments, ataxia, spasticity, dystonia, and other paroxysmal disorders. GLUT1 DS may cause a myriad of clinical conditions seen in child neurology including epilepsy, intellectual disability and learning problems, movement disorders, behavioral problems such as attention-deficit hyperactivity disorder and paroxysmal dysphoria, alternating hemiplegia of childhood, and familial hemiplegic migraine. The presentations may be both paroxysmal (particularly early) and permanent (later in the course).

The initial cutoff value for diagnosing hypoglycorrhachia was a CSF glucose concentration of 40 mg/dL (2.2 mM) for suspected GLUT1 deficiency cases. More than 90% of patients still fulfill this original criterion, with a small number, usually with a milder clinical phenotype, now having CSF glucose values in the 40s and 50s. In the past, significance also has been placed on the ratio of CSF glucose to serum glucose, with the cutoff value for GLUT1 DS set at less than 0.4, and with normal values being greater than 0.6 (28). In our practice, we have placed greater emphasis on the absolute CSF glucose value. The ratio can be influenced by the glucose value in both body compartments, thereby diminishing the specificity and sensitivity of this marker. The measurements are even more reliable if the patient is postabsorptive with nothing to eat or drink for a period of 4 to 8 hours before the blood sample is taken, followed immediately by performance of the lumbar puncture. As mentioned earlier, however, this CSF biomarker profile is necessary, but not sufficient, for the diagnosis of GLUT1 DS.

With the increasing recognition of milder allelic variants, higher CSF glucose values of 41 to 52 mg/dL are now being described (7,29–32). In our experience, the CSF glucose values in 150 cases of GLUT1 DS always have been less than 60 mg/dL, and the vast majority (greater than 90%) of values have been less than 40 mg/dL (unpublished observations) (23,24,33). These observations also indicate that the normal range for CSF glucose has never been defined properly. A low CSF glucose concentration can also be found in other neurological conditions such as infectious meningitis, hypoglycemic states, subarachnoid hemorrhage, and meningeal carcinomatosis, and must be ruled out clinically by assessing cell count and imaging findings (34–38).

Although not a strict diagnostic requirement, brain imaging characteristics in GLUT1 DS deserve attention owing to frequent use of neuroimaging in assessing patients with epilepsy. The first GLUT1 DS patient had MRI studies showing mild delay in myelination at age 7.5 months, and subsequent cases have demonstrated normal or minor, nonspecific abnormalities with slight brain hypotrophy at various ages in childhood (3,17,39). One group has reported a case in which brain hypotrophy noted at age 5 years before KD initiation was replaced by normal brain growth at 7 years on the KD, a finding that underscores the importance of appropriate early diagnosis and treatment (39). Significant specific findings on F-fluoro-deoxyglucose positron emission tomography (FDG-PET) have been reported and include a diffused decrease in cortical uptake of glucose and a striking regional hypometabolism in the cerebellum, thalamus, frontal, parietal, and temporal neocortex, and relative sparing of the basal ganglia and occipital cortex (40,41) (Figure 23.1). These abnormalities were present in infancy and persistent through adulthood, and are not rectified by ketosis. In retrospect, these immutable findings correlate with the developmental arrest of cerebral angiogenesis that has been documented recently in the GLUT1 model mice (68).
MANAGEMENT

Management of patients with GLUT1 DS should focus on two clinical goals: (a) treatment of the cardinal clinical symptoms with a KD in an effort to meet the metabolic energy demands of the growing brain; and (b) provision of rehabilitation and nutritional support services to address the needs of children and adults with chronic developmental disabilities.

The gold standard for treatment of GLUT1 DS is the KD, which provides the only alternative fuel for brain metabolism. The response to the KD is rapid and dramatic, and this salutary response permits the weaning of the previously instituted anti-seizure medicines. In general, the risks of the medicines clearly outweigh any possible benefits. In our experience, better neurological growth and development follow the control of the epilepsy. Best results are obtained by maintaining the highest blood beta-hydroxybutyrate (BHB) levels possible. We recommend values around 5 mM, rather than the standard 2 to 3 mM (2,8). It is clear that good seizure control can be achieved with the KD at lower blood BHB levels. But seizure control is not the primary goal. Rather, it is nourishment of the “starving brain” that is the primary goal. We speculate that brain lactate values are abnormally low in the untreated patient, and we know that brain lactate levels can be elevated in the animal model for the KD. Neurons preferentially utilize astrocyte-derived lactate.

For this reason, we recommend blood BHB measurements by fingerstick, not urine dips (falsely reassuring). Ideally, the KD should be maintained at least through adolescence to provide adequate fuel support for the developing brain. This recommendation is designed to mitigate structural and functional damage until the brain is mature. It also is likely that the mature brain will function better with ketones available for fuel needs. This speculation is counterbalanced by issues of lifestyle and compliance.

In theory, certain medicines may be associated with clinical worsening in GLUT1 DS. Common anti-seizure medicines known to inhibit the GLUT1 transporter in vitro, specifically phenobarbital, valproate, and benzodiazepines, are relatively contraindicated in GLUT1 DS (42,43). Valproate contributes to hypocarnitinemia and also inhibits fatty acid oxidation. For these reasons, valproate should not be combined with the KD. The KD carries with it a risk for kidney stones. Drugs that inhibit the enzyme carbonic anhydrase, such as acetazolamide, topiramate, and lamotrigine, carry a similar risk. Combining these antiepileptic drugs (AEDs) with the KD will potentiate this risk and generally is ill advised.

Finally, as hypocarnitinemia develops in patients treated with the KD, oral L-carnitine supplementation at a dose of 50 to 100 mg/kg/d in divided doses, up to a maximum of 2 g/d, should be considered for all GLUT1 DS patients on the KD.

Patients with GLUT1 DS require frequent monitoring for neurodevelopmental progress and the treatment of epilepsy and movement disorders. At our institution, we have developed a semiquantitative tool, the Columbia Neurological Score, to assess 12 domains of neurological function to define a patient’s clinical trajectory. This yields a “central nervous system (CNS) score” based on the 12 domains: (a) height, weight, and head circumference; (b) general medical exam; (c) funduscopic exam; (d) cranial nerves; (e) stance and gait; (f) involuntary movements; (g) sensation; (h) cerebellar function; (i) muscle bulk, tone, and strength; (j) tendon reflexes; (k) Babinski sign; and (l) other findings. The CNS score ranges from 0 to 76 (normal); scores of 40 to 49 indicate severe impairment; 50 to 59 moderate impairment; 60 to 69 mild impairment; and 70 to 76 minimal impairment and overlapping with normal scores. This tool provides a high interrater reliability and has been demonstrated to correlate with other measures of disease severity (44).

Management of GLUT1 DS patients is multifaceted and often involves a multidisciplinary team approach, with neurologists who are conversant with

Figure 23.1 FDG-PET signature of GLUT1 DS displaying diffuse and regional vulnerabilities: decreased glucose uptake in cerebellum, thalamus, and neocortex, with relative sparing of the occipital cortex and basal ganglia.

GLUT1 DS, glucose transporter type 1 deficiency syndrome; FDG-PET, F-fluoro-deoxyglucose positron emission tomography.
the management of epilepsy, movement disorders, and intellectual disability; nutritionists familiar with the KD; geneticists and genetic counselors; and therapists knowledgeable in rehabilitative services. The application of video EEG to determine the nature of the paroxysmal events and the choice of treatments is essential for optimal long-term management. Monitoring of blood and urine parameters while on the KD and anti-seizure drugs, if continued after starting the KD, is essential to avoid unintended side effects. Skillful management of the patient while on the KD can mitigate compliance issues and dietary indiscretions and facilitate long-term use of the diet as an essential management strategy for patients with this chronic metabolic encephalopathy.

In recent years, the modified Atkins diet (MAD) has been introduced as an alternative treatment option to overcome compliance concerns in epilepsy practice. MAD is more palatable for patients and practical for caregivers; conversely, it provides lesser degrees of ketosis compared to the KD. A clinical report describing six Japanese patients treated with MAD documented improvement in clinical seizures, alertness and background EEG activity, and disappearance of epileptic activity (10). However, the primary goal in the treatment of the GLUT1 DS patient is nourishment of the “starving brain,” not just seizure control.

Ketosis provides indispensable fuel for brain energy metabolism; therefore, the milder ketosis provided by MAD poses a special risk for the growing brain of the child with GLUT1 DS. The classical KD should remain the goal standard of treatment for infants and young children to meet the high energy demands of the growing brain. MAD can be considered as a management strategy for the teenager or adult GLUT1 DS patients if the classical KD proves to be intolerable.

Triheptanoin is an emerging investigational drug currently under study for GLUT1 DS. Triheptanoin, otherwise known as C7 oil, is an odd-chain triglyceride with anapleurotic properties; that is, the metabolites of this 7-carbon triglyceride can yield acetyl CoA (2 carbons) and propionyl CoA (5 carbons) that will replenish the acetyl CoA and the oxaloacetate pools of the Krebs cycle and optimize the production of citric acid. GLUT1 deficiency is expected to slow the glycolytic flux and the production of pyruvate resulting in decreased lactate, oxaloacetate, and acetyl CoA.

An open-labeled study demonstrated that triheptanoin improved EEG findings, cerebral metabolic rate, and neuropsychological status in 11 patients (45). Another study examined the effectiveness of triheptanoin on nonepileptic paroxysmal motor events in eight patients with GLUT1 DS. Paroxysmal events significantly improved with triheptanoin treatment and recurred when triheptanoin was withdrawn (46,47).

Longitudinal follow-up with a geneticist is important to guide families through diagnosis and family planning, and to assist with future reproductive decisions (27). Involvement of physical, speech, and occupational therapists should be ordered as needed to treat neurodevelopmental delays. Long-term quality of life is largely determined by early diagnosis and prompt treatment with a classical KD.

**MOVEMENT DISORDERS**

Two decades since the seminal paper by De Vivo et al., the phenotypic spectrum of GLUT1 deficiency has expanded, although the salient clinical features remain the same as originally described (3). All manner of episodic movement disorders have been described in GLUT1 DS, including dysarthria, ataxia, eye–head movements, choreoathetosis, myoclonus, spasticity, dystonia and weakness, independent of seizure activity (12,48). Characteristic exacerbation of these symptoms with fatigue, dietary noncompliance with KD, and excitement has been noted. By 2008, a literature review of 100 published cases revealed 3 cases of ataxia without epilepsy (33). Alternating hemiplegia of childhood (AHC), which is often genetically associated in a small number of cases with mutations in ATP1A2 and CACNA1A, is now also a recognized phenotypic presentation of GLUT1 deficiency (48). As in many cases of AHC, these children experience hemiplegic, tonic, and dystonic episodes starting before 18 months, with subsequent progressive ataxia and cognitive impairment (48). Paroxysmal exertion-induced dyskinesia, or DYT18, is yet another new phenotype associated with mutations in SLC2A1 (49). A recent clinical report described the clinical course of 13 individuals recently diagnosed with GLUT1 DS over four generations in a Norwegian family (50). Exercise-induced dyskinesia, early-onset epilepsy, and mild learning disability were the pertinent clinical symptoms which improved over time without any treatment. Moreover, once the GLUT1 DS diagnosis was established, the application of dietary treatment even in adulthood improved patient quality of life.

**EPILEPSY**

The most common symptoms across all presentations of GLUT1 DS are seizures, affecting approximately 90% of our patient population. The seizures often present early in infancy and are refractory to standard anti-seizure medications. Accordingly, one aim of this chapter is to review the current understanding of the epilepsy component of this condition, highlighting the semiology,
neurophysiology, and treatment response aspects of epilepsy in GLUT1 DS.

The long-recognized wide variation in seizure semiology seen in GLUT1 DS has led to its designation as “the great mimicker.” As with many genetic entities, variable penetrance and variable expressivity represent challenges to the diagnostician.

The initial two cases described by De Vivo et al. epitomize the key clinical and electrographic characteristics now well described in the GLUT1 DS literature (3,7). Both patients manifested as early onset or refractory epilepsy at age 2 months, characterized by loss of responsiveness, and focal myoclonic or horizontal roving eye movements that correlated with seizure activity on the EEG. The initial EEG tracings revealed a right frontal focus in one case and progressed from normal to generalized spike and wave in the second. Failed medication trials included the typical agents used in infancy, including phenobarbital and benzodiazepines, and later valproate and carbamazepine. Both patients experienced complete resolution on the KD, within 4 and 7 days of ketosis, followed by weaning of standard medicines. As is often the case with newly discovered conditions, the index cases represent the severe end of the spectrum, prior to identification of a gold standard preventive treatment. Both children ultimately showed neurological delays despite seizure freedom.

Literature review of the subsequent two decades provides 109 cases of GLUT1 DS patients with documented epilepsy and associated clinical features. Although the two original index cases presented in early infancy, the average age of seizure onset as described in 102 cases was 12 months, likely reflecting identification of milder cases over time (6,8,9,25,29,51–55).

Possible nonepileptic paroxysmal events include periodic confusion, ataxia, weakness, headache, and sleep changes, which may require characterization with EEG (7). Later in childhood, mixed seizure types prevail.

Our earlier report in 2003 with a special focus on epilepsy describes the spectrum of clinical seizures and EEG findings in GLUT1 DS. Of the 20 children with confirmed GLUT1 DS, generalized tonic or clonic seizures prevailed (14 of 20), followed by absence (10), focal (9), myoclonic (6), and astatic (4) (25).

In another series of 15 patients, followed respectively for 2 to 5 years, Klepper et al. described absence (7 of 15), myoclonic (7 of 15), generalized tonic–clonic (GTC) (4 of 15), and tonic (2 of 15) seizures in addition to seizures associated with episodic irregular eye movements (9 of 15) and cyanosis (3 of 15), at the time of the GLUT1 DS diagnosis (51).

A larger cohort of GLUT1 DS from our center also confirms the broad range of seizure semiology. The average age of seizure onset was 8 months while the average age at diagnosis was 5 years in the classic phenotype. This finding highlights the clinical reality that a long delay still exists between the clinical onset and the diagnosis of GLUT1 DS (24). Absence, myoclonic, and GTC seizures are the most common seizure types (24). However, axial tonic seizures and infantile spasms also are reported, but rarely. The majority of patients may present with a combination of various seizure types (24,25). Myoclonic–absence seizures are also described (56). In contrast, convulsive status epilepticus or progressive epileptic encephalopathy have not been reported in GLUT1 DS (24). Focal seizures occur in young age groups, particularly in infants, while generalized seizures can be seen in any age group. Fasting and exertion often trigger seizures, dystonia, and mental status changes.

Familial studies of GLUT1 DS have expanded the epilepsy spectrum broadly with variable ages of onset and seizure types (52). In two families, seizure onset extended in age from early childhood to adulthood, and typical absence seizures were the most prevalent seizure type (83%). Focal seizures were also reported within the same family. Moreover, familial GLUT1 DS was associated with a milder clinical course, with a variable age of seizure onset (8 months to 5 years), and with a more favorable response to drug treatment. Despite infantile-onset seizures, seizures abated later in life and freedom from seizures was the general rule in the adult age groups.

The potential for misclassification of symptomatic generalized seizures resulting from neuroglycopenia is hardly a new concept. In 2003, Leary et al. noted that the most common EEG abnormality in their childhood patients was the 2.5 to 4 Hz generalized spike-wave, the hallmark of idiopathic generalized epilepsies (IGE) (25). Shortly after, Oguni et al. recognized that the infantile phenomenon of myoclonic seizures could easily be misinterpreted as benign myoclonic epilepsy in infancy, prior to the development of other symptoms (11). An illustrative case was indeed reported by Roulez-Perez in 2008, when a child with occasional myoclonic seizures in infancy and short absences was given a diagnosis of IGE (54). She was treated with valproate, ethosuximide, and clonazepam with only minimal improvement. The correct diagnosis was established at age 10 years after identification of periodic confusion before meals, atypical features on EEG, and learning difficulties. She did well on the KD, but continues to show mild neurological delays.

Newer work has focused on early absence epilepsy in GLUT1 DS, yet another syndrome easily misdiagnosed as IGE. Sul et al. studied 34 patients with early onset absence epilepsy before 4 years, and found 4 of 34 cases with SLC2A1 mutations by direct sequencing (nearly 12%) (15). These cases showed inconsistent AED treatment responses ranging from easily controlled to refractory and had normal development prior to seizure onset. The authors concluded that seizure phenotype of mutation-positive cases could not be distinguished from mutation-negative early-onset cases or from classic.
childhood absence epilepsy (CAE), except for the earlier age of onset.

Variability of phenotype and, particularly, variability of seizure expression within a family may also be seen in GLUT1 DS, as evidenced by subsequent work by the same group (52). From the probands with early onset absence, Mullen et al. identified two families with SLC2A1 mutations and identified 15 patients with mutations. Of these, 12 of 15 were found to have epilepsy with variable seizure types: 10 of 12 had absence seizures with onset between 3 and 34 years, and 3 of 12 patients had nonconvulsive status epilepticus. One sibling pair was reported to have myoclonic atatic epilepsy (MAE) with absence, GTC seizures, and atonic seizures at age 4 years, and intellectual delay. Temporal lobe epilepsy and focal dyscognitive seizures with multifocal epileptiform discharges on EEG were reported in two patients, one diagnosed with temporal lobe epilepsy (seizure onset at age 15 years) and the other with multifocal epilepsy (seizure onset at age 3 years). Both patients also developed paroxysmal dyskinesia during the late teens. Finally, isolated febrile seizures were found in one mutation carrier without further development of symptoms or delay. Of note, seven family members were identified with subtle PED, and two mutation carriers were unaffected (52).

Following the discovery of GLUT1 DS in absence epilepsy syndromes, two reports examined the prevalence of GLUT1 DS in 504 patients diagnosed with IGE (57,58). SLC2A1 mutations were present in 1.4% (7 of 504) of patients with IGE; three showed the autosomal dominant pattern of inheritance (58). CAE was reported in two, juvenile absence epilepsy in three, and juvenile myoclonic epilepsy (JME) and generalized epilepsy with GTC seizures in one patient each. Furthermore, CAE transitioned to JME in one patient.

In a familial cohort of IGE (n = 95), an SLC2A1 mutation was detected in nine (9.4%) patients. All nine patients received the diagnosis of absence epilepsy with variable age of onset ranging from early infancy to adulthood. Again, one patient, initially diagnosed with CAE, later developed JME. With the exception of one case, outcome was excellent, and all became seizure free (57).

Myoclonic epilepsy syndromes have been described in several small GLUT1 DS series. MAE was reported in familial GLUT1 DS. Of 15 patients identified with SLC2A1 mutations in two families, two siblings received the diagnosis of MAE. Both siblings had mild intellectual disability without any other cardinal signs of GLUT1 DS (15,52). A follow-up report specifically focused on the frequency of GLUT1 deficiency in 84 unrelated patients diagnosed with the MAE syndrome (59). The authors found only four patients (5%) with a missense mutation in SLC2A1 gene. All four patients had mild disability, and two later developed paroxysmal dyskinesia. Outcome was excellent with ultimate seizure freedom in all four patients. In contrast, a newer study failed to replicate the same results. Among 150 patients diagnosed with MAE, none of the patients harbored an SLC2A1 mutation, whereas 10% of CAE (5 of 50) did have a disease-causing mutation in the SLC2A1 gene (14).

Neither Lennox–Gastaut syndrome nor early infantile epileptic encephalopathy syndromes, such as Ohtahara syndrome and early myoclonic epilepsy, have been reported in association with GLUT1 DS (24).

These clinical reports underline the diagnostic challenges associated with GLUT1 DS in patients presenting with well-recognized generalized epilepsy syndromes. The coexistence of GLUT1 DS and childhood epilepsy syndromes suggests causation rather than coincidence. GLUT1 DS should be suspected in the presence of dystonia, dyskinesia, or intellectual disability associated with clinical seizures and peculiar EEG findings that are consistent with the diagnosis of “childhood onset epilepsy syndromes.”

NEUROPHYSIOLOGY

Neurophysiologic features of GLUT1 DS were first studied systematically by Boles et al. in 1999, who performed repeated studies on two children prior to and during KD treatment (60). Not surprisingly, they found both normal recordings and generalized 2 to 2.5 Hz paroxysmal spike-wave discharges in both patients. One patient had more frequent interictal discharges and absence seizures while not in ketosis, suggesting improvement with delivery of ketones across the blood–brain barrier. In 2002, Von Moers et al. elucidated the relationship between epileptiform activity and feeding; by increasing the blood glucose concentrations, one might facilitate passage of glucose via the deficient GLUT1 transporter (61). Two children, later confirmed to have GLUT1 mutations, were studied with EEG prior to breakfast, and 1 and 2 hours thereafter. The epileptiform activity at each interval was quantified as 48%, 0 and 0 (patient 1) and 28%, 13 and 10 (patient 2) at these time points. Based on the dramatic decrease or abolition of epileptiform activity after a normal meal, the authors suggested using preprandial and postprandial EEG recordings as a simple screening test for GLUT1 DS. Seizures were reported as myoclonic jerks of the shoulders and arms or nodding of the head, and corresponded with some of the generalized paroxysms of spike-waves. Subsequently, both children were placed on the KD with significant reduction in seizures and improvement in development.

Subsequent larger case series have recapitulated the findings of generalized spike-wave on EEG, but also demonstrated frequent focal and multifocal ictal and interictal findings. Leary et al., in their case series of
20 patients described previously, reviewed 24 continuous 24-hour EEG recordings and found a mixed picture of background abnormalities: generalized 2.5 to 4 Hz spike-waves (41%), generalized slowing or attenuation (34%), no abnormalities (34%), focal spike-waves (13%), and focal slowing or attenuation (9%) (25). The authors noted a trend toward increased focal versus generalized abnormalities in those under 2 years of age, attributed to immaturity of myelination, but this did not reach statistical significance ($p < .1$). The differences in EEG abnormalities prior to and after KD were also not statistically significant ($p > .10$).

A recent study from our group evaluated moment-to-moment neurophysiological and neuropsychological function in response to hyperglycemia in GLUT1 DS, which leads to substrate saturation of the GLUT1 transporter (62). Six children were recorded continuously on video EEG starting 2 hours before and continuing for 6 hours after oral glucose loading. The tracings revealed continuous background slowing, generalized spike-wave discharges, and focal frontal and central spike discharges in the preloading state. In the first 10 to 180 minutes after oral glucose loading, there were marked improvements in background activity with normalization, with complete disappearance of spike-wave activity and seizures. Improvement was also observed in certain neuropsychological tasks (coordination and attention). All clinical and EEG abnormalities gradually returned to baseline after 180 minutes. These findings underscore the critical minute-to-minute dependence of specific neurological functions on glucose transport across the blood–brain barrier. GLUT1 transport clearly is a rate-limiting event in this context.

Seizure activation with hyperventilation and photic stimulation has also been reported in two cases prior to initiation of KD. These children experienced seizures presenting with upward eye deviation, behavioral arrest, and head drop correlating with less than 3 seconds of generalized spike-wave on EEG (Figure 23.2) (54). This phenomenon has not yet been replicated on a larger scale.

The tendency toward multiple seizure types in individuals with GLUT1 DS is mirrored by the frequent occurrence of mixed EEG findings. EEG recordings may range from normal to abnormal with generalized, focal, or multifocal spike-wave discharges, and slowing or attenuation of the background (25). Abnormalities may depend on the neurodevelopmental stage, perhaps with increased focal or multifocal findings in infants due to incomplete myelination, and have been shown to vary in response to feeding status, ketosis, or the overall metabolic state. Ultimately, GLUT1 DS is a unique genetic condition where the EEG and seizure phenotype is not limited to generalized seizure types or correlative EEG features; and, importantly, variation of clinical and electrographic expression may be seen in individuals and across affected family members (52).

OUTCOME

The glucose transport defect, fortunately, does not affect fetal development. The intrauterine environment is not metabolically demanding, and most metabolic diseases emerge clinically after birth. Apgar scores generally are normal at birth. The first clinical signs of GLUT1 DS emerge postnatally. In fact, there is only one longitudinal study in the literature describing the clinical course of 13 patients diagnosed with GLUT1 DS (63). Earliest symptoms are paroxysmal, in an infant who otherwise appears to be developing normally, and dominated by seizures and eye movement abnormalities events. Other early changes involve muscle strength and tone, and breathing abnormalities that often overlap with seizures (23). Despite the fact that seizures herald the onset of the condition, the seizure prognosis is not dismal. The seizure frequency declines gradually through late infancy and early childhood, and often abates by adolescence or early adulthood. Despite normal birthweight and head circumference, there is deceleration of head growth in early infancy. Ataxia and neurodevelopmental delay become more evident during infancy and early childhood. The infantile epileptic phenotype is gradually replaced by a childhood dystonic phenotype dominated by dystonia. Unfortunately, outcome measures and intellectual ability do not improve over time. The metabolic encephalopathy remains constant and is punctuated by paroxysmal dyskinesias.

This longitudinal study of the clinical course suggests that the critical therapeutic window of opportunity is the presymptomatic moment in early infancy, or soon after the first clinical event when the infant appears, otherwise, to be developing normally (Figure 23.3). In order to diagnose the presymptomatic infant at risk for GLUT1 DS, newborn screening will be necessary. However, diagnosis of the infant immediately after the first clinical event will be an important step in the right direction.

FUTURE DIRECTIONS

Our knowledge about the clinical and molecular aspects of GLUT1 DS have evolved rapidly over the past 2 decades since the discovery of this condition in humans. Nonetheless, many important areas for future research and clinical advances remain largely untapped.

The ultimate goal in GLUT1 DS, as with all metabolic diseases, is to make an early, correct diagnosis and to
apply this knowledge to institute the best available treatment in the hopes of preventing neurodevelopmental deficits. Development of a newborn screen for GLUT1 DS will be an important next step to facilitate this goal. Newborn screening will need to evolve into a molecular screen to capture these patients. The search for other biomarkers for the condition is moving at a rapid pace, including the work by De Vivo et al., to develop the erythrocyte glucose uptake assay as a gold standard for diagnosis. This functional assay complements the molecular interrogation of the SLC2A1 gene and helps to assess the relative pathogenicity of the gene variant. Further work in this area also will enable the medical community to better understand the disease mechanisms underlying the SLC2A1 gene mutation-negative cases that have a consistent GLUT1 DS phenotype and CSF biomarkers.

In the treatment arena, we anticipate the development of further agents to provide fuel for brain metabolism. An anapleurotic 7-carbon fatty acid, 3-heptanone, originally developed as a treatment for disorders of

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**Figure 23.2** EEG findings of absence seizures in a child diagnosed with GLUT1 DS. EEG findings are similar to the EEG findings seen in childhood onset absence epilepsy. 3Hz spike and slow wave discharges with abrupt onset and offset. LFF 1Hz, HFF 70Hz, sensitivity: 7uv/mm.

**GLUT1 DS**, glucose transporter type 1 deficiency syndrome.

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**Figure 23.3** Longitudinal clinical course of GLUT1 DS throughout the life cycle: prevalence of symptoms during sequential developmental epochs. Each patient was treated at some point with the KD, thereby possibly altering the natural history of the condition.

**GLUT1 DS**, glucose transporter type 1 deficiency syndrome; **KD**, ketogenic diet.
GLUT1 DS is a unique, treatable metabolic encephalopathy associated with various clinical presentations. The current standard of care is treatment with a KD, which provides the only alternative metabolic fuel for the human brain. Most commonly, the disorder presents after normal pregnancy and early infancy, with refractory epilepsy. Seizure types may include focal or multifocal clonic or myoclonic seizures, with staring, loss of responsiveness, head nodding, and irregular episodic horizontal eye–head movements. These eye–head movements are distinctive and possibly diagnostic, for GLUT1 DS, and differ from opsoclonus. Untreated patients experience delays in the motor and cognitive domains, with acquired microcephaly and spasticity, dystonia, and ataxia. In childhood, absence, myoclonic, tonic, or clonic seizures prevail and patients may experience nonconvulsive status epilepticus. Variability in phenotype may be explained by GLUT1 haploinsufficiency, as measured by the erythrocyte glucose uptake assay. MRI findings may be normal initially, but show brain hypotrophy over time. Neurophysiological studies may also be normal, but more often show generalized, focal, or multifocal slowing and epileptiform discharges, which may vary over time and improve with glucose loading or treatment with KD. FDG-PET shows lifelong decreased cortical metabolic activity in contrast to an apparent relative increase in caudate and lentiform nuclear metabolic activity. In the 2 decades since the identification of GLUT1 DS in humans, allelic variants with more prominent motor manifestations have been discovered, including many cases without epilepsy. KD remains the standard of care for the nonepileptic forms of GLUT1 DS. These individuals may manifest dysarthria, ataxia, distinctive eye–head movements, choreoathetosis, myoclonus, spasticity, and weakness. These symptoms may be influenced by environmental stressors such as fasting, fever, infection, and emotional stress. Alternating hemiplegia of childhood, hemiplegic migraine, and paroxysmal exertional dyskinesia also have been associated with mutations in the SLC2A1 gene. With increasing awareness of this treatable metabolic encephalopathy, we anticipate further discoveries of yet milder phenotypes, facilitated by the development of newer genetic testing platforms and novel therapies. The primary treatment goal for GLUT1 DS is the nourishment of the immature “starving brain” to allow for the normal sculpting of the developing brain. Neuroglycopenia, left untreated, results in a developmental arrest in cerebral angiogenesis and a permanent limitation of brain function. Early diagnosis of the condition and prompt treatment will minimize this prognostic expectation.
The clinical condition results from deficient transport of glucose across the blood–brain barrier, causing neuroglycopenia and hypoglycorrhachia.

Most patients have loss of function mutations in the SLC2A1 gene located on chromosome 1p34.2. Inheritance pattern is mainly autosomal dominant and rarely autosomal recessive. Most patients have de novo mutations. Somatic mosaicism and compound heterozygotes have also been described.

GLUT1 haploinsufficiency parallels disease severity, and is reflected in the functional radiometric RBC glucose uptake assay. The RBC and the blood–brain barrier GLUT1 proteins are chemically and immunologically identical.

The classical phenotype begins in infancy with epilepsy, distinctive eye–head movements, acquired microcephaly, motor and cognitive delays, hypotonia, and hyperreflexia.

Other phenotypes, including children with milder delays and mixed seizure disorders, often with early onset absence epilepsy, also have been described.

Movement disorders with paroxysmal ataxia, dystonia, dysarthria, choreoathetosis, myoclonus, and eye–head movement abnormalities have also been identified as allelic variants.

Ninety percent of identified children have epilepsy, usually beginning in infancy.

Seizure types encompass focal or generalized myoclonic, tonic, clonic, astatic, focal dyscognitive, absence, and nonconvulsive status epilepticus.

Epilepsy may occur without accompanying motor or cognitive symptoms of GLUT1 DS and, without appropriate diagnostic testing or lumbar puncture, may be misclassified as IGE.

Clinical suspicion is based on history, neurological examination, and diagnostic lumbar puncture. Blood samples for glucose and lactate should be obtained immediately before the lumbar puncture. Hypoglycorrhachia and low or low-normal CSF lactate are necessary, but not sufficient, for diagnostic confirmation. Decreased RBC glucose uptake, SLC2A1 gene mutation, or both, confirm the clinical diagnosis. KD treatment should be started when the condition is suspected, and continued if confirmed.

EEG findings include normal background features, focal or generalized slowing or attenuation, or generalized focal or multifocal spike-and-wave. EEG findings may vary depending on age, metabolic status, and treatment.

MRI findings may be normal or nonspecific. Diffuse hypotrophy may be apparent over time, particularly without KD treatment.

Treatment with KD is the current standard of care for all forms of GLUT1 DS. The dietary regimen should be adjusted to achieve blood BHB levels around 5 mM. The goal is to provide optimal amounts of metabolic fuel for the developing brain. Seizure control can be achieved at lower blood BHB levels.

Epilepsy in GLUT1 DS is often refractory to standard antiseizure medicines, but responds rapidly and dramatically to the KD.

KD provides the only alternative metabolic fuel for brain development at this time and promotes brain growth and neurological development.

Prognosis is determined by early identification of the underlying metabolic condition, causing the clinical symptoms and prompt initiation of treatment with KD.

 Genetic counseling for families with an affected child is recommended.

REFERENCES


