

NARRATIVE REVIEW

Inherited metabolic epilepsies—established diseases, new approaches

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Abstract

Inherited metabolic epilepsies (IMEs) represent the inherited metabolic disorders (IMDs) in which epilepsy is a prevailing component, often determining other neurodevelopmental outcomes associated with the disorder. The different metabolic pathways affected by individual IMEs are the basis of their rarity and heterogeneity. These characteristics make it particularly challenging to establish their targeted therapies, and many of the IMEs are treated nowadays only symptomatically and supportively. However, owing to immense molecular and genetic progress in the last decades, important features of their pathomechanisms have been elucidated. This has led to advancements in the development of novel diagnostic approaches and specific therapies for a considerable number of these unique disorders. This review provides an overview of the broad approach to the diagnosis and management of IMEs, along with their eminent and new individual treatment options, ranging from dietary therapies and vitamins to enzyme and gene replacement therapies.

Plain Language Summary: Inherited metabolic disorders (IMDs) in which epilepsy is a main symptom are considered inherited metabolic epilepsies (IMEs). It is challenging to develop targeted therapies for IMEs since they are rare and individually different in characteristics. Therefore, many of the IMEs are currently treated only symptomatically. However, scientific progress in the last decades led to the creation of specific treatments for many of these unique disorders. This review provides an overview of the approach to the diagnosis and management of IMEs, including the available newer therapeutic modalities.

KEYWORDS

inborn errors of metabolism, novel, seizures, therapy, treatment

1 | INTRODUCTION

We are honored to contribute to this special issue celebrating the legacy of Solomon “Nico” Moshé, MD, an innovative clinical investigator, neuroscientist, and mentor who

made immense contributions to pediatric epilepsy and neurophysiology.

Inherited metabolic epilepsies (IMEs) reflect those inherited metabolic disorders (IMDs) in which epilepsy is a prominent component and determinant of outcome.

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Approximately 20% of the IMDs are considered IMEs.¹ The genotypical and phenotypical heterogeneity and rarity of IMEs pose a significant challenge to managing them, discovering their diagnostic biomarkers, and developing disease-specific treatments.² An additional burdensome element lies in the urgency of diagnosis.³ The rationale behind this is that a selected number of these disorders are responsive to targeted treatments (ranging from accessible and relatively inexpensive dietary treatments and vitamins to complicated and costly gene-based therapeutic modalities) only if given at the earliest possible time point in life.⁴ Therefore, epileptologists must be familiar with their clinical symptoms, pathomechanisms, diagnostic biomarkers, and available therapies.

This review provides an overview of the clinical manifestations and management approach to IMEs presenting from the neonatal period to adulthood. The notable currently investigated and approved treatments of each disorder are described. The individual IMEs are introduced according to a pathophysiology-based classification system,⁵ including (1) *small molecule disorders* caused by deficiency or accumulation of low-molecular-weight compounds (aminoacidemias, organic acidurias, and urea cycle disorders); (2) *large molecule disorders* caused by deficiency, accumulation, or abnormal conversion of large molecular weight compounds (lysosomal storage diseases, peroxisomal biosynthesis disorders, and congenital disorders of glycosylation); (3) *disorders of energy metabolism* caused by a disturbance of utilization or production of energy, mostly affecting the high-energy demanding organs such as the brain, liver, muscles, and myocardium (mitochondrial diseases and glucose transporter protein type 1 [GLUT-1] deficiency); (4) *disorders of vitamins* caused by a deficiency or dependency of vitamins and their cofactors (pyridoxine-dependent epilepsy, cerebral folate deficiency, and biotinidase deficiency); and (5) *disorders of neurotransmitters* caused by deficiencies or accumulation of neurotransmitters and their associated metabolites and cofactors, negatively impacting the cortical excitation-inhibition balance (glycine encephalopathy, aromatic L-amino acid decarboxylase [AADC] deficiency, and succinic semialdehyde dehydrogenase [SSADH] deficiency).

2 | CLINICAL PRESENTATION OF INHERITED METABOLIC EPILEPSIES

In line with their diverse genotypes, IMEs may present with different types of epilepsies and seizure types. Typically, the earlier the seizure onset, the more likely they are intractable, and if left untreated, associated with worse outcomes.⁶ The most common seizure types

Key points

- Despite being individually rare, the combined prevalence of inherited metabolic epilepsies (IMEs) is considerable, making their management challenging.
- The clinical presentation of seizures in IMEs is variable and nonspecific; family history, EEG, neuroimaging, and metabolic and genetic tests may complete their clinical picture.
- Substantial recent molecular and genetic advancements have led to the development of novel diagnostic biomarkers and targeted therapies for several IMEs.
- Diagnosing treatable IMEs via deep phenotyping, metabolic, genetic, and clinical tests is rewarding, especially if done early, as specific treatments may lead to seizure control and improved outcomes.

appearing in IMEs presenting in the neonatal and infancy periods are myoclonic, which at times are part of an early infantile developmental and epileptic encephalopathy (EIDEE) syndrome. Progressive myoclonus epilepsy (PME) may ensue, as well as infantile epileptic spasms syndrome (IESS) and Lenox–Gastaut syndrome.⁷ Suspicion of a metabolic cause should be raised if these early-onset seizures are drug resistant and their etiology is otherwise unknown.⁸ The phenotype of IMEs presenting with early-onset seizures may overlap; however, there are a few distinguishing features between them. Small molecule disorders are affiliated with an early presentation of lethargy, encephalopathy, pulmonary complications, vomiting, and symmetric motor tone changes. Disorders of energy metabolism may be linked to stressors such as fasting, eating specific foods, illness, or medications. Large molecule disorders may be associated with systemic (cardiac, hepatic, ophthalmic, orthopedic) abnormalities, microcephaly, dysmorphism, and neurodevelopmental delays. Neurotransmitter disorders may be accompanied by movement, behavior, and autonomic disturbances.⁵ Notably, subdural and retinal hemorrhages may be part of the presentation of the IMEs glutaric acidemia type I, cobalamin C deficiency, and Menkes disease.^{9–11} Since these manifestations are also linked to nonaccidental injuries, keeping in mind these IMEs as part of the differential diagnosis is important. Seizures with an unknown etiology beginning during late childhood, adolescence, and adulthood may be suggestive of an IME, especially if accompanied by signs and symptoms including cognitive

stagnation or regression, psychiatric and behavior problems, dystonia, ataxia, cerebral vascular accident, and cardiac and endocrine complications.¹²

3 | DIAGNOSTIC APPROACH TO INHERITED METABOLIC EPILEPSIES

While newborn screening programs can reveal a growing number of these disorders, they are not inclusive of all IMEs and differ between geographic regions. When clinical suspicion of an IME is raised, concurrent metabolic and genetic tests should be performed. Depending on the availability, a whole exome study (WES) should be the first genetic test taken, as it offers the highest diagnostic yield.¹³ Otherwise, epilepsy panels (consisting of many IME-related genes) and single-gene sequencing may be considered. A whole genome study (WGS) may be completed if the WES is negative. Abnormalities in chromosomal microarray analysis (CMA), methylation studies, and repeat expansion tests are uncommon in IMEs, aside from a few examples (CMA-derived multi-exon, single gene or microdeletions or -duplications including genes associated with IMEs, methylation tests to

rule out Angelman syndrome, and triplet repeat expansion to rule out fragile X syndrome).¹³ When clinically relevant, the mitochondrial DNA (mtDNA) genome should be assessed.¹⁴ Compared to metabolic tests, genetic tests have a higher diagnostic yield in cases of epilepsy from an unknown origin.¹⁵ However, basic plasma and urinary metabolic tests may be quicker to attain and more accessible, and they may reveal findings (e.g., hypoglycemia and hyperammonemia) that may lead to the swift initiation of life-saving treatments. Before ordering metabolic laboratories, it is advisable to consult a metabolic disorders specialist, which may narrow the list of needed tests. Metabolic tests have additional advantages; they may complete the diagnostic picture when genetic testing reveals variants of uncertain significance (VUSs). Once an IME is confirmed, metabolite profiles can serve as biomarkers of severity, valuable for prognostication. An IME stepwise diagnostic algorithm is displayed in Figure 1, and notable metabolic biomarkers are shown in Table 1. As indicated earlier, the clinical presentation of most IMEs is not sufficiently specific to diagnose them. However, certain neuroimaging patterns (magnetic resonance imaging [MRI] and magnetic resonance spectroscopy [MRS]) can support or refute the diagnosis of a considerable number of IMEs (Table 2) and

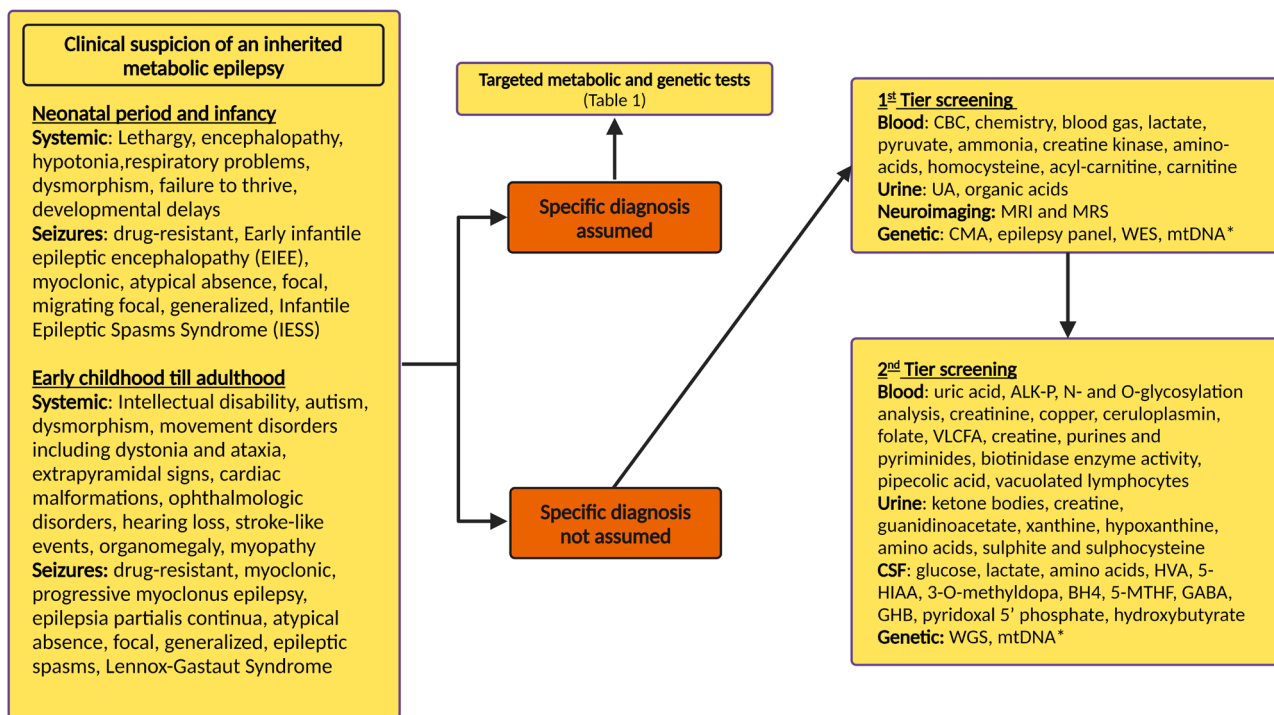


FIGURE 1 A proposed diagnostic algorithm when an inherited metabolic epilepsy is suspected. 3-OMD, 3-O-methyl-dopa; 5-HIAA, 5-hydroxyindole acetic acid; 5-MTHF, 5-methyltetrahydrofolate; ALK-P, alkaline phosphatase; BH4, tetrahydrobiopterin; GABA, γ -aminobutyrate; GHB, γ -hydroxybutyrate; HVA, homovanillic acid; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; mtDNA, mitochondrial DNA; UA, urinalysis; VLCFA, very long-chain fatty acids. *mtDNA may be assessed as part of the first or second tier screening, depending on the clinical context.

TABLE 1 Metabolic biomarkers of inherited metabolic epilepsies.

Metabolic biomarker	Inherited metabolic epilepsy
Blood	
Complete blood count ^a	Low Hb and high MCV—forms of homocysteinemia and MMA Anemia—orotic aciduria, organic acidemias, certain mitochondrial diseases Thrombocytopenia—organic acidemias, disorders of cobalamin and folate
Chemistry ^a	Hyperglycemia—glycogen storage diseases Hypoglycemia, ketotic—MSUD, organic acidurias Hypoglycemia, nonketotic—FAO disorders, HMG-CoA lyase deficiency Transaminitis—mitochondrial diseases, CDGs, Zellweger syndrome, certain LSDs Increased lactate—mitochondrial diseases, pyruvate dehydrogenase complex deficiency, biotinidase deficiency Increased lactate/pyruvate ratio—differentiates mitochondrial diseases of electron transport chain from pyruvate metabolism
Blood gas ^a	High anion gap metabolic acidosis—certain mitochondrial diseases, organic acidemias, UCD (mild), FAO disorders (mild)
Ammonia ^a	Hyperammonemia—UCDs, organic acidemias, FAO disorders
Total carnitine and acylcarnitine profile ^a	Abnormal in FAO and carnitine disorders, organic acidemias, biotinidase deficiency
Amino acids ^a	High phenylalanine—PKU High glycine—glycine encephalopathy High glycine and threonine—PDE and PNPO deficiencies Low serine—serine biosynthesis disorders Low glutamine—glutamine synthase deficiency
Total homocysteine ^a	Homocystinurias and disorders of cobalamin metabolism
Uric acid	Low in molybdenum cofactor deficiency
Copper and ceruloplasmin	Low in Menkes syndrome
VLCFA	High in Zellweger syndrome and other peroxisomal biosynthesis disorders
Biotinidase enzyme activity	Low in biotinidase deficiency
Transferrin isoelectric analysis	Abnormal glycoforms in CDGs
Pipecolic acid	PDE, peroxisomal biogenesis disorders
Alkaline phosphatase	High/low in certain GPI-anchor defects
Creatine kinase ^a	High in dystroglycanopathies
Vacuolated lymphocytes	Present in NCL
Urine	
Urinalysis ^a	Ketonuria—in the neonatal period is always abnormal. Ketosis—organic acidemias, malonyl-CoA decarboxylase deficiency, disorders of ketolysis MSUD—disorders associated with hypoglycemia (ketosis is an appropriate response to hypoglycemia)
Organic acids ^a	Specific organic acids corresponding to specific organic acidurias Vanillacetate in PNPO deficiency Dicarboxylic aciduria—FAO disorders High orotic acid—orotic aciduria High GHB—SSADHD
Creatine and guanidinoacetate	Low creatine—GAMT and AGAT deficiencies High creatine—creatine transporter deficiency High guanidinoacetate in GAMT deficiency Low guanidinoacetate in AGAT deficiency
Alpha-aminoadipic semialdehyde	High PDE, MoCoD, sulfite oxidase deficiency

TABLE 1 (Continued)

Metabolic biomarker	Inherited metabolic epilepsy
Xanthine and hypoxanthine	High xanthine and hypoxanthine–MocoD Succinyladenosine–adenylosuccinate lyase deficiency
Sulfite and sulphocysteine	High-sulfite oxidase deficiency and MoCoD
Amino acids	Abnormal lysinuric protein intolerance and mitochondrial disorders involving renal tubulopathy
CSF	
Glucose (simultaneously with plasma)	Low CSF: blood glucose ratio (<0.4) in GLUT-1 deficiency
Lactate	High-mitochondrial respiratory chain disorders and pyruvate dehydrogenase complex deficiency
Amino acids	High-glycine CSF:plasma glycine ratio (>0.06, normal <0.04)–glycine encephalopathy Low serine–serine deficiency syndromes and some cases of asparagine synthetase deficiency High threonine and glycine–PDE and PNPO
HVA	Abnormal in primary and secondary disorders of biogenic amine metabolism
5-HIAA	Low PDE and PNPO
3-OMD	
BH4	Abnormal in disorders of biopterin metabolism
5-Methyltetrahydrofolate	Low-cerebral folate transporter deficiency (<i>FOLR1</i>), dihydropyridine reductase deficiency, methylene tetrahydrofolate synthase deficiency, mitochondrial diseases (Kearns–Sayre syndrome), serine biosynthesis disorders
GABA	High GABA–GABA transaminase deficiency, SSADHD
GHB	
Pyridoxal-5'-phosphate	Low-PNPO, PDE, hypophosphatasia, hypoproteinemia type II

Abbreviations: 3-OMD, 3-O-methyl-dopa; 5-HIAA, 5-hydroxyindole acetic acid; 5-MTHF, 5-methyltetrahydrofolate; AGAT, arginine:glycine amidinotransferase; BH4, tetrahydrobiopterin; CDG, congenital disorders of glycosylation; CSF, cerebrospinal fluid; FAO, fatty acid oxidation; GABA, γ -aminobutyrate; GAMT, guanidinoacetate N-methyltransferase; GHB, γ -hydroxybutyrate; HVA, homovanillic acid; LSD, lysosomal storage diseases; MCV, mean corpuscular volume; MMA, methylmalonic acidemia; MoCoD, molybdenum cofactor deficiency; MSUD, maple syrup urine disease; NCL, neuronal ceroid lipofuscinoses; PDE, pyridoxine-dependent epilepsy; PKU, phenylketonuria; PNPO, pyridoxamine-5'-phosphate oxidase; SSADHD, succinic semialdehyde dehydrogenase deficiency; UCD, urea cycle disorders; VLCFA, very long-chain fatty acids.

^aPart of the first tier of tests suggested as part of the investigation for seizures originating from an inherited metabolic disorder.

are thus also part of the first tier of their diagnostic tests (Figure 1). MRI-derived examples include T2-weighted hyperintensities in the basal ganglia in organic acidurias, mitochondrial diseases, and urea cycle defects, polymicrogyria in Zellweger syndrome, intracerebral hemorrhage or stroke in mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), and cystic encephalomalacia in isolated sulfite oxidase deficiency or molybdenum cofactor deficiency.¹⁶ MRS-derived examples consist of decreased creatine + phosphocreatine in creatine deficiency disorders, increased lactate in mitochondrial disorders, increased branched chain amino acids (leucine, isoleucine, and valine) in maple syrup urine disease, and increased γ -aminobutyric acid in succinic semialdehyde dehydrogenase deficiency.¹⁷ Electroencephalography (EEG) is another diagnostic modality that may help to narrow the diagnosis of IMEs. Typically, EEG has a higher sensitivity than specificity in IMEs, though some IMEs are associated with distinctive EEG patterns (Table 3). Some examples include repetitive high-amplitude delta with

spikes or polyspikes (RHADS) in *POLG*-related mitochondrial disease, burst-suppression in glycine encephalopathy, phenylketonuria, and other aminoacidemias, and a comb-like, 7- to 9-Hz midline rhythm in MSUD and propionic academia.¹⁸

4 | TREATMENT APPROACH TO INHERITED METABOLIC EPILEPSIES–ACUTE SETTING

Most IMEs are currently managed by supportive and symptomatic treatments. However, there are many ongoing investigational processes for targeted treatments of IMEs, and a selected number of conditions have disease-specific approved treatments¹⁹ (Table 4). As outlined in greater detail in the sections next, these treatments may not only decrease the seizure burden but also improve neurodevelopmental and systemic outcomes. There are a few general management steps that should be implemented in the acute presentation of seizures stemming

MRI pattern	Inherited metabolic epilepsy
Cerebellar/Pontocerebellar Hypoplasia	CDGs, glycine encephalopathy, mitochondrial diseases, NCL, PDE, Zellweger syndrome
Cerebrovascular accident	Canavan disease, CDGs, citrullinemia type 1, complex III deficiency, CoQ deficiency, CPS1, glutaric aciduria type I, Leigh syndrome, MELAS, MERRF, MMA, OTC deficiency, PA, PDE, POLG1
Corpus callosum abnormalities	CDGs, glycine encephalopathy, PDD, PDE, Zellweger syndrome
Cortical atrophy	CFD, creatine disorders, Glut-1 (mild), MELAS, MLD (late stages), MMA, NCL, PA, PDE, PNPO deficiency, SSADHD (mild) UCDs (severe cases)
Cystic encephalomalacia	ISOD/MoCo, Krabbe disease, mitochondrial diseases, Zellweger syndrome
Hyperintense T2 signals	Glutaric aciduria type I, organic acidurias
Basal ganglia	Tay-Sachs and Sandhoff diseases
Brainstem	Mitochondrial diseases
Dentate nuclei	UCD, SSADHD
Globus pallidi	Glutaric aciduria type I, SSADHD
Thalami	Glutaric aciduria type I, ISOD/MoCo, Krabbe disease, Krabbe disease, L2-hydroxy glutaric aciduria, Mitochondrial diseases, MSUD, NCL, PA, SSADHD
Migration abnormalities	Zellweger syndrome
Myelination abnormalities	Canavan disease, CDGs, CFD, creatine disorders, GM2 gangliosidosis, Krabbe disease, mitochondrial diseases, MLD (sparing U-fibers), MMA, NCL, PA, PDE, PKU, PNPO deficiency, UCDs (severe cases), X-linked Adrenoleukodystrophy, Zellweger syndrome
Subdural hematomas	Cobalamin C deficiency, glutaric aciduria type I, Menkes disease
Widened Sylvian operculum	Glutaric aciduria type I

Abbreviations: CDGs, congenital disorders of glycosylation; CFD, cerebral folate deficiency; CoQ, coenzyme Q10; CPS1, carbamoyl phosphate synthetase 1; Glut-1, glucose transporter 1; ISOD, isolated sulfite oxidase deficiency; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MLD, metachromatic leukodystrophy; MMA, methylmalonic acidemia; MoCo, molybdenum cofactor deficiency; MSUD, maple syrup urine disease; NCL, neuronal ceroid lipofuscinosis; OTC, ornithine transcarbamylase; PA, propionic acidemia; PCD, pyruvate carboxylase deficiency; PDD, pyruvate dehydrogenase deficiency; PDE, pyridoxine-dependent epilepsy; PKU, phenylketonuria; PNPO, pyridoxine-5'-phosphate oxidase; POLG1, DNA polymerase subunit gamma; SSADHD, succinic semialdehyde dehydrogenase deficiency; UCDs, urea cycle disorders.

TABLE 2 Common MRI patterns associated with inherited metabolic epilepsies.

from a suspected IME. To prevent the effects of potentially harmful food components, the patient should be made “nothing per os (NPO).” Concurrently, an intravenous infusion of a dextrose-containing fluid should be initiated as a dietary replacement to prevent hypoglycemia and to signal the cell to cease catabolism. Insulin can be added to strengthen the signal to end catabolism and to prevent hyperglycemia. Electrolyte disturbances should be corrected, and fluids and medications that favor acidosis (such as lactated Ringers and valproic acid) should

be avoided.⁵ In cases of an unknown etiology and while metabolic and genetic tests are pending, empirical trials of pyridoxine, pyridoxal-5'-phosphate, folinic acid,²⁰ and biotin²¹ are indicated. IV levocarnitine may also be considered. Antiseizure medications (ASMs) should be given for seizures according to the standard of epilepsy care, aside from a few cases in which certain ASMs should be used with precaution (Table 5). ASMs may reduce the seizure burden but will seldom lead to seizure resolution if not accompanied by the appropriate metabolic intervention.

TABLE 3 Common EEG patterns associated with inherited metabolic epilepsies.

EEG pattern	Inherited metabolic epilepsy
Burst suppression	D-Glycine acidemia, holocarboxylase synthetase deficiency, Leigh syndrome, Menkes disease, molybdenum cofactor deficiency, neonatal adrenoleukodystrophy, neonatal citrullinemia, glycine encephalopathy, propionic acidemia
Sleep-activated reduction in spikes	Progressive myoclonus epilepsy
Fast central spikes	Tay–Sachs disease
Giant somatosensory evoked potentials	Progressive myoclonus epilepsy
Hypsarrhythmia	CDGs, neonatal adrenoleukodystrophy, neuroaxonal dystrophy, glycine encephalopathy, PKU, Zellweger syndrome, PA, MMA
Photoparoxysmal response	Progressive myoclonus epilepsy and neuronal ceroid lipofuscinosis type II
RHADS Comb-like (mu-like) rhythm	MSUD, <i>POLG1</i> -related disorder, propionic acidemia
Vanishing electroencephalogram	Infantile neuronal ceroid lipofuscinosis type I

Abbreviations: CDGs, congenital disorders of glycosylation; MMA, methylmalonic acidemia; MSUD, maple syrup urine disease; PA, propionic acidemia; PKU, phenylketonuria; *POLG1*, DNA polymerase subunit gamma; RHADS, rhythmic high-amplitude delta waves with (poly)spikes.

TABLE 4 Treatable inherited metabolic epilepsies.

Disorder group	Disorder	Treatment
Small molecule disorders	Phenylketonuria	Phenylalanine-restricted diet; phenylalanine ammonia-lyase or pegvaliase
	6-Pyruvoyl-tetrahydropterin synthase deficiency	Sepiapterin
	Serine synthesis defects	L-Serine
	Glycine encephalopathy	Sodium benzoate; NMDA receptor antagonists
	Urea cycle disorders	Arginine or citrulline Sodium phenylbutyrate, sodium benzoate, glycerol phenylbutyrate
Large molecule disorders	CAD deficiency	Uridine
	CLN2 disease	Cerliponase alfa (enzyme-replacement therapy)
Energy metabolism disorders	Creatine synthesis defects	Creatine, sodium benzoate, ornithine, and dietary arginine restriction
	Glut-1 transporter defects	Ketogenic diet
Vitamin disorders	Biotinidase deficiency	Biotin
	Pyridoxine-dependent epilepsy	Pyridoxine
	PNPO deficiency	Pyridoxal-5'-phosphate
	Cerebral folate deficiency	DL-folinic acid, levo-folinic acid, or levo-5-methyl-tetrahydrofolate (depending on the cause)
Neurotransmitter disorders	AADC deficiency	Eladocogene exuparvovec (gene-replacement therapy)

Abbreviations: AADC, aromatic L-amino acid decarboxylase; CAD, carbamoyl phosphate synthetase, aspartate transcarbamylase, dihydroorotase; CLN2, ceroid lipofuscinosis type 2; Glut-1, glucose transporter type I; NMDA, N-methyl-D-aspartate; PNPO, pyridoxamine-5'-phosphate oxidase.

Antiseizure medication	Inherited metabolic epilepsy	Rationale of contraindication
Diazepam	GLUT1 deficiency	Exacerbates GLUT1 inhibition
Ketogenic diet	Carnitine deficiency, CPT I or II deficiency, fatty acid oxidation defects, organic acidurias, pyruvate carboxylase deficiency	Exacerbation of metabolic defect
Lacosamide	Phenylketonuria	Contains aspartame—a source of phenylalanine
Na ⁺ channel blockers	Progressive myoclonus epilepsies	Exacerbates seizures
Phenobarbital	GLUT1 deficiency	Exacerbates GLUT1 inhibition
	Porphyria	Exacerbates porphyrin precursor synthesis
Topiramate	Purine and pyrimidine disorders	Increases the risk of nephrolithiasis
Valproate	Mitochondrial diseases	Possible hepatotoxicity
	<i>POLG1</i> -related diseases	Exacerbation of epilepsy partialis continua
	Urea cycle disorders	Exacerbation of hyperammonemia
	Glut-1 deficiency syndrome	Exacerbates GLUT1 inhibition
	SSADH deficiency	Inhibits residual SSADH activity
	Glutaric acidemia type I	Disrupts the acetyl CoA/CoA ratio- exacerbates metabolic disbalance
	Glycine encephalopathy	Exacerbates hyperglycinemia
	Fatty acid oxidation disorders	Interferes with β -oxidation
Zonisamide	Carnitine deficiency	Depletes carnitine stores
	CPT I or II	
Zonisamide	Purine and pyrimidine disorders	Increases the risk of nephrolithiasis

Abbreviations: CoA, coenzyme A; CPT, carnitine palmitoyl transferase; GLUT1, glucose transporter type 1; *POLG1*, DNA polymerase subunit gamma; SSADH, succinic semialdehyde dehydrogenase deficiency.

TABLE 5 Precautions involving antiseizure medications in inherited metabolic epilepsies.

5 | SMALL MOLECULE DISORDERS

Aminoacidemias. The broad treatment approach for this group of disorders is to reduce the toxicity instigated by accumulated metabolites and increase the molecular activity of the impaired enzymes.

Maple syrup urine disease (MSUD) results from a deficiency of the branched chain α -ketoacid dehydrogenase complex residing in the mitochondria, leading to accumulated branched chain amino acids (BCAA) and branched chain α -ketoacids. The phenotype ranges in severity and

is classified into five types (classic, intermediate, intermittent, thiamine responsive, and dihydrolipoyl dehydrogenase [E3] deficiency).²² Seizures are common in MSUD, and untreated cases may lead to mortality. The EEG shows a diffusely slow background, a loss of reactivity to auditory stimuli, multifocal epileptiform patterns, and, at times, a photoparoxysmal response.²³ A central mu-like or “comb-like” rhythm is characteristic.^{24,25} Early seizure control can improve the outcome of classic MSUD.²⁶ Treatment is based on a BCAA-free dietary formula, protein restriction, and isoleucine, valine, and thiamine supplementation.²⁷ Newer dietary formulas can reduce cerebral-BCAA

levels by optimizing the transport of the amino acids that otherwise compete with BCAA cerebral transport.²⁸ Cases that are nonresponsive to dietary management may be candidates for liver transplantation, acknowledging the risks of surgery and immunosuppression.²⁹ Other therapy approaches for MSUD consist of sodium phenylbutyrate, which enhances the activity of branched chain ketoacid dehydrogenase,³⁰ and L-carnitine, which aims to decrease oxidative stress.³¹

Phenylketonuria (PKU) is primarily caused by a lack of phenylalanine hydroxylase and, in less than 5% of cases, by a lack of tetrahydrobiopterin (BH4), an integral cofactor in the conversion of phenylalanine to tyrosine. Regardless of the pathomechanism, the accumulated phenylalanine leads to neurotoxicity.³² Untreated individuals are affected cognitively and by different seizure types, including IESS. Treated individuals may develop normally and be seizure-free. The mainstay dietary treatment of PKU consists of low phenylalanine and protein and supplemented tyrosine. BH4-dependent cases are treated with BH4 or its synthetic versions, sapropterin dihydrochloride³³ and sepiapterin, which have enhanced biological activity compared to sapropterin.³⁴ Other therapeutic modalities for PKU include the provision of large, neutral amino acids that can lower intestinal phenylalanine absorption and renal reuptake,³⁵ and supplementation of long-chain omega-3 polyunsaturated fatty acids and carnitine which mitigate phenylalanine's neurotoxicity.³⁶ Phenylalanine concentrations may also be reduced by a relatively newer compound, phenylalanine ammonia lyase (PAL), or its pegylated form, pegvaliase. This nonmammalian enzyme converts Phe into a harmless transcinamic acid.³⁷

Organic acidurias. Propionic acidemia (PA), methylmalonic acidemia (MMA), and isovaleric acidemia (IVA) are caused by a deficiency in propionyl-CoA carboxylase, methylmalonic acid (or impairments in cobalamin metabolism), and isovaleryl-CoA dehydrogenase, respectively. Common clinical features of these conditions include an early presentation of an acute metabolic crisis with hypotonia, lethargy, and refractory seizures of various types. Cases appearing later in life may present with developmental delay, acute encephalopathy, and episodic ketoacidosis. Their treatment also shares common objectives: to reverse harmful catabolic effects, scavenge toxic metabolites, and supplement necessary substrates.³⁸ If conventional treatment fails, liver transplantation is optional.³⁹ Other specific treatments include glycine and carnitine for IVA. By conjugating with isovaleryl-CoA, they form nontoxic products.^{40,41} There are several ongoing investigations aimed at developing genetic therapies for MMA and PA.^{42–46}

Urea cycle disorders (UCDs) are caused by a deficiency of one of the enzymes of the urea cycle (carbonyl phosphate

synthetase I [CPSI], ornithine transcarbamylase [OTC], arginosuccinate synthetase [ASS], argininosuccinate lyase [ASL], N-acetyl glutamate synthetase [NAGS], and arginase) amenable for the conversion of nitrogen to urea.⁴⁷ The hyperammonia that typically ensues following protein intake presents with signs of encephalopathy and seizures, both electroclinical and electrographic.⁴⁸ Acute treatment of hyperammonemic crises combines protein restriction, hemodialysis if needed, and nitrogen-scavenging agents (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate, and glycerol phenylbutyrate). L-Arginine and its precursor, L-citrulline, are indicated for almost all the UCDs (except arginase 1 [ARG1] deficiency). Moreover, in ASS deficiency, citrulline aids in the urinary removal of nitrogen.⁴⁹ Chronic treatment of UCDs is based on a protein-restricted diet, provision of urea cycle intermediates, and an alternative pathway-based therapy.⁴⁹ Cases resistant to conservative treatments may be managed by liver transplantation.⁵⁰ Currently investigated therapeutic modalities include nitrous oxide donor drugs, which have been shown to improve the symptoms of nitrous oxide depletion in ASL- and ASS-deficient murine models,⁵¹ and ongoing clinical trials are assessing their efficacy in humans.⁵² There are several ongoing preclinical and clinical trials of enzyme or gene replacement therapies for ARG1, OTC, ASS, and ASL deficiencies.^{53–55}

6 | LARGE MOLECULE DISORDERS

Lysosomal storage diseases (LSDs) result from an impairment in one of many enzymes responsible for lysosomal function, leaving undegraded material in accumulation, leading to cellular malfunction. Notable LSDs associated with seizures include GM1 gangliosidosis types I and II, GM2 gangliosidosis (Tay–Sachs and Sandhoff diseases), Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, Gaucher disease type III, and neuronal ceroid lipofuscinoses (NCL). Aside from a few exceptions (e.g., *CLN1* and *CLN10*), seizures typically develop later in the course of these disorders, during early or late childhood and, at times, adolescence and adulthood. LSDs are mostly treated with supportive care. However, some emerging therapies for LSDs are mentionable. Recombinant human enzyme replacement therapy is approved for several LSDs in which seizures are not a dominant characteristic (Gaucher, Fabry, Pompe, and some of the mucopolysaccharidoses [MPS]–Hurler [MPS I H/S], Hunter [MPS II], Morquio A [MPS IVA], and Maroteaux–Lamy [MPS VI]).⁵⁶ Recombinant human tripeptidyl peptidase 1 (TPP1) or cerliponase alfa is now available for late infantile neuronal ceroid

lipofuscinosis or CLN2, a disorder associated with progressive myoclonus epilepsy. It has been shown to reduce the seizure burden and improve outcomes.⁵⁷ Another therapeutic modality employed for LSDs is substrate reduction, which does not degrade the macromolecules but slows their accumulation.⁵⁸ Examples of substrate-reducing drugs include miglustat and eliglustat, which are approved for mild-to-moderate Gaucher patients who are not candidates for ERT.⁵⁹ Miglustat has also been repurposed to treat Niemann–Pick type C.⁶⁰ Ongoing preclinical and clinical gene-replacement studies (in vivo [using AAV] or ex vivo [using autotransplantation of hematopoietic stem cells]) demonstrate promising findings in various LSDs.^{61,62}

Peroxisomal disorders include three subgroups of disorders: (1) peroxisomal biogenesis or assembly disorders (Zellweger syndrome spectrum, resulting from pathogenic variants in one of 12 *PEX* genes); (2) single peroxisomal enzyme disorders (X-linked adrenoleukodystrophy [XLALD] and acyl-coenzyme A oxidase deficiency); and (3) deficiencies of multiple peroxisomal enzymes (rhizomelic chondrodysplasia punctata).⁶³ Despite attempts to develop lipid-based or gene-replacement targeted treatments for peroxisomal biogenesis disorders, they are currently unavailable, rendering seizures hard to control and outcomes poor.⁶⁴ Until recently, the situation was similar for XLALD, for which only inefficient treatments existed (VLCFA restriction, Lorenzo's oil [glyceryl trioleate and glyceryl trierucate], high-dose steroids, intravenous immune globulin [IVIG], and cyclophosphamide).⁶⁵ A treatment that yielded more success was bone marrow transplantation, which improved outcomes in boys with cerebral disease at its early stages.^{66–68} In the last decade, a novel gene therapy, elivaldogene autotemcel (Lenti-D™, SKYSONA™), has been approved for XLALD,^{69,70} showing encouraging results of stabilizing the disorder's manifestations.⁷¹

Congenital disorders of glycosylation (CDGs) are a heterogeneous group of diseases caused by pathogenic variants in genes related to glycosylation of N- and O-linked glycoproteins and glycolipids, glycosaminoglycan biosynthesis, and glycoposphatidylinositol (GPI) anchoring.⁷² In addition to the many systemic symptoms associated with CDGs, various types of drug-resistant seizures ensue, including myoclonic, atonic, focal migratory, generalized, and IEES.⁷² Treatment for these disorders is predominantly supportive. Some examples of attempted supplementation therapies that have been shown to yield partial clinical efficacy include galactose for *PGM1*-CDG⁷³ and possibly *SLC35A2*-CDG,⁷⁴ galactose and manganese for *SLC39A8*-CDG⁷⁵ and *TMEM165*-CDG,⁷⁶ fructose for *SLC35C1*-CDG,⁷⁷ and pyridoxine for seizures in *PIGO*-CDG and *PIGS*-CDG.⁷⁸ Ongoing trials of mannose-containing

liposomes for *PMM2*-CDG demonstrate encouraging results.⁷⁹ Two notable examples of successful supplementation therapy for CDGs include uridine, a glycosylated pyrimidine, which significantly improved seizure control and neurodevelopment in *CAD* deficiency,⁸⁰ and butyrate, a short-chain fatty acid working by enhancing histone acetylation, which improved outcomes and seizure control in the GPI anchoring defect *PIGM*-CDG.⁸¹ Addressing the multisystemic involvement of these disorders, reports of successful organ transplantation treatments consist of liver transplantation for *MPI*-CDG and *CCDC115*-CDG⁸² and heart transplantation in response to the cardiomyopathy in *DOLK*-CDG.⁸³

7 | DISORDERS OF ENERGY METABOLISM

Mitochondrial diseases (MDs) result from impairment in one of the many essential mitochondrial functions, which, among others, consist of energy production, apoptosis initiation, and removal of reactive oxygen species. This leads to a myriad of multisystemic symptoms, neurodevelopmental delays, and seizures. Several mitochondrial diseases are associated with progressive myoclonus epilepsy. Others, such as Leigh syndrome, the mtDNA depletion syndrome related to *POLG1*, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome, can present with epilepsy partialis continua (EPC). However, almost every seizure type has been reported in this heterogeneous group of disorders.⁸⁴ To date, mitochondrial diseases are treated symptomatically. Certain clinical utility is reported with cofactor supplementation of thiamine, riboflavin, or biotin for a selected number of mitochondrial diseases, coenzyme Q₁₀ for primary and secondary coenzyme Q₁₀ deficiencies, L-arginine and taurine for MELAS, and the antioxidant idebenone for Leber hereditary optic neuropathy (LHON).⁸⁵ Ongoing promising investigations of treatment development for MDs are based on mtDNA base editing, cell replacement therapy, mitochondrial replacement therapy (MRT), and mitochondrial augmentation therapy (MAT).⁸⁶

Glucose transporter type I (GLUT1) deficiency caused by pathogenic variants in *SLC2A1* leads to decreased amounts of glucose transport through the blood–brain barrier (BBB), directly decreasing cerebral glucose. Seizure types are predominated by atypical absence, generalized tonic–clonic, myoclonic, and atonic. The ketogenic diet replenishes cerebral energy with ketone bodies and is the main long-term treatment for this disorder.⁸⁷ There are ongoing efforts to develop gene replacement therapy for GLUT1 deficiency.⁸⁸

8 | DISORDERS OF VITAMINS

Pyridoxine-dependent epilepsy (PDE) is driven by pathogenic variants in *ALDH7A1* (the antiquitin gene), leading to a deficiency of the enzyme α -aminoacidic semialdehyde (α -AASA) dehydrogenase. Other related forms of PDE include pyridoxamine-5'-phosphate oxidase (PNPO) deficiency, folinic acid-responsive epilepsy, PLPBP deficiency, hyperprolinemia type II, and severe neonatal hypophosphatasia.^{89–92} They can all present with different types of neonatal and infantile onset seizures, including IESS, which are resistant to ASMs. The mainstay treatment for PDE is lifelong pyridoxine supplementation. A lysine-restricted diet is also advised.²⁰ Pyridoxal-5'-phosphate (PLP) dependency is partially or not responsive to pyridoxine and treated with PLP.⁹³ As its name implies, the folinic acid-responsive form of PDE responds to folinic acid.⁹⁴

Cerebral folate deficiency (CFD) reflects the case of low CSF and normal plasma concentrations of 5-methyltetrahydrofolate (5-MTHF). Primarily, it results from pathogenic variants in *FOLR1* encoding for a folate transporter. Secondary etiologies consist of deficiencies of other folate-related enzymes such as methylene tetrahydrofolate reductase (MTHFR) (in its severe form), 5,10-methyltetrahydrofolate synthetase, dihydrofolate reductase (DHFR), and dihydropyridine reductase, as well as folate receptor autoantibodies, serine deficiency syndromes, mitochondrial diseases, valproic acid side effect, and low dietary consumption of folate.⁹⁵ Seizures in CFD can be myoclonic, tonic, atonic, clonic, and atypical absence. Treatment depends on CFD's causative factor and may consist of a high dose of DL-folinic acid, levo-folinic acid, or levo-5-methyl-tetrahydrofolate.⁹⁵

Biotinidase deficiency is driven by the dysfunction of biotin recycling and, consequently, the deficiency of several biotin-dependent carboxylases. In addition to developmental delays, hypotonia, and characteristic dermatitis and alopecia, focal and generalized seizures occur in more than 50% of patients. The disorder responds well to biotin, especially if started at an early point.⁹⁶

9 | NEUROTRANSMITTER DISORDERS

Glycine encephalopathy is primarily caused by pathogenic variants not only in *GLDC* and *AMT*,⁹⁷ but also in *LIAS*, *GLYT1*, *GLYT2*, *BOLA3*, and *GLRX5*, encoding the multienzyme complex amenable for glycine cleavage.^{98,99} The resultant metabolic defect is high concentrations of cortical and systemic glycine. Most patients present in the first week of life with respiratory problems and apnea,

as well as epileptic encephalopathy, including myoclonic seizures and epileptic spasms. The clinical course evolves into early infantile developmental epileptic encephalopathy (EIDEE) and, later, IESS and Lennox–Gastaut syndromes.¹⁰⁰ A later occurring presentation has also been described,¹⁰¹ and there is a transient variant of the disorder that begins similarly, but glycine normalizes in the first months of life, and outcomes are better.¹⁰² Treatment of glycine encephalopathy includes NMDA antagonists, which offer partial improvement in seizure control.¹⁰³

Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by pathogenic variants in the dopa decarboxylase gene (*DDC*). The metabolic consequence of deficient AADC is decreased synthesis of dopamine and serotonin, leading to profound hypotonia and developmental impairment in addition to movement disorders, oculogyric crises, behavior and mood problems, and autonomic signs. Seizures are not common in AADC deficiency. Moreover, the extrapyramidal symptoms characterizing the disorder may be misinterpreted as seizures.¹⁰⁴ Recently developed targeted therapy, eladocagene exuparvovec, an adeno-associated virus vector (AAV)-based gene therapy injected into the putamen or substantia nigra shows promising results in safety and efficacy.¹⁰⁵

Succinic semialdehyde dehydrogenase deficiency (SSADHD) results from biallelic pathogenic variants in *ALDH5A1*. The absence or dysfunction of SSADH results in the accumulation of the neurotransmitter γ -aminobutyric acid (GABA) and other GABA-related metabolites, such as γ -hydroxybutyrate (GHB).¹⁰⁶ Considering the inhibitory properties of GABA, an excess of it leads to an excitation:inhibition disbalance in the CNS. This affects normal development, cognition, communication, movement, behavior, and epileptogenesis.^{107–110} Seizures are seen in approximately half of patients and seem to worsen with age and the associated gradual and relative decrease in GABA levels.¹¹¹ This has been proposed to occur due to the use-dependent downregulation of GABA receptors.¹¹² The currently available treatment of SSADHD is supportive. Seizures are treated according to the standard of care in epilepsy, and valproic acid is generally avoided, for it may inhibit any residual enzyme activity.¹⁰⁹ There are ongoing preclinical studies aiming to develop enzyme and gene-replacement therapies for SSADHD.¹¹³

10 | CONCLUSIONS

Despite being individually rare, the combined prevalence of inherited metabolic epilepsies is considerable, making their management an arduous task for epileptologists. The clinical presentation of seizures in inherited metabolic epilepsies may come in almost every shape and form

and is seldom distinctive enough to establish their diagnosis. The other clinical symptoms associated with these disorders, along with family history, EEG findings, neuroimaging, and metabolic and genetic tests, complete their clinical picture. Substantial molecular and genetic advancements that emerged over the last two decades, along with multicenter and international collaborations, have led to improved understanding of their pathophysiology and development of novel diagnostic biomarkers and targeted therapies. Diagnosing treatable inherited metabolic epilepsies via deep phenotyping, metabolic and genetic tests, and neuroimaging and neurophysiologic modalities is rewarding, especially if done at an early point in the disease course, as specific treatments may lead to seizure control and improved outcomes. The ongoing careful investigation of individuals with inherited metabolic epilepsies holds promise for the development of more targeted therapies for this unique group of disorders. Additionally, it advances our understanding of pathomechanisms leading to epileptogenesis.

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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