Seizures and Metabolic Disease

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Current Neurology and Neuroscience Reports 2005, **5:**127–133
Current Science Inc. ISSN 1528-4042

Seizures represent an important clinical manifestation of inborn errors of metabolism. The presence of myoclonic seizures and very early onset are clues to a metabolic disorder. Specific correlations between age of seizure onset and electroencephalogram patterns with inborn errors of metabolism are discussed. The explosion of information in neurogenetics and metabolism mandates increasing awareness of appropriate metabolic diagnostic and therapeutic strategies in the setting of certain epilepsies. Specific laboratory, imaging, and treatment considerations are included to present updated material in a field that continues to expand rapidly.

Introduction

The accelerating level of information in neurogenetics and neurometabolism has raised a host of new diagnostic, therapeutic, and ethical issues. Clinical cases have been selected to illustrate updates in the field.

Sample Cases

A pregnant woman with prior history of a newborn deceased of refractory neonatal seizures presents with unusual, persistent fetal movements at 36 weeks of gestation. Fetal monitoring demonstrates fetal tachycardia and an absence of uterine contractions. What diagnoses should be considered? How should the mother and neonate be managed in the peripartum?

A 3.5-year-old girl presents with impaired cognitive skills (IQ of 70), microcephaly, and cerebellar and pyramidal tract signs. She has a history of seizures since 3 months of age. Early paroxysmal events were characterized by brief episodes of staring with subtle eyelid fluttering and darting, and conjugate movements of the eyes in all directions, usually lasting 1 to 2 minutes. A generalized convulsion occurred at 6 months of age. Both electroencephalogram (EEG) and magnetic resonance imaging (MRI) results were normal, so phenobarbital was begun, followed by valproate. However, her seizures continued, and motor and behavioral developmental regression occurred. At age 27 months, with profound developmental delay, she was started on the ketogenic diet. She had dramatic resolution of seizures and improvement in development. Phenobarbital was discontinued and her progress accelerated. Cerebrospinal fluid (CSF) revealed no pleocytosis, with protein level of 40 mg/dL, glucose level of 30 mg/dL, and lactate level of 0.9 mmol/L. What is this patient's diagnosis, and how should she be treated?

A 5-year-old boy presents with severe hyperactivity and a first generalized tonic-clonic seizure. He appears minimally verbal and nondysmorphic, with mild hypotonia, hyporeflexia, and gait ataxia. Psychoeducational testing shows mild mental retardation (verbal IQ of 55, performance IQ of 65) and deficient adaptive behaviors on the Vineland test. EEG reveals mild background slowing during wakefulness and intermittent generalized spike-wave activity during sleep. Valproate is begun, but is associated with lethargy. An MRI is obtained, demonstrating increased T2-weighted signal in the globus pallidi. Urine organic acid analysis revealed 4-OH-butyric aciduria. What diagnosis should be made for this patient? What treatment should be administered?

General Principles

Seizures are often caused by metabolic disturbances, some of which are due to inborn errors of metabolism (IEM). Hundreds of such defects have been described; most are rare and some are extremely rare. A rough incidence range is 0.1 to 300 per 100,000 live births. Cumulatively, seizures caused by metabolic disease amount to a significant problem for the clinician. A precise diagnosis is imperative for optimal treatment, prevention, and counseling. Within the family history, one should look for consanguinity, or inheritance pattern, to suggest autosomal recessive (or sometimes maternal [mitochondrial], X-linked, or even autosomal dominant) transmission. The time course of the condition may be inexorably progressive, as in the storage disorders, or be intermittent, as with disorders of intermediary metabolism.

A metabolic etiology should be considered, especially with seizures that occur early in life, particularly during the latter half of the first week. Myoclonic seizures, constant hiccupping, or unusually early hypsarrhythmia

suggest metabolic disease. In the neonate presenting with a clinical scenario leading to a "sepsis work-up," metabolic error should be suspected if the blood pressure is more easily maintained than in typical sepsis, if acidosis (if present) is relatively unresponsive to the usual means of respiratory and circulatory support, if ketoacidosis is present, or if cultures are sterile (expect for association of galactosemia and sepsis caused by *Escherichia coli*).

Several possibilities exist regarding the pathophysiology of seizures in metabolic disease [1]. Seizures could result from excessive excitatory or deficient inhibitory mediators, or from dysregulation of mediators [2,3]. Alternatively, there could be deficient energy substrate, as in glucose transporter deficiency. In the examples of Zellweger syndrome, glutaric aciduria type II, and nonketotic hyperglycinemia (NKH), there may be associated neuronal migrational anomalies. Accumulation of abnormal products could lead to structural disruption of cell membranes, altered intercellular signaling, impaired neuronal development, or downstream inflammatory processes.

The traditional clinician's approach has been to classify metabolic encephalopathies as gray versus white matter disorders. Characteristics of poliodystrophies include early dementia, retinal disease, and seizures. Examples include Tay Sachs, Niemann Pick, and neuronal ceroid lipofuscinosis (NCL). Leukodystrophies, presenting with initial spasticity, blindness (optic nerve), and deafness, include Krabbe's, metachromatic leukodystrophy (MLD) and adrenoleukodystrophy (ALD). Newer classification schemes have focused on the organelle. Mitochondrial disorders present with a vast array of clinical manifestations, including seizures, strokes, optic atrophy, cerebellar ataxia, neuropathy, myopathy, cardiomyopathy, sensorineural deafness, and diabetes mellitus [4]. They can be attributed to mutations in the mitochondrial genome or nuclear genome. The peroxisomal disorders have enlarged in scope, with the prototype being ALD, and the Golgi body and ribosomes are the altered organelles in the congenital disorders of glycosylation (CDG).

Other neurometabolic diseases are being identified at the level of the neurotransmitter. Diseases of the monoamines include Segawa-type dopa-responsive dystonia, or GTP cyclohydrolase-1 deficiency [5]. Tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase deficiency, folinic acid responsive seizures, methylene tetrahydrofolate reductase deficiency, and pterin/sepiapterin defects are included in the wide range of monamine deficiencies [6]. Gamma aminobutyric acid (GABA) disorders that may cause seizures are pyridoxine-dependent epilepsy, GABA transaminase deficiency, and succinic semialdehyde dehydrogenase (SSADH) deficiency [7•]. NKH presents with intractable seizures and demonstrates that glycine has not only inhibitory (spinal cord), but also excitatory (cerebral cortex), properties. In 3-phosphoglycerate dehydrogenase deficiency, a disorder of serine (a precursor of glycine), seizures can be eliminated with amino acid therapy [8]. Clinical disorders related to altered metabolism of other neurotransmitters (*eg*, glutamate and melatonin) remain to be identified.

Channelopathies involving Na+, K+, and Ca++ ion channels should also be considered in the diagnosis of seizures related to metabolic disease. Na+ channelopathy causes generalized epilepsy with febrile seizures, plus other seizures, whereas K+ channelopathy causes both episodic ataxia type I and benign familial neonatal convulsions. Episodic ataxia type 2, familial hemiplegic migraine, and spinocerebellar ataxia (SCA) 6 may result from Ca++ channelopathies. Of the many identified forms of autosomal dominant hereditary ataxias, SCA 10 is associated with seizures. In SCA, the average age of onset is 36 years and average duration is 9 years.

Insidious brain energy failure is a heretofore relatively unknown mechanism for metabolic disease and seizures. Defects of fuel availability arise from hypoglycemic and hypoketonemic syndromes. Fuel transport defects, such as glucose transporter 1 deficiency, appear to have a wide and variable clinical phenotype. Mitochondrial and glycolytic defects may preclude fuel combustion, providing further examples of brain energy failure [9•].

Clues from the Laboratory

There are several laboratory findings that can help elucidate the diagnosis of a metabolic disease–related seizure disorder. Persistent hypoglycemia is seen in pyruvate carboxylase deficiency, organic acidurias, and amino acidopathies. Organic acidurias will cause acidosis with raised lactate and ammonia levels. In contrast, urea cycle defects are evidenced by alkalosis with high ammonia levels. Abnormal plasma urate levels (either high or low) are the result of purine disorders. Leukopenia and thrombocytopenia are characteristic of organic acidopathies and storage disorders. Urine positive for reducing substances is seen with carbohydrate disorders, and ketonuria suggests IEMs, especially in newborns. Urine test strips can reveal sulfite oxidase deficiency and mucopolysaccharides. Blood lactate and ammonia levels are often seen to rise as soon as a tourniquet is applied and to increase rapidly in struggling or crying patients; lactate, ammonia, and particularly pyruvate are all unstable and require free-flowing (usually arterial) blood for accurate sampling. Tandem mass spectrometry, a relatively new technology that permits more comprehensive detection of metabolic disorders, may replace newborn screening programs, as issues related to cost, technical feasibility, and interpretation are resolved [10•].

Radiologic Aspects

Magnetic resonance imaging, along with diffusion tensor imaging and MR spectroscopy (MRS), is a useful and non-

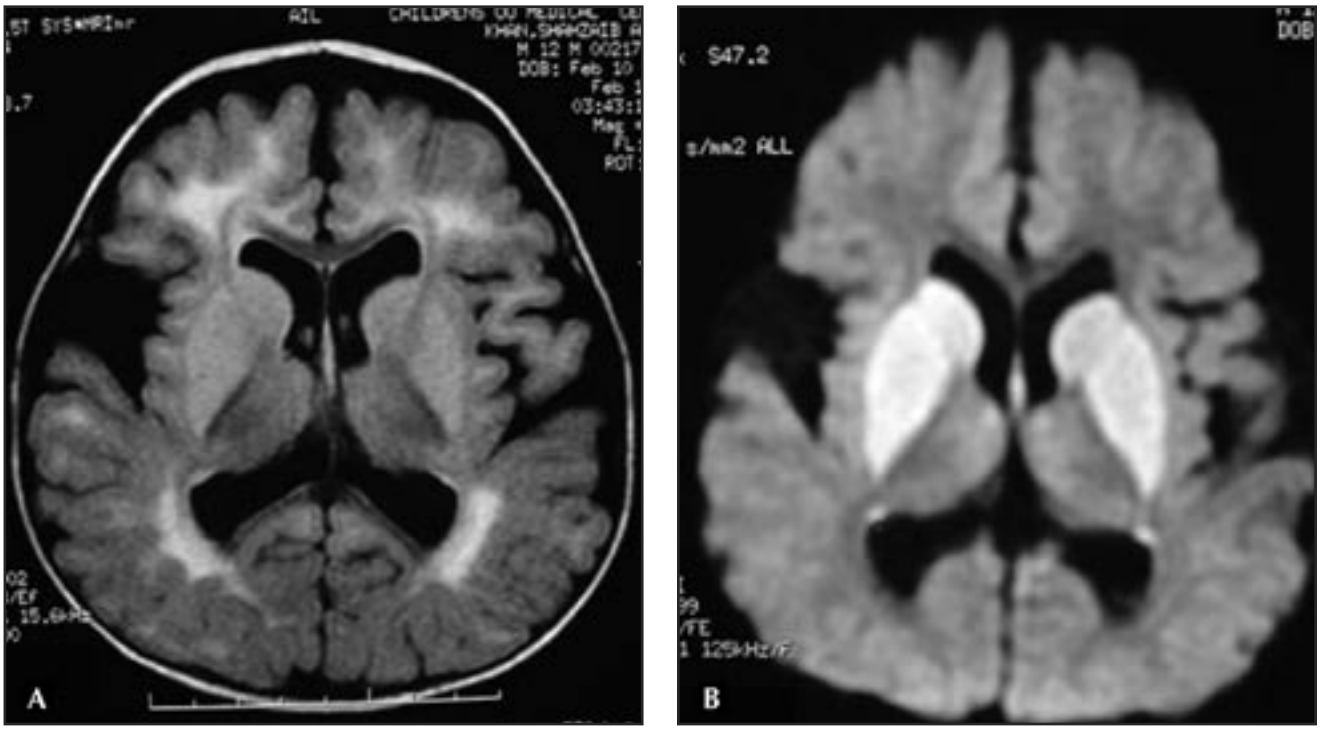

Figure 1. A, Magnetic resonance image (T2-weighted) of patient with glutaric aciduria type I, showing enlarged perisylvian fissures. **B,** Magnetic resonance image (T2-weighted) of same patient showing bright signal of the caudate and putamen bilaterally. (***Courtesy of*** T. Chang, MD.)

invasive technique for the detection of various diseases [11]. Extensive dysmyelination is observed in MLD, Krabbe's, ALD (posterior early), Canavan, and Pelizaeus-Merzbacher disease. White matter is absent in connatal Pelizaeus-Merzbacher disease (type II or Seitelberg variant). Both atrophic changes and cysts may be observed in the frontal and temporal lobes, along with striatal necrosis, in glutaric aciduria type 1 (Fig. 1). The T2 signal is often increased in the globus pallidus in organic acidopathies. Mitochondrial disorders result in abnormal corpus striatum, as well as cerebellar atrophy, and cortical-subcortical ischemia. Agenesis of the corpus callosum may occur in pyruvate dehydrogenase deficiency, and a tiny cerebellum is associated with CDG. Subdural effusions are seen in pyruvate carboxylase deficiency and glutaric aciduria. MRS is used to detect lactate peaks in mitochondrial defects and the absence of creatine in defects of creatine biosynthesis and transport. Recent MRS applications have been helpful in the elucidation of the pediatric neurotransmitter diseases, particularly NKH and SSADH deficiency (Fig. 2) [12,13].

Therapeutic Tips

Patients who suffer from seizures related to metabolic disturbance can be treated with a variety of therapies. The neonate or young infant with numerous intractable seizures or status epilepticus may demonstrate major EEG changes and abnormal neurologic development without an immediate perinatal or prenatal insult. In this case, a therapeutic trial with vitamin B_6 and biotin should be considered [14,15••]. The adherence to a ketogenic diet can be a very successful treatment for pyruvate dehydrogenase deficiency and glucose transporter protein 1 deficiency [9•]. The ketogenic diet, however, is contraindicated in practically all other metabolic disorders, especially in pyruvate carboxylase deficiency. In PC deficiency, patients are unable to produce adequate amounts of oxaloacetate, the rate-determining substrate in Kreb cycle metabolism (Fig. 3). When treating a patient with preexisting metabolic acidosis, one should avoid drugs inducing metabolic acidosis, such as acetazolamide, topiramate, and zonisamide. Clinical worsening upon valproate administration should raise concern regarding the existence of an underlying metabolic disorder, as well as raise the option of carnitine co-administration [16]. Therapies to avoid include phenobarbital in complex I deficiency of the respiratory chain and corticotrophin in pyruvate carboxylase deficiency [17•]. Finally, patients with glucose transporter 1 protein deficiency syndrome should not be given phenobarbital or methylxanthines, as these suppress glucose transport. Alternatively, the potential glucose transport activator thioctic acid (alpha-lipoic acid) may be administered [9•].

Discussion of Clinical Cases

The first sample case in this article illustrated in utero seizures, which is a classic presentation of nonketotic

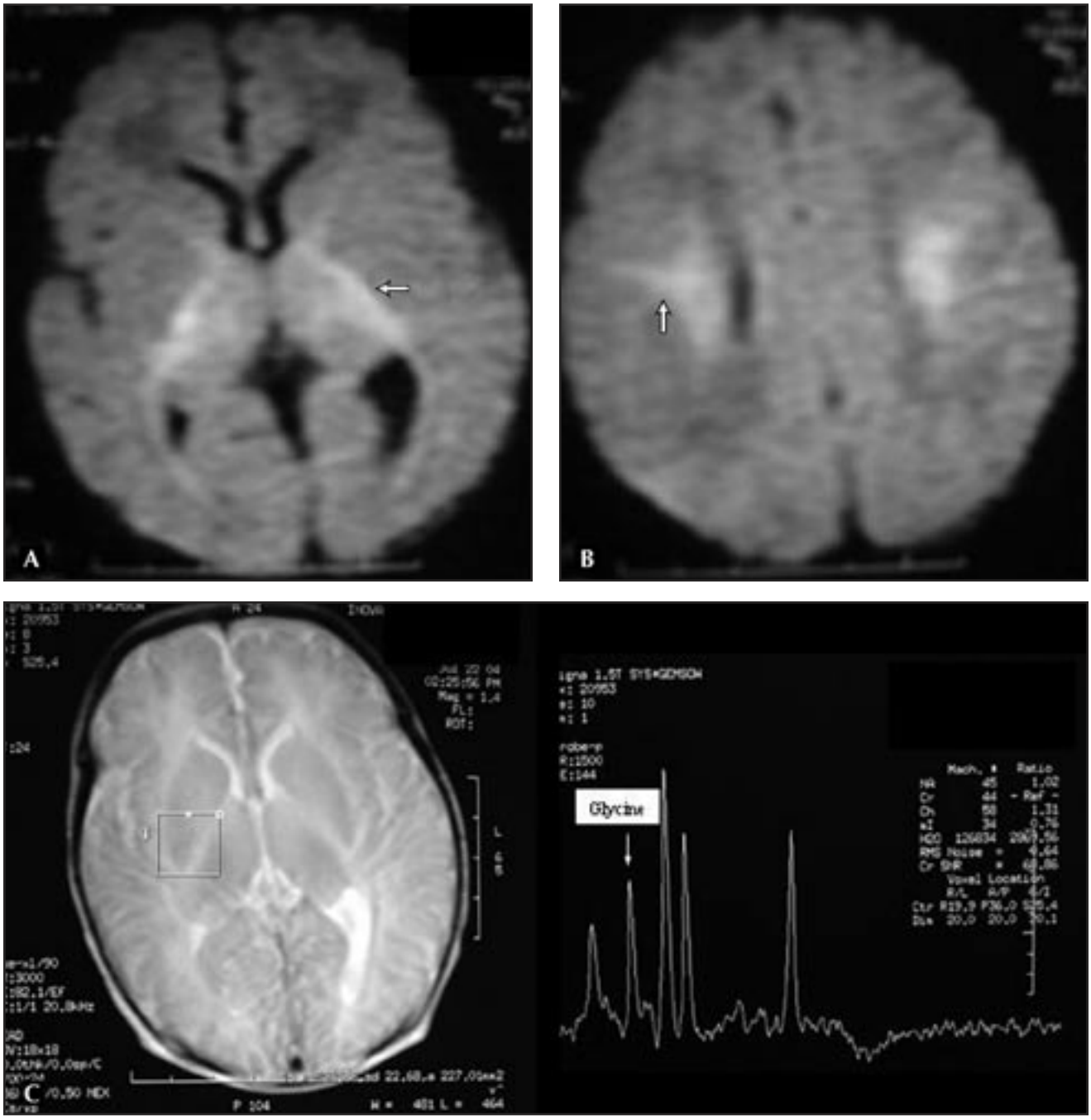

Figure 2. A and **B,** Diffusion-weighted magnetic resonance image of a 10-day-old patient with nonketotic hyperglycinemia. Note the bright signal demonstrating edema of the corticospinal tracts (***arrow***, Fig. 2A), corona radiata, and perirolandic regions (***arrow***, Fig. 2B). **C,** Magnetic resonance spectroscopy of same patient; note glycine peak **(*arrow*).** (***Courtesy of*** T. Chang, MD.)

hyperglycinemia. This is a defect of the glycine cleavage enzyme system, an intramitochondrial enzyme complex with four components: P protein (pyridoxal phosphate-dependent glycine decarboxylase); H protein (a lipoic acid–containing hydrogen-carrier protein); T protein (tetrahydrofolate dependent); and L protein (lipoamide dehydrogenase). Most patients have refractory neonatal seizures with associated lethargy and hypotonia, progressing to apnea and death or profound encephalopathy. Although there is no curative therapy, patients have been treated with benzoate or dextromethorphan with mixed success [18]. The other IEM presenting with this scenario is pyridoxine-dependent epilepsy. Although this metabolic error had traditionally been attributed to insufficiency of the primary inhibitory neurotransmitter GABA, owing to the role of pyridoxal-5-phosphate as a cofactor with glutamic acid decarboxylase in GABA synthesis, the primary metabolic defect is unknown. The mother should be treated with 100 mg/d of vitamin B_6 through delivery, and treatment should be continued

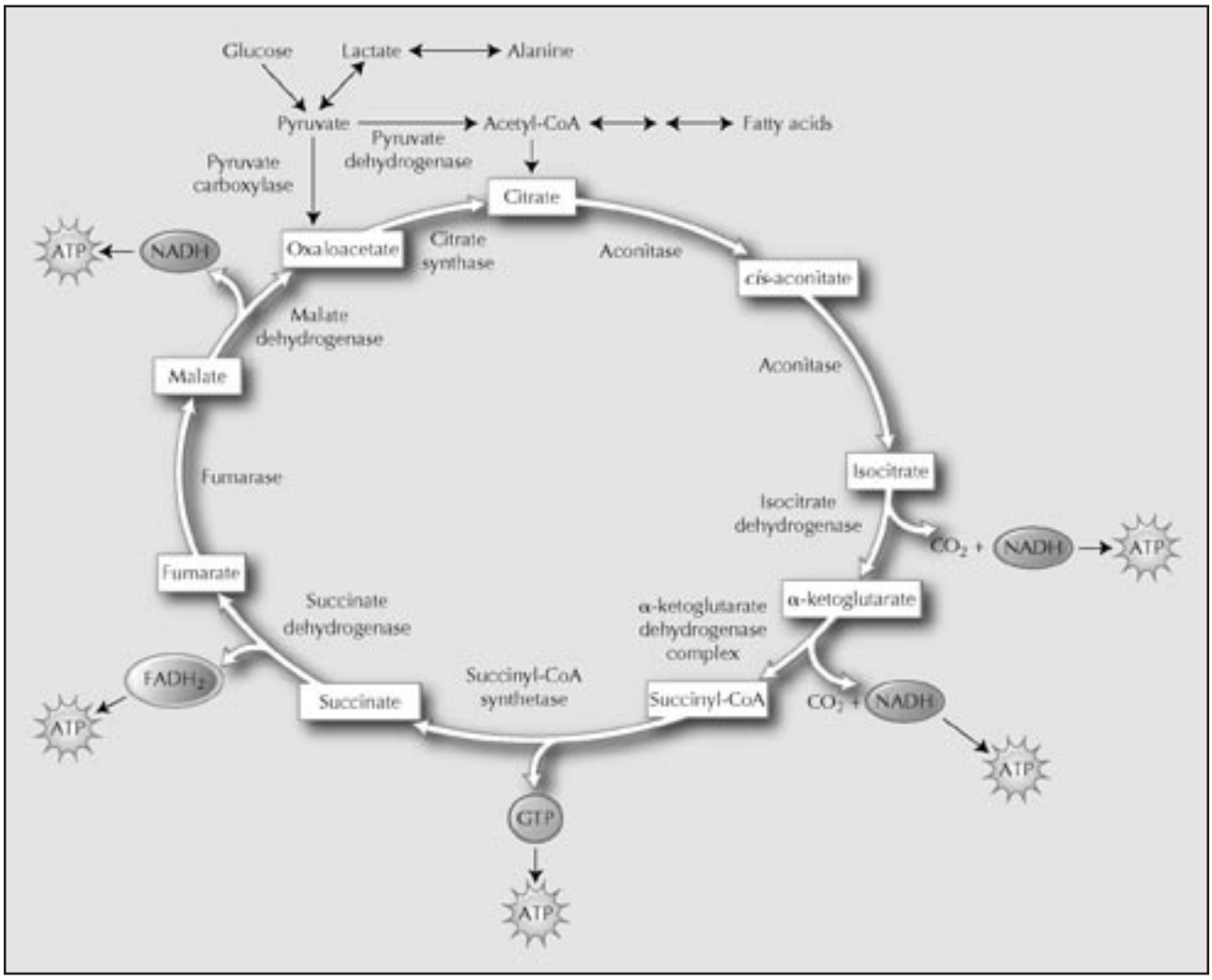

Figure 3. Diagram of the Krebs cycle. In pyruvate dehydrogenate (PDH) deficiency, the ketogenic diet is therapeutic, as it obviates the conversion of glucose to pyruvate and the PDH-mediated entry of pyruvate into the Krebs cycle. Conversely, the ketogenic diet is contraindicated in other metabolic disorders, particularly in pyruvate carboxlase deficiency, as these patients cannot generate oxaloacetate from pyruvate. (CoA—coenzyme A; $FADH_2$—flavin adenine dinucleotide [reduced form].)

in the neonate. In the presence of neonatal seizures, the clinician should assess the baby with EEG and a concomitant dose of 100 mg pyridoxine intravenously. Within 2 to 6 minutes of administration of the drug, a clinical and EEG response should be observed. At least 24 hours after administration, the baby should be checked for signs of lethargy or apnea. Although initial dosing is generally 15 to 30 mg/kg/d, maintenance dosages appear to be much lower, in the range of 0.5 to 2.0 mg/kg/d. There has been an increasing emphasis on atypical cases, with later onset or pyridoxine responsivity instead of dependency [15••].

The second clinical case presented in this article, a girl with seizure disorder, microcephaly, developmental disorder, and improvement on the ketogenic diet, was notable for hypoglycorrhachia. She had further improvement when discontinued from phenobarbital. The diagnosis is glucose transporter 1 deficiency. EEGs ultimately show 2.5- to 4-Hz generalized spike wave discharges. Curiously, infantile apnea and oscillatory eye movements, reminiscent of opsoclonus, are frequently reported as the earliest clinical signs. Mutations of the GLUT1 gene have been identified in some families, and transmission of the mutation is autosomal dominant. Clinical expression appears to depend on the amount of residual glucose transporter 1 function in addition to other genetic and environmental factors. The phenotype of this disorder is remarkably diverse. Treatment should avoid barbiturates and methylxanthines, but thioctic (alpha-lipoic) acid and the ketogenic diet, which provide an alternative fuel to glucose for brain energy, are recommended [9•].

In the final sample case, a hyperactive boy with cognitive retardation experienced his first seizure at 5 years of age and demonstrated T2-weighted hyperintensities of the globus pallidi on MRI. Urine organic acids demonstrated

Table 1. Inborn errors of metabolism with prominent seizures by age

Seizure activity and age of onset	Very frequent seizures	Frequent seizures
Neonatal and early infancy (< 1 y of age)	Alpers syndrome	Mitochondrial disorders
	Aminoacidopathies	
	B_6 dependency	Peroxisomal disorders
	Biotin disorders	
	Glucose transporter I deficiency	Urea cycle disorders
	Molybdenum cofactor deficiency	
	NKH	
	Organic acidopathies	
Late infancy and early childhood (1–6 y of age)	Alpers syndrome	Lysosomal storage disorders
	B_6 dependency	
	Biotin disorders	
	NCL2 (late infantile)	
	Sialidosis type II	
Childhood and adolescence (7–18 y of age)	Baltic myoclonus	Acute intermittent porphyria
	Juvenile Gaucher	Batten's disease (CLN3)
	Lafora body disease	Huntington disease
	MERRF	Juvenile GM2 gangliosidosis
		Mucopolysaccharidosis II

CLN3—ceroid lipofuscinoses 3; MERRF—myoclonus epilepsy with ragged red fibers; NCL2—neuronal ceroid lipofuscinoses 2; NKH—nonketotic hyperglycinemia.

Table 2. Electroencephalogram patterns and associated disorders

Pattern	Disorder
Comblike rhythm	Maple syrup urine disease, propionic acidemia
Fast central spikes	Tay Sachs disease, biotinidase deficiency
Rhythmic vertex-positive spikes	Sialidosis (type I)
Vanishing electroencephalogram	Infantile NCL (early infantile/type I/Haltia-Santavouri, locus 1p32, mutation in the palmitoyl-protein thioesterase gene)
High-amplitude (16–24 Hz) activity	Infantile neuroaxonal dystrophy
Giant SSEPs	Progressive myoclonic epilepsy
Marked photosensitivity	Progressive myoclonic epilepsy (Lafora) and NCL, particularly late infantile (type II/Bielschowsky, CLN2)
Burst suppression	Adrenoleukodystrophy (neonatal), citrullinemia, D-glyceric acidemia, holocarboxylase synthetase deficiency, Leigh disease, Mb cofactor deficiency, Menkes, MTHFR deficiency, NKH, PDH/PC deficiency, propionic acidemia, sulfite oxidase deficiency
Hypsarrhythmia	Adrenoleukodystrophy (neonatal), CDG (type III), HHH, Menkes, neuroaxonal dystrophy, NKH, PDH, PEHO, phenylketonuria, Zellweger
Low-amplitude slowing	Urea cycle defects (carbamylphosphate synthetase, OTC, argininosuccinate synthetase)

CDG—congenital disorders of glycosylation; CLN2—ceroid lipofuscinoses 2; HHH—hyperornithinemia, hyperammonemia, homocitrullinuria; MTHFR—methylene tetrahydrofolate reductase; NCL—neuronal ceroid lipofuscinoses; NKH—nonketotic hyperglycinemia; PDH/PC—pyruvate dehydrogenase/pyruvate carboxylase; PEHO—progessive encephalopathy with edema and hypsarrhythmia; OTC—ornithine transcaramylase; SSEP—somatosenory evoked potential.

elevated 4-OH-butyric acid, and the diagnosis of SSADH deficiency was confirmed in leukocytes. As opposed to a progressive or intermittent clinical course, this disorder simulates a nonprogressive encephalopathy or even shows partial improvement in deficits such as cerebellar ataxia, thus rendering a metabolic diagnosis even more difficult [7•]. Valproate is generally contraindicated in this condition, as any residual enzymatic activity can be inhibited. Vigabatrin, a GABA-transaminase inhibitor that should theoretically avoid the enzymatic block in this disease, has been associated with inconsistent results, possibly because of further increases in GABA levels despite lowered 4-OH-butyric acid concentrations [20].

Conclusions

Metabolic disorders in aggregate represent a significant and not uncommon problem, and the information explosion in neurogenetics has led to increasing complexity in the clinical management of these disorders. Classification has delved into the organelle, neurotransmitter, and ion channel levels. Laboratory and neuroimaging procedures have allowed for increased detection as well as differentiation of these disorders. Matching features such as age of seizure onset [21], epilepsy syndrome, and EEG findings to metabolic diagnoses remains a clinical challenge (Tables 1,2) [22•]. In some cases, metabolic encephalopathies featuring epilepsy have particular therapeutic implications, whereas strategies ranging from traditional antiepileptics such as phenobarbital or valproate, to the ketogenic diet, vitamin B_6, or neuroprotective agents have roles that may be therapeutic or sometimes deleterious.

Acknowledgments

We thank Philip Capp for his assistance with Figure 3. This work is supported in part by the Pediatric Neurotransmitter Disease Association.

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