Chapter 10

Approach to the Diagnosis of the Inborn Errors of Metabolism Associated with Epilepsy and their Clinical Genetics

Richard E. Frye and Stephen G. Kahler

Introduction

Metabolic disease can be an underlying cause of epilepsy, particularly in drug-resistant epilepsies and those associated with neurodevelopmental or neurodegenerative disease. Early diagnosis is important as many respond to appropriate treatment such as specific supplements or dietary changes [1–3] and delay in applying treatment will worsen outcome. The ketogenic diet also can be helpful in a wide range of metabolic abnormalities [4], resulting in significant seizure improvement in drug-resistant epilepsy [5]. A metabolic workup for epilepsy should be considered before considering invasive therapies such as epilepsy surgery [6].

The exact proportion of epilepsy that is associated with an underlying metabolic disease is not clear since workups for metabolic disease are often not carried out. Epilepsy is common in many metabolic diseases. Inborn errors of metabolism usually have a genetic basis, but are rare, and so in overall terms they are not a common cause of epilepsy. However, where epilepsy is drug resistant and is associated with progressive neurologic dysfunction, inborn errors of metabolism are more commonly found to be the cause. For example, one study using focused NGS found that inborn errors of metabolism accounted for the cause of the epilepsy in 7% of children with epileptic encephalopathy referred to a genetics clinic [7]. One of the most difficult aspects of diagnosing inborn errors of metabolism is the need to differentiate primary inborn errors of metabolism from metabolic derangements that are secondary to the pathophysiological effect of epilepsy [8, 9].

This chapter outlines the inborn errors of metabolism that may cause epilepsy, their unique symptoms, key diagnostic tests and specific associated genes. Later chapters will explore these topics in more detail.

Differential Diagnosis

Table 10.1 lists the major metabolic disorders associated with epilepsy, their distinctive clinical features as well as the key metabolic tests for each disorder. Even though some of these disorders may be tested for on newborn screening, they can present after the newborn period and need to be considered even if the newborn screening panel was negative.

Table 10.2 outlines the genes associated with these inborn errors of metabolism as well as the inheritance patterns. Genetic testing is becoming the primary laboratory diagnostic method for metabolic disorders. There is considerable overlap in symptoms among metabolic disorders. Table 10.3 lists key

Table 10.1 Inborn errors of metabolism associated with epilepsy

Disorder	Principal clinical features	Diagnostic testing
	Disorders of energy metabolism	
Mitochondrial disease	Children: global developmental delay including gross motor delay; developmental regression; ataxia; failure to thrive; epileptic encephalopathy Adult: myopathy; renal tubulopathy; liver failure General: gastrointestinal abnormalities; fatigability; cardiomyopathy	• Fasting serum lactate, pyruvate, amino acids and urine organic acids • Brain MRI- Respiratory chain enzyme assay
Mitochondria DNA depletion syndromes	Onset in infancy or early childhood; sudden onset of drug-resistant epilepsy, developmental regression and liver failure; ophthalmoplegia, ataxia, ptosis, intestinal pseudo-obstruction, renal tubulopathy	• Mitochondria DNA copy number in muscle or liver
Fatty acid oxidation deficiency*	Onset usually <30 months; hypoketotic hypoglycemia during physiologic stress including infection, fasting, or intercurrent illness. Maternal history of HELLP syndrome, hepatomegaly	• Acyl-carnitine and carnitine panel • Urine acyl-glycines

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Table 10.1 (cont.)

Disorder	Principal clinical features	Diagnostic testing
	Disorders of organic acid metabolism	
Propionic acidemia*	Infantile onset; encephalopathy, coma, acidosis, ketosis, hypoglycemia, hyperglycinemia, hyperglycinuria, neutropenia, development delay, thrombocytopenia, hypogammaglobulinemia, intolerance to protein	• Urine organic acids • Acyl-carnitine and carnitine panel • Serum lactate and ammonia
Methylmalonic aciduria*	Infantile onset but older onset possible; dysmorphic, failure to thrive, developmental delay, thromboembolism, thrombocytopenia, anemia, neutropenia, cortical atrophy, dystonia, spasticity	• Serum/urine homocysteine • Acyl-carnitine and carnitine panel • Urine organic acids
L-2-Hydroxyglutaric aciduria	Neonatal onset; progressive psychomotor regression, spasticity; optic atrophy, nystagmus, hearing loss, brain MRI with generalized atrophy along with white matter loss and cystic cavitation	• Urine, serum and CSF organic acids
D-2-Hydroxyglutaric aciduria	Neonatal onset and early infantile onset; macrocephaly, cardiomyopathy, aortic insufficiency, inspiratory stridor with apnea, episodic vomiting, severe developmental delay, weakness, brain MRI with delayed myelination and gyration, subependymal cysts and enlarged ventricles.	• Urine, serum and CSF organic acids
D-Glyceric aciduria	Neonatal to infantile onset; failure to thrive, microcephaly, developmental delay, hypotonia, spasticity, opisthotonus, myoclonus, hypsarrhythmia, cortical atrophy	• Urine, serum and CSF organic acids
Isovaleric acidemia*	Infantile onset; sweaty feet odor, feeding refusal, protein aversion, emesis, lethargy, coma, pancytopenia with hypoplastic bone marrow, ketoacidosis	• Acyl-carnitine and carnitine panel • Urine organic acids
	Disorders of porphyrin metabolism	
Acute intermittent porphyria Hereditary coproporphyria Variegate porphyria	Attacks of abdominal pain, red urine, psychosis and seizures; attacks triggered by fasting and medications including some AEDs. Neuropathy with ascending paralysis, hypernatremia, anemia	• Stool, urine and blood porphyins • Electrolytes and complete blood count
	Disorders of blood–brain-barrier transport	
Cerebral folate deficiency	Onset in 1st year of life with developmental regression, ataxia, pyramidal signs, acquired microcephaly, dyskinesias, seizures and eventually visual and hearing loss	• Folate receptor alpha autoantibodies • CSF 5-methyltetrahydrofolate level
Glucose transport deficiency	Infantile onset with drug-resistant epilepsy, acquired microcephaly, ataxia, spasticity, hyperreflexia, hypertonia, chorea, hypoglycorrhachia, low CSF lactate	• CSF glucose and lactate
	Disorders of cofactor (vitamin) metabolism	
Biotinidase deficiency*	Developmental delays, feeding difficulties, vomiting, brain atrophy, ataxia seborrheic dermatitis, alopecia, diarrhea	• Biotinidase activity
Carnitine biosynthesis deficiency	Non-dysmorphic males with autism from multiplex families, episodic regression	• Plasma and/or urine 6-N-trimethyllysine and γ-butyrobetaine
Coenzyme Q10 deficiency	Onset from infancy to late childhood; deafness, vision loss, cardiomyopathy, liver failure, fatigue, intellectual disability, ataxia, hypotonia or hypertonia and/or dystonia	• Serum lactic acid • Coenzyme Q10 in skeletal muscle

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Table 10.1 (cont.)

Disorder	Principal clinical features	Diagnostic testing
Cerebral creatine deficiency	Global developmental delay, hypotonia and/or spasticity, dyskinesia, chorea, autism, brain MRS shows decreased creatine peak	• Magnetic resonance spectroscopy • Urine/serum creatine & guanidinoacetic acid
Menkes disease	Infantile onset with severe neurologic degeneration; twisted, steely, kinky, sparse hair with partial breaks on magnification	• Serum copper and ceruloplasmin
Molybdenum cofactor deficiency	Infantile onset and can mimic hypoxic ischemic encephalopathy, dysautonomia, dysmorphic facial features, exaggerated startle reactions, progressive spasticity, microcephaly, early death, MRI with multicystic cerebral lesions	• Urine sulfite, *S*-sulfocysteine, thiosulfate, xanthine, uric acid • Serum uric acid
Pyridoxine-dependent & responsive seizures	Prenatal onset with abnormal intrauterine movements and fetal distress, global developmental delay, atypical breathing, self-injurious behavior, autism, normalization of EEG with pyridoxine	• Plasma & cerebrospinal fluid pipecolic acid • Urine α-aminoadipic semialdehyde
	Disorders of Cholesterol Metabolism	
Smith–Lemli–Opitz syndrome	Failure to thrive, eczema, congenital structural defects in heart, gastrointestinal tract, genitalia, kidney, limbs, face and brain, developmental delay, autism, dysmorphic	• Blood 7-dehydrocholesterol and cholesterol
	Disorder of γ-aminobutyric acid metabolism	
Succinic semialdehyde dehydrogenase deficiency	Global developmental delay from infancy or regression in early childhood, hypotonia, hyperreflexia, ataxia, autism, aggressiveness, myoclonus, hallucinations, ataxia, choreoathetosis & dystonia	• Urine, serum, CSF 4-hydroxybutyric acid
	Disorders of pyrimidine and purine metabolism	
Adenylosuccinate lyase deficiency	Global developmental delay, microcephaly, failure to thrive, dysmorphic, cerebellar vermis hypoplasia, brain atrophy, excessive laughter, very happy	• Urine and/or cerebrospinal fluid succinyladenosine
Lesch–Nyhan syndrome	Global developmental delay, failure to thrive; nephrolithiasis, choreoathetosis, dystonia, self-injurious behavior	• Serum uric acid - Urinary urate-to-creatinine ratio - Hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme activity
	Disorders of amino acid metabolism and urea cycle disorders	
Phenylketonuria*	Global developmental delay, mental retardation, microcephaly, spasticity, ataxia, poor growth, poor skin pigmentation, aggressive behavior	• Serum phenylalanine
Branched chain ketoacid dehydrogenase kinase deficiency*	Onset of seizures, sometimes febrile, in early childhood; autism, schizophrenia, intellectual disability, low branched chain amino acids in serum and CSF	• Plasma and CSF amino acids
Maple syrup urine disease*	Onset infantile to early childhood; encephalopathy, coma, acidosis, ketosis, hypoglycemia, cerebral edema, maple syrup urine odor	• Serum amino acids • Urine organic acids
Nonketotic hyperglycinemia	Neonatal onset; hiccups, hypotonia, myoclonus, coma, burst suppression	• CSF/serum glycine

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Table 10.1 (cont.)

Disorder	Principal clinical features	Diagnostic testing
Serine deficiency	Prenatal onset with intrauterine growth retardation or childhood onset with intellectual disabilities; microcephaly, global developmental delay, spasticity, nystagmus, brain atrophy with hypomyelination, cataracts, hernias, hypogonadism, megaloblastic anemia.	• Fasting serum and CSF serine and glycine are decreased. However, these are normal in transporter variant
Sulfite oxidase deficiency	Infantile onset or regression in childhood, ataxia, dystonia, choreoathetosis, irritability, ectopia lentis	• Urine sulfite increased & sulfate decrease
Urea cycle disorder*	Global developmental delay; failure to thrive; protein intolerance, temperature instability, episodic somnolence, lethargy, coma, ataxia, cyclic vomiting, irritability and psychosis	• Plasma ammonia & amino acids • Urine orotic acid
	Peroxisomal disorders	
Zellweger syndrome	Neonatal onset with microcephaly and dysmorphology, cataracts, failure to thrive, hepatomegaly, renal abnormalities, hypotonia, hyporeflexia, migration abnormalities, retinopathy	• Serum very long-chain fatty acids • Serum phytanic and pipecolic acid • Red blood cell plasmalogen content
	Lysosomal storage disorders	
Gaucher disease	Subacute neurologic deterioration with onset ranging from infancy to childhood; supranuclear gaze palsy with vertical movements preserved, hepatomegaly, splenomegaly, pancytopenia	• Leukocyte beta-glucocerebrosidase activity
Neuronal ceroid lipofuscinosis	Age of onset is variable from infancy to adulthood; rapid neurological degeneration, cerebral atrophy, spasticity, ataxia, extrapyramidal signs, myoclonus	• Intracellular autofluorescent lipopigment material in fibroblasts or sclera neurons
Sialidosis	Age of onset is variable from infancy to adolescence; cherry-red spot, myoclonus, ataxia, tremor Infantile form with hepatosplenomegaly, dysostosis multiplex and coarse facial features.	• Urine oligosaccharides • Leukocyte alpha-neuraminidase activity
Niemann–Pick disease	Infantile to early childhood onset; developmental delay or neurologic regression, spasticity, dystonia, ataxia, vertical supranuclear gaze palsy; hepatosplenomegaly, fetal ascites, gout	• Bone marrow biopsy for foam cells • Leukocyte sphingomyelinase activity
Salla disease	Infantile onset; global developmental delay, exotropia, nystagmus, growth retardation	• Urinary free sialic acid
Tay–Sachs disease	Infantile onset; neurological regression, hyperekplexia, blindness, cherry-red spot	• Leukocyte hexosaminidase A activity
Schindler disease	Rapid neurodevelopmental regression at the end of the first year of life; atrophy of cerebellum, brainstem and cervical spinal cord	• Alpha-N-acetylgalactosaminidase activity • Urinary oligosaccharides
	Leukodystrophies	
Alexander disease	Infantile to childhood onset; neurologic regression with progressive macrocephaly	• Brain MRI
	Congenital disorders of glycosylation and deglycosylation	
Various	Epileptic encephalopathy, developmental delay, neuropathy, dysmorphology, hypotonia, congenital malformations, brain malformations with white matter abnormalities and/or atrophy, cerebellar hypoplasia	• Isoelectric focusing of serum transferrin, gas chromatography–mass spectrometry, capillary electrophoresis

* These disorders are examined by some newborn screening but should be reconsidered even if newborn screening is negative if symptoms appear consistent with the disorder.

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Table 10.2 Genes association with inborn errors of metabolism associated with epilepsy

Disorder	*Genes (inheritance pattern)*
Disorders of energy metabolism	
Mitochondrial disease	Mitochondrial DNA (maternal), mitochondrial nuclear DNA (AR/AD)
Mitochondria DNA depletion syndromes	*PLOG (AR/AD), RRM2B (AR/AD), DGUOK (AR), FBXL4 (AR), TWNK (AR/AD), SUCLA2 (AR)*
Fatty acid oxidation deficiency	*CPT1A (AR), CPT2 (AR/AD), ETFA (AR), ETFB (AR), ETFDH (AR), HADHA (AR), HADHB (AR), ACADM (AR), SLC25A20 (AR)*
Disorders of organic acid metabolism	
Propionic acidemia	*PCCA (AR), PCCB (AR)*
Methylmalonic aciduria	*MMACHC (AR), MMACHC (AR), PRDX1 (AR), MMAA (AR), MTR (AR), MTRR (AR), HFCF1 (XR)*
L-2-Hydroxyglutaric aciduria	*L2HGDH (AR), SLC25A1 (AR)*
D-2-Hydroxyglutaric aciduria	*D2HGDH (AR), SLC25A1 (AR)*
D-Glyceric aciduria	*GLYCTK (AR)*
Isovaleric acidemia	*IVD (AR)*
Disorders of porphyrin metabolism	
Acute intermittent porphyria	*HMBS (AD)*
Hereditary coproporphyria	*CPOX (AD)*
Variegate porphyria	*PPOX (AD), HFE (AD)*
Disorders of blood–brain-barrier transport	
Cerebral folate deficiency	*FOLR1 (AR)*
Glucose transport deficiency	*SLC2A1 (AD/AR)*
Disorders of cofactor (vitamin) metabolism	
Biotinidase deficiency	*BTD (AR)*
Carnitine biosynthesis deficiency	*TMLHE (XR)*
Coenzyme Q10 deficiency	*ADCK3 (AR), COQ2 (AR), COQ4 (AR), COQ6 (AR), COQ9 (AR), PDSS1 (AR), PDSS2 (AR)*
Cerebral creatine deficiency	*SLC6A8 (XR), GAMT (AR)*
Menkes disease	*ATP7A (XR)*
Molybdenum cofactor deficiency	*MOCS1 (AR), MOCS2 (AR), GPHN*
Pyridoxine dependent & responsive seizures	*ALDH7A1 (AR)*
Disorders of Cholesterol Metabolism	
Smith–Lemli–Opitz syndrome	*DHCR7 (AR)*
Disorder of γ-aminobutyric acid metabolism	
Succinic semialdehyde dehydrogenase deficiency	*ALDH5A1 (AR)*
Disorders of pyrimidine and purine metabolism	
Adenylosuccinate lyase deficiency	*ADSL (AR)*
Lesch–Nyhan syndrome	*HPRT1 (XR)*
Disorders of amino acid metabolism and urea cycle disorders	
Phenylketonuria	*PAH (AR)*
Branched chain ketoacid dehydrogenase kinase deficiency	*BCKDK (AR)*
Maple syrup urine disease	*BCKDHA (AR), BCKDHB (AR), DBT (AR), DLD (AR)*
Nonketotic hyperglycinemia	*GLDC (AR), GCSH (AR), AMT (AR)*
Serine deficiency	*PHGDH (AR), PSAT (AR), PSPH (AR), SLC1A4 (AR)*
Sulfite oxidase deficiency	*SUOX (AR)*
Urea cycle disorder	*OTC (XR), CPS1 (AR), ASL (AR), ARG1 (AR), ASS1 (AR), SLC25A15 (AR), NAGS (AR)*
Peroxisomal disorders	
Zellweger syndrome	*PEX1 (AR), PEX2 (AR), PEX6 (AR), PEX7 (AR)*
Peroxisomal fatty Acyl-CoA reductase disorder	*FAR1 (AR)*
D-bifunctional protein deficiency	*HSD17B4 (AR)*
Defective mitochondrial peroxisomal fission	*DNM1L (AD)*

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Table 10.2 (cont.)

Disorder	*Genes (inheritance pattern)*
Lysosomal storage disorders	
Gaucher disease	*GBA (AR)*
Neuronal ceroid lipofuscinosis	*PPT1 (AR), MFSD8 (AR), CLN8 (AR), CTSD (AR), CLN2 (AR), CTSF (AR), CLN5 (AR), CLN6 (AR), CLN3 (AR), GRN (AR), CLN9 (AR), DNAJC5 (AD)*
Sialidosis	*NEU1 (AR)*
Niemann–Pick disease	*NPC1 (AR)*
Salla disease	*SLC17A5 (AR)*
Tay–Sachs disease	*HEXA (AR)*
Schindler disease	*NAGA (AR)*
Leukodystrophies	
Alexander disease	*GFAP (AD)*
Congenital disorders of glycosylation and deglycosylation	
Congenital disorders of glycosylation	*ALG1 (AR), ALG2 (AR), ALG3 (AR), ALG6 (AR), ALG9, ALG11 (AR), ALG12, CCDC115 (AR), COG4 (AR), COG6 (AR), COG7, COG8, DPAGT1 (AR), DPM1 (AR), DPM2 (AR), MGAT2 (AR), MOGS (AR), MPDU1 (AR), NUS1 (AR), PMM2 (AR), RFT1 (AR), SLC35A2 (XD), SLC35C1 (AR), SLC39A8 (AR), SRD5A3 (AR), SSR4 (XR), STT3B (AR), TMEM15 (AR), TMEM165 (AR)*
Congenital disorder of deglycosylation	*NGLY1 (AR)*

Table 10.3 Common symptoms and metabolic disorders

Autistic features	Cerebral folate deficiency, cerebral creatine deficiency, pyridoxine dependent & responsive seizures, Smith–Lemli–Opitz syndrome, succinic semialdehyde dehydrogenase deficiency, branched chain ketoacid dehydrogenase kinase deficiency
Developmental delays	Mitochondrial disorders, biotinidase deficiency, carnitine biosynthesis deficiency, cerebral creatine deficiency, pyridoxine dependent & responsive seizures, Smith–Lemli–Opitz syndrome, succinic semialdehyde dehydrogenase deficiency, adenylosuccinate lyase deficiency, Lesch–Nyhan syndrome, phenylketonuria, branched chain ketoacid dehydrogenase kinase deficiency, serine deficiency, sulfite oxidase deficiency, urea cycle defects, congenital disorders of glycosylation
Encephalopathy/ coma	Organic acidemias, molybdenum cofactor deficiency, maple syrup urine disease, nonketotic hyperglycinemia, serine deficiency, sulfite oxidase deficiency, congenital disorders of glycosylation
Acute regression	Mitochondrial DNA depletion syndrome, mitochondrial disorder, coenzyme Q10 deficiency
Progressive neurodegeneration	Mitochondrial disease, cerebral folate deficiency, glucose transport deficiency, Menkes disease, storage diseases, leukodystrophies, neuronal ceroid lipofuscinosis
Periodic attacks	Porphyria, urea cycle defects, fatty acid oxidation defects
GI symptoms	Mitochondrial disorders, porphyria, organic acidemia
Odorous urine	Organic acidemias
Coma	Porphyria, urea cycle defects, fatty acid oxidation defects
X-linked recessive inheritance	Carnitine biosynthesis deficiency, cerebral creatine transporter deficiency, Menkes disease, Lesch–Nyhan syndrome, ornithine carbamoyltransferase, congenital disorder of glycosylation type 1y

symptoms associated with inborn errors of metabolism, which are helpful in raising the index of suspicion for a particular metabolic disorder.

Individuals with mitochondrial disease commonly have epilepsy [10]. The mitochondria contain complex and important pathways, including the citric acid (Krebs) cycle, the electron transport chain and fatty acid oxidation pathways, which, when impaired, can result in symptoms in tissues that have high energy demands, including the central and peripheral nervous system, the gastrointestinal system and the heart, kidney and muscles. Mitochondrial disease should be suspected when a patient has disorders in three or more organ systems [11]. Adults tend to present with well-defined mitochondrial syndromes whereas mitochondrial disease in children is less likely to be syndromic and may not be explained by known genetic defects [12–14]. In fact, some have pointed to

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environmental and iatrogenic causes of mitochondrial dysfunction in children [15, 16]. Childhood mitochondrial disorders are often associated with developmental delays and/or abrupt regression, particularly regression triggered by physiological stress, while mitochondrial disorders in adulthood are usually associated with a progressive downhill course, including worsening epilepsy.

The genetics of mitochondrial disorders is particularly complex because two genomes control mitochondrial function and numbers; nuclear genes (inherited from both parents) and genes in the mitochondria themselves, inherited from the mother. Each mitochondrion has many copies of the mitochondrial genome, descended from the many mitochondria present in the oocyte at conception. Genetic mutations may be present in some or all of those mitochondria, or arise later and sometimes are present in selected tissues only. One person can have variations in a particular gene throughout the mitochondrial genome; this is known as heteroplasmy. Homoplasmy is the term used where there is uniformity in the mitochondrial genome in all mitochondria throughout the cell.

When a mitochondrial disorder is suspected, a systematic workup should be carried out – see [12] or [17] for example algorithms. When symptoms or biomarkers are suggestive of mitochondrial disease, a comprehensive genetic analysis including sequencing of both mitochondrial and nuclear genomes may be required. However, for cases in which the pattern is rather distinctive such as fatty acid oxidation defects (particularly defects of long-chain fatty acid oxidation and transportation) and mitochondrial depletion syndromes, specific genetic defects may be targeted (see Table 10.2). Mitochondrial disorders can be particularly difficult to diagnosis because defects in the enzyme systems that indirectly support metabolic pathways, and other defects in cellular metabolism, can cause secondary mitochondrial dysfunction [9].

Organic acidemias arise from defects in metabolism resulting in the build-up of toxic intermediates that result in acidemia. These disorders are usually severe and arise in infancy, with symptoms that include lethargy and failure to thrive. In some cases, the illness is less severe and may present with more subtle symptoms in older age groups and even in adults.

The porphyrias are divided into acute and cutaneous types except for variegate porphyria, which has features of both. Acute porphyrias, which are associated with seizures, can be triggered by fasting and also by ingestion of many common drugs including sulfanamides, antifungals, antibiotics, antivirals, and antiepileptic drugs such as carbamazepine, phenytoin, phenobarbital and valproate.

Two important disorders, cerebral folate deficiency and glucose transport deficiency, involve a failure of transport of nutrients across the BBB. Diagnosis requires a high index of suspicion and examination of cerebrospinal fluid. Importantly, the great majority of cases of cerebral folate deficiency are caused by non-genetic causes, including mitochondrial disease and folate receptor alpha autoantibodies, so genetic analysis of *FOLR1* is not very useful in diagnosing this condition.

There are many disorders in which cofactors for important enzymes are not available in sufficient quantity to allow normal enzyme functioning. In many of these cases, diagnosis is made not by measuring the blood concentration of the cofactor but by measurement of distinctive metabolites that result from disruption of enzymes that are not functioning because of the cofactor insufficiency.

Disorders involving metabolism of gamma-aminobutyric acid, purines, and amino acid metabolism tend to present early in life with onset in the neonatal period. Exceptions are mild maple syrup urine disease and certain urine cycle defects which can go unrecognized throughout childhood and manifest later during times of physiological stress.

Zellweger syndrome is the prototypical peroxisomal disorder. Peroxisomal disorders tend to present with symptoms early in life and are rapidly progressive. Lysosomal storage diseases tend to have epilepsy while other storage diseases, such as glycogen storage diseases, do not typically have seizures as a prominent symptom.

Alexander disease is the only leukodystrophy in which seizures are prominent at the time of diagnosis. Seizures can occur in other leukodystrophies, but usually at the end stage of the disease.

Congenital disorders of glycosylation are being increasingly recognized as inborn errors of metabolism that cause various neurological abnormalities, particular early-onset epileptic encephalopathies [18]. These disorders should be investigated in the context of congenital malformations.

It is important to consider the inheritance pattern of inborn errors of metabolism to assist in diagnosis. Most inborn errors of metabolism have autosomal recessive inheritance but there are a number of exceptions. Mitochondrial diseases with defects in the mitochondrial genome have non-mendelian maternal inheritance. Nuclear genetic defects causing mitochondrial disease are usually autosomal recessive but may be autosomal dominant; this is also true for the glucose transporter disorder. Most porphyrias have autosomal dominant inheritance. Of the remaining inborn errors of metabolism, only a rare peroxisomal disease (caused by mutations in *DNM1L*) and an adult onset form of neuronal ceroid lipofuscinosis have an autosomal dominant inheritance. X-linked recessive inborn errors of metabolism typically affect only males (although female carriers sometimes are found to be mildly affected, for instance with only learning disabilities) and include: carnitine biosynthesis deficiency, creatine transporter disorder, Menkes disease, Lesch–Nyhan syndrome, ornithine carbamoyltransferase deficiency and congenital disorder of glycosylation type 1y. Congenital disorder of glycosylation type 2m is the only X-linked dominant inborn error of metabolism with epilepsy. Females with Turner syndrome (XO karyotype) or partial deletion of the X chromosome may have full expression of such disorders. It should not be forgotten, however, that the genetic mutations resulting in inborn errors of metabolism are not uncommonly *de novo* or recessive, and so from the point of view of diagnosis, a negative family history is less meaningful than a positive family history.

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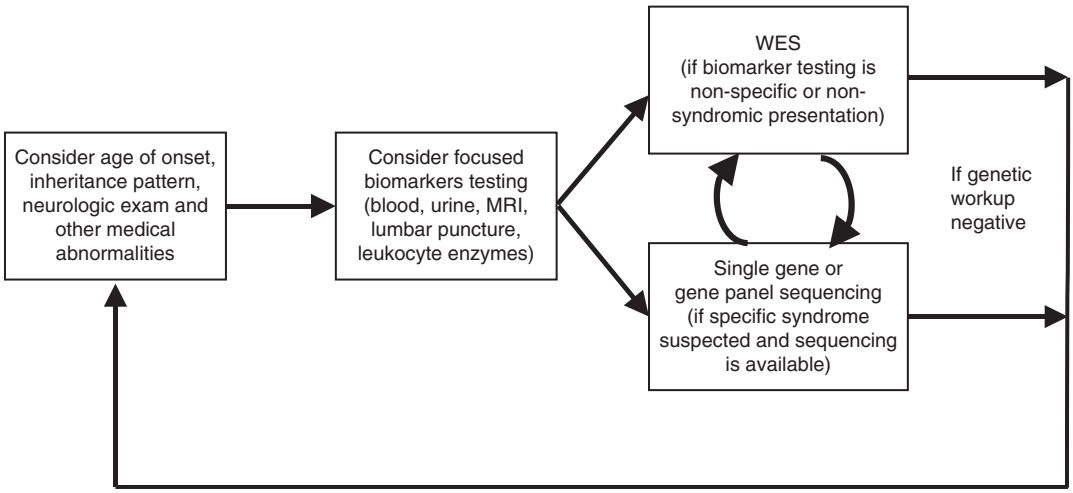

Figure 10.1 Diagnostic evaluation pathway for identifying the etiology of inborn errors of metabolism associated with epilepsy

Diagnostic Tests

Table 10.1 (right hand column) provides a comprehensive list of diagnostic tests for specific inborn errors of metabolism, and Table 10.2 outlines the associated genes. Figure 10.1 outlines a pathway for approaching the diagnosis of inborn errors of metabolism in epilepsy.

Inborn errors of metabolism usually, but not always, manifest with associated clinical and biochemical features, so in most cases there will be other clues besides epilepsy that point to the diagnosis. Much information can be provided by the standard workup for epilepsy, including a careful history and physical examination and the findings from imaging and EEG. Specific metabolic or other diagnostic testing can help confirm and focus the differential diagnosis.

Targeted genetic sequencing, WES or metabolic/epilepsy genetic panels can be confirmatory. However, genetic testing can often take weeks to months. WES provides a wide coverage of the genome, but may not sequence genes to the same depth as panels which focus on specific genes. On the other hand, where inborn errors of metabolism present with atypical symptoms they may be missed by the use of focused panels. WES can be helpful when findings are non-specific, and furthermore can reveal the involvement of unexpected genes [19]. These techniques can also identify novel variations in target genes that are of uncertain significance in isolation; such variants of unknown significance can support and complement a careful clinical investigation.

Caveats, Limitations and Considerations

One major issue in diagnosing metabolic disease is that a definitive genetic defect cannot always be ascertained, due to novel genetic variants, complex heterozygosity or other polygenic mechanism. In such cases, biochemical evidence of an inborn error of metabolism may be present but the exact genetic cause may be elusive. Furthermore, there are many variations of the biochemical defects resulting in milder forms that present with less severe symptoms and an older age of onset than the more severe forms.

Given the safety of many of the therapies for treating metabolic disease, empirical treatment can be considered while the workup is ongoing. For example, empirical trials of pyridoxine and/or folinic acid are reasonable while awaiting pyridoxine and 5-methyltetrahydrofolate cerebrospinal fluid concentrations or if a diagnostic lumbar puncture cannot be obtained. Treatments that involve complicated changes in diet require more solid biochemical evidence to support, although the ketogenic diet, which is helpful in several metabolic syndromes, is useful in many treatment-resistant epilepsies even in the absence of a specific metabolic disease [5]. However, the ketogenic diet could worsen symptoms with some metabolic disorders, so careful observation is necessary when starting this diet.

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