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Treatable Genetic Metabolic Epilepsies

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Opinion statement

In the absence of a culprit epileptogenic lesion, pharmacoresistant seizures should prompt the physician to consider potentially treatable metabolic epilepsies, especially in the presence of developmental delays. Even though the anti-seizure treatment of the epilepsies remains symptomatic and usually tailored to an electroclinical phenotype rather than to an underlying etiology, a thorough metabolic workup might reveal a disease with an etiology-specific treatment. Early diagnosis is essential in the case of treatable metabolic epilepsies allowing timely intervention. Despite the advances in genetic testing, biochemical testing including cerebrospinal fluid studies are still needed to expedite the diagnostic workup and potential therapeutic trials. The diagnostician should have a high index of suspicion despite potential clinical digressions from seminal publications describing the initial cases, as these index patients may represent the most severe form of the condition rather than its most common presenting form. The often gratifying developmental outcome and seizure control with early treatment calls for a prompt diagnostic consideration of treatable metabolic diseases; even though relatively rare or potentially only seemingly so.

Introduction

When the etiology of the epilepsy is not readily identified and when there is no identifiable lesion on brain magnetic resonance imaging (MRI) or a suspected subtle lesion suggested by a unifocal electroencephalogram (EEG), a diagnosis of "idiopathic" or "presumed genetic epilepsy" is not sufficient in children with treatment-resistant seizures, particularly in those with developmental delays or regression. A thorough workup might reveal inherited metabolic epilepsies amenable to treatments tailored to the etiology. This may be life saving, resulting in improved neurological development and seizure control. While a comprehensive review of genetic metabolic epilepsies is beyond the scope of one article, in this review, we include those in which early diagnosis and treatment may improve the clinical course and help prevent future affected siblings (Table 1).

Epilepsies treatable with pyridoxine and pyridoxal phosphate

Pyridoxine-dependent epilepsy (PDE) was initially characterized through the sequential elimination of the components of a multivitamin that successfully suppressed standard treatment-resistant seizures in a neonate [1]. The majority of PDE cases are caused by autosomal recessive mutations in the *ALDH7A1* gene encoding the antiquitin protein. The mutation leads to a deficit in lysine degradation, and the subsequent accumulation of α-aminoadipic semialdehyde (AASA) in the urine, plasma, and cerebrospinal fluid (CSF), a diagnostic feature of the disease. Accumulated AASA inactivates pyridoxal phosphate (PLP), the active form of vitamin B6, a cofactor in a multitude of metabolic reactions related to neurotransmitters and amino acids [2]. In addition to *ALDH7A1*, mutations in *PROSC*, a gene encoding a PLP-binding protein, have recently been implicated in PDE [3••]. PDE usually manifests within hours to days after birth, and may mimic hypoxic encephalopathy of the newborn. Case series reporting a relatively high rate of response in neonates empirically treated with pyridoxine suggest that the disease is not as rare as previously reported [4]. Late-onset PDE around 2 months of age or cases declaring themselves with recurrence of refractory seizures later in infancy after an initial response to standard anti-seizure medications have been described [5]. Additionally, childhood-onset PDE has been also reported [6]. The initial presentation is usually stormy with various seizure types, including myoclonic, tonic, and partial ones. Later, generalized convulsions, infantile spasms, and atonic seizures may occur [5]. While there usually are no specific electrographic signatures, the electroclinical phenotype may be consistent with one of the early neonatal encephalopathies with burst suppression patterns, such as early myoclonic encephalopathy of infancy (EMEI) and, less commonly, the usually malformative Ohtahara syndrome. Variable combinations of cognitive deficits, motor delays with hypotonia, in addition to autistic and obsessive compulsive features may occur [5]. Structural abnormalities may encompass ventriculomegaly, corpus callosum hypoplasia, and heterotopias [7, 8].

Seizures are not responsive to standard anti-seizure medications even with large doses and poly-pharmacy, and often culminate in status epilepticus when supplemental therapy is not initiated [9]. Seizures, however, may stop within minutes after administration of an intravenous pyridoxine bolus (starting with 100 mg) [10]. It is essential to maintain life-long regular oral pharmacologic doses of pyridoxine (15–30 mg/kg/day) to prevent recurrent seizures, even after

Table 1. Summary of currently treatable metabolic epilepsies with a description of the primary genetic and biochemical defect, and their treatment options

	Primary defect	Pathophysiology	Important biochemical findings	Treatment
Pyridoxine-dependent epilepsy	*ALDH7A1* (antiquitin)	PLP inactivation by AASA accumulation	↑ U, P, and CSF AASA ↓ CSF PLP	Pyridoxine ± folinic acid, PLP
	PROSC (PLP binding protein)	Disturbed PLP homeostasis	↓ CSF PLP	
	PNPO (PNPO enzyme)	Impaired pyridoxine conversion into PLP	↓ CSF PLP	
GLUT1DS	*SLC2A1* (GLUT1)	Impaired glucose transport into the CSF	↓ CSF glucose (<40 mg/dL) ↓ CSF/P glucose ratio (<0.4)	Ketogenic diet
DEND syndrome	*KCNJ11* (Kir6.2 subunit of K_{ATP} channel)	Inhibition of K_{ATP}-dependent insulin and neurotransmitter release	↑ P glucose	Sulphonylureas
HI/HA	*GLUD1* (GDH enzyme)	Increased K_{ATP}-dependent insulin release	↓ P glucose ↑ P ammonia	Diazoxide
Creatine deficiency syndromes	*SLC6A8* (CrT transporter)	Impaired creatine transport into neurons	↑ U creatine/creatinine ratio (in boys)	Creatine, arginine, glycine
	GATM (AGAT enzyme)	Defective creatine synthesis	↓ U, P, and CSF creatine ↓ U, P, and CSF GAA	Creatine
	GAMT (GAMT enzyme)	Defective creatine synthesis	↓ U, P, and CSF creatine ↑ U, P, and CSF GAA	Creatine, ornithine, benzoate, arginine-restricted diet
Serine biosynthesis defects	*PHGDH* (3-PGDH enzyme), *PSAT1* (PSAT enzyme), *PSPH* (PSP enzyme)	Defective serine biosynthesis	↓ CSF and P serine ↓ CSF 5 MTHF (in PGDH deficiency)	Serine, glycine
BH_4 deficiency	*PTPS* (PTPS enzyme) and *GCH1* (GTPCH enzyme)	Defective BH_4 biosynthesis	↑ P Phe ↓ U and CSF biopterin	BH_4, L-dopa, 5-HTP
	SPR (SR enzyme)	Defective BH_4 biosynthesis	↑ CSF BH_2 ↑ CSF and U sepiapterin	L-Dopa, 5-HTP
	QDPR (DHPR enzyme)	Impaired BH_4 recycling	↑ CSF BH_2 ↑ P Phe ↓ CSF 5 MTHF	Folinic acid, L-dopa, 5-HTP, low Phe diet

Table 1. (Continued)

	Primary defect	Pathophysiology	Important biochemical findings	Treatment
Cerebral folate deficiency	*FOLR1* (FRα transporter)	Failure of folate transfer into CSF via FRα-mediated endocytosis Secondary etiologies include DHPR-related BH_4 deficiency and PGDH-related serine biosynthesis	↓ CSF 5MTHF	Folinic acid
Biotinidase deficiency	*BTD* (biotinidase)	Impaired biotin recycling	↑ U 3-hydroxy-isovalerate ↑ P lactate	Biotin
NKH	*GLDC* and *AMT* (encoding glycine cleavage system proteins)	Disrupted glycine cleavage system	↑ CSF and P glycine ↑ CSF/P glycine ratio (>0.02)	Benzoate, dextrometorphan

3-PGDH 3-phosphoglycerate dehydrogenase, *5-HTP* 5-hydroxytryptophan, *5MTHF* 5-methyltetrahydrofolate, *AGAT* arginine:glycine amidinotransferase, BH_2 dihydrobiopterin, BH_4 tetrahydrobiopterin, *CrT* creatine transporter, *CSF* cerebrospinal fluid, *DEND* developmental delay, epilepsy, and neonatal diabetes, *DHPR* dihydropteridine reductase, *FRα* folate receptor alpha, *GAA* guanidinacetic acid, *GAMT* guanidinoacetate methyltransferase, *GDH* glutamate dehydrogenase, *GLUT1* glucose transporter 1, *GLUT1DS* GLUT1 deficiency syndrome, *GTPCH* GTP cyclohydrolase I, *HI/HA* hyperinsulinism and hyperammonemia, K_{ATP} ATP-dependent potassium channel, *NKH* nonketotic hyperglycinemia, *P* plasma, *Phe* phenylalanine, *PLP* pyridoxal phosphate, *AASA* aminoadipic acid semialdehyde, *PNPO* pyridoxamine 5′-phosphate oxidase, *PSAT* phosphoserine aminotransferase, *PSP* phosphoserine phosphatase, *PTPS* 6-pyruvoyl-tetrahydropterin synthase, *U* urine

achieving seizure control [10]. Although 75% of the patients continue to have neurodevelopmental deficits and behavioral disturbances, they generally improve with early diagnosis and treatment [5]. Adverse effects include cardiorespiratory collapse when administering a bolus. Peripheral neuropathy may occur with chronic pyridoxine administration [10]. The dose of pyridoxine should be doubled during febrile illnesses as seizure threshold is decreased [9]. Pregnant mothers of children with PDE are advised to take pyridoxine supplementation (50–100 mg/day) during the last half of gestation [9]. Additionally, lysine restriction and arginine supplementation may ameliorate neurodevelopmental outcomes [11].

Two other conditions closely related to PDE are folinic acid-responsive seizures and pyridoxal phosphate-responsive (PLP) seizures. These make the diagnosis and appropriate therapy more challenging, especially in the acute phase when urgent treatment is needed. The serendipitous discovery of folinic acid-responsive seizures in neonates with treatment-resistant epileptic encephalopathy and a specific pattern of peaks on high-performance liquid chromatography (HPLC) analysis of cerebrospinal fluid (CSF) was followed by the discovery that such cases have allelic mutations in PDE-related genes [12]. This fell in line with the clinical observation of a complete response to pyridoxine/folinic acid combination in some PDE cases following a partial response to pyridoxine-only therapy. PLP-dependent epilepsy is another condition that overlaps in clinical characteristics with PDE; yet, the underlying deficit is in the gene encoding the enzyme pyridoxamine 5′-phosphate oxidase (PNPO). This enzyme converts pyridoxine to its active form PLP [13]. Although these patients should primarily respond to PLP supplementation, some of them respond to pyridoxine, while others may worsen with PLP therapy, which challenges the intuitive understanding of their underlying physio-pathologic mechanisms [14••]. As exact mechanisms remain elusive, the diagnostic and therapeutic approach to the neonate with encephalopathy and intractable seizure is also based on clinical observations. While genetic analyses/CSF studies are pending, therapeutic trials (under EEG guidance in the infant experiencing status epilepticus) should be performed with pyridoxine. Usually, 100–500 mg is given intravenously in sequential 100 mg doses every 10 min. This should be followed by a maintenance dose of 30 mg/kg/day in two divided doses and not exceeding 500 mg/day, in addition to folinic acid (3–5 mg/kg/day orally for one week). In the absence of a favorable response, a therapeutic trial with PLP (30–50 mg/kg/day orally in four divided doses for 1 week) should follow.

Glucose transporter 1 deficiency syndrome

The hallmark clinical characteristics of glucose transporter 1 deficiency syndrome (GLUT1DS) are infantile-onset anti-convulsant-resistant epilepsy, variable developmental delay, movement disorders, hypotonia, ataxia, and acquired microcephaly. Following the seminal paper describing "DeVivo disease" [15], an expanding spectrum of protean clinical manifestations has been recognized [16•], suggesting that this condition is underdiagnosed. Epilepsy occurs in 90% of the children affected by GLUT1DS [17], can be the only manifestation of the disease, and usually emerges in the first year of life with resistance to standard anti-convulsants. A variety of seizure types can occur,

including generalized, partial, myoclonic, and spasms. These may be associated with irregular eye movements [16•, 18]. In many of the metabolic diseases described here, a disruption of electrophysiological homeostasis is reflected on EEG with multiple foci of brain hyperexcitability in the form of multifocal spikes and spike waves, as well as generalized spike waves (GSW), likely representing rapid secondary generalization or bilateral synchrony. Even though there are no pathognomonic EEG signatures or MRI findings, the GLUT1DS is a notorious protean mimicker of multiple electroclinical phenotypes. Indeed, GLUT1DS accounts for up to 5% of the cases of myoclonic astatic epilepsy (MAE) [19], and may electroclinically mimic at its onset some of the benign genetic nonlesional epilepsies such as benign myoclonic epilepsy of infancy (BMEI) [16•], or childhood absence epilepsy (CAE) [20•]. These manifest an electrical signature of GSW superimposed on a normal background, or 3-Hz GSW complexes, respectively. GLUT1DS testing should be considered in infants with an electroclinical phenotype compatible with BMEI, in children with MAE and CAE who do not readily respond to standard anti-seizure medications, and in patients with an early "CAE" presentation prior to the age of 3 years. Of note, in addition to weakness, and movement disorders, GLUT1DS can produce several nonepileptic paroxysms such as opsoclonus, alternating hemiplegia of childhood, paroxysmal exertion-induced dyskinesia type 2 (DYT18), and autonomic paroxysms [16•]. Some of these may require a prolonged video-EEG monitoring to characterize their nature.

Most cases are due to a dominant de novo mutation in the *SLC2A1* gene, encoding glucose transporter 1 (GLUT1) [21], although autosomal recessive cases have been reported. Glucose is transferred to the brain via GLUT1, providing the main energy source for brain function and maturation, and for electrophysiological homeostasis. A CSF glucose level less than 40 mg/dL, or a ratio of CSF to plasma glucose of less than 0.4, along with low to normal CSF lactate levels are diagnostic. This can be confirmed with genetic testing [16•].

Early treatment with the ketogenic diet (KD) throughout childhood, and possibly adulthood, provides an alternative source of energy to the brain, suppressing seizures, and may prevent worsening of developmental delays and even improve cognitive functions in some cases [22].It is recommended to maintain a betahydroxybutyrate level at ~5 mM for optimal seizure control [23], usually with an initial KD target ratio of 4:1, or 3:1 in infants [24]. L-Carnitine supplementation (100 mg/kg/day, up to 2 g/day) may be needed to circumvent KD-related hypocarnitinemia [25]. Additionally, methylxanthines, phenobarbital, diazepam, and alcohol are relatively contra-indicated, as they inhibit GLUT-1 [25].Regardless of the treatment modality, age at the time of treatment initiation is the most important prognostic factor [18••].

DEND syndrome

Neonatal diabetes (ND) is a rare inherited form of diabetes that presents with severe hyperglycemia in the first 6 months of life due to gain of function mutations in ATP-sensitive potassium channels (K_{ATP}) [26, 27]. About 3% of the patients with ND have neurological features that include developmental delays, epilepsy, and dysmorphic features, hence the acronym developmental delay, epilepsy, and neonatal diabetes (DEND) [28]. Epileptic seizures occur in

the first year of life, and most commonly consist of infantile spasms, tonic-clonic, and myoclonic seizures [27]. Dysmorphic features include prominent metopic sutures, downturned mouths, bilateral ptosis, and limb contracture [26]. Some patients with a milder presentation, termed intermediate DEND, may present with seizures after the first year of life [28]. Mutations leading to ND or DEND are due to enhancements in the open state of the K_{ATP} channel which causes membrane hyperpolarization. This leads to the inhibition of K_{ATP} pathway-dependent insulin release in pancreatic cells, and to the inhibition of neurotransmitter release. The exact mechanism of seizure generation remains elusive but may be related to decreased activity in inhibitory neurons [29]. Oral sulphonylureas are K_{ATP} channel blockers that restore insulin secretion, and may attenuate seizures and improve neurological outcomes [30]. In addition, standard anti-seizure medications tailored to the seizure types and epilepsy syndromes are used.

Hyperinsulinism and hyperammonemia

Hyperinsulinism and hyperammonemia (HI/HA) syndrome is characterized by recurrent fasting as well as postprandial episodes of hypoglycemia, persistent hyperammonemia, and the presence of seizures and developmental delays. It presents in infancy, but late diagnosis is common, due to the transient nature of hypoglycemia, and the fact that hyperammonemia in children with epilepsy may be mistakenly attributed to some anti-epileptic drugs, of which valproic acid is the usual culprit. Children often present with hypoglycemic focal seizures [31] with or without rapid generalization, and may be diagnosed with refractory epilepsy. Of note, some patients may have nonhypoglycemic seizures related to a remote hypoglycemic brain lesion, and yet more intriguingly, ~60% have nonlesional epilepsy [32, 33]. Counterintuitively, epilepsy may manifest with a primarily generalized electroclinical phenotype, including atypical absences with or without eyelid myoclonus, as well as myoclonic seizures that can be triggered by photic stimulation or hyperventilation [34]. In addition to possible rapid secondary generalization or rapid bilateral synchrony, this also may reflect a potential subcortical mechanism of seizure generation. Episodes of hypoglycemia-related lethargy and hypotonia can occur, and most patients have a varying degree of intellectual disability [32, 33]. Cognitive disability and the occurrence of slowing on EEG do not correlate with ammonia levels. Children who do not have epilepsy tend to have a normal EEG and are less likely to have intellectual disability [32, 33].

HI/HA syndrome is caused by dominant mutations in the *GLUD1* gene, whose protein activates the mitochondrial enzyme glutamate dehydrogenase (GDH) [31]. GDH over-activation leads to increased conversion of glutamate to alpha-ketoglutarate, with subsequent ATP generation, leading to K_{ATP}-related insulin release, as well as impaired detoxification of ammonia in the liver [35]. In addition to the resulting fasting hypoglycemia, postprandial hypoglycemia is a distinctive feature of this condition, and is most likely related to GDH unregulated over-activation by the ingested amino acid leucine, an allosteric activator of the enzyme [32]. This condition is managed with diazoxide (5–15 mg/kg/day), which inhibits insulin release by activating K_{ATP}, counteracting the effect of GDH. To prevent fluid retention from diazoxide, a thiazide diuretic

is recommended as well. In addition, dietary protein restriction and intermittent glucagon administration may be helpful [36]. Standard anti-seizure medications may also be needed. Since patients do not exhibit identifiable signs or symptoms of acute or chronic hyperammonemia, the benefits of treatment with ammonia-lowering agents are not clear.

Creatine deficiency syndromes

Creatine deficiency syndromes (CDS) are characterized by global developmental delays with significant language impairment, hypotonia, seizures, movement disorder, and autistic features. Creatine is required in the energy-driven cellular reactions, and deficits in its biosynthesis or in its transport into neurons result in the different forms of CDS. The CDS's are likely extremely underdiagnosed given that the resulting biochemical derangements are rarely screened for. Indeed, one of the CDS forms, X-linked creatine transporter (CrT) deficiency (CTD), may be the second most common cause of X-linked intellectual disability in boys, following Fragile X [37]. An elevated creatine-to-creatinine ratio in urine serves as a screening tool for boys with CTD [38]. While currently not amenable to specific treatment modalities, standard anti-seizure drugs can be efficacious and supplementation with creatine primarily and creatine precursors L-arginine (400 mg/kg/day) and L-glycine (150 mg/kg/day) may occasionally improve neurodevelopmental outcomes in the milder cases, particularly when instituted early [39].

Autosomal recessive defects in the creatine biosynthetic enzymes, arginine:glycine amidinotransferase (AGAT), and guanidinoacetate methyltransferase (GAMT) are at the origin of the two other more treatable forms of CDS. Genetic testing confirms the diagnosis, but urinary testing can be helpful to differentiate between the different syndromes. Urinary creatine/creatinine levels are normal with both AGAT and GAMT deficiencies but increased with CTD. Guanidinacetic acid (GAA) levels are decreased with AGAT deficiency, increased with GAMT deficiency, and normal with CTD [38].While epilepsy has not been described in patients with AGAT deficiency, defects in GAMT are associated with seizures in 50% of the cases, in addition to the invariable occurrence of developmental delay [40]. A variety of nonspecific partial and generalized electroclinical phenotypes have been described. In addition, a noteworthy 2–3-Hz GSW pattern manifesting with absence seizures has been reported [41] in a similar manner to the herein described GLUT1DS, hinting to potential commonalities in energy failure-related physio-pathologic mechanisms of seizure generation. Specific findings on MRI and magnetic resonance spectroscopy (MRS) have also been described in GAMT patients with an increased globus pallidus signal, and the absence of a creatine peak [42]. Patients with AGAT or GAMT deficiency must be supplemented with creatine monohydrate (350–2000 mg/kg/day) [43].

Children with GAMT are also placed on an arginine-restricted diet (15–25 mg/kg/day) to reduce high levels of neurotoxic GAA [44]. Ornithine (starting dose of 100 mg/kg/day) must be supplemented to circumvent an arginine restriction-related deficiency, with a target plasma ornithine range between 100 and 200 μmol/L. A higher dose of ornithine (up to 800 mg/kg/day) may also be used to achieve a competitive inhibition of AGAT activity [44]. Benzoate

(100 mg/kg/day) is administered to reduce the levels of the GAA precursor, glycine [38]. Seizures and movement disorders readily respond to the aforementioned treatments; yet, developmental delays only improve modestly. Additional standard anti-seizure medications may be needed to completely suppress seizures.

Epilepsies secondary to serine deficiency

Serine deficiency is the prototypical genetic epilepsy that can be reversed with early diagnosis and treatment, illustrating the importance of a high index of suspicion and prompt diagnosis. Most cases present in infancy with intrauterine growth retardation, congenital microcephaly, and intractable seizures mimicking a perinatal injury. Treatment-resistant seizures emerge within weeks or months after birth, and are followed by developmental stagnation, and progressive spasticity [45]. Generalized atrophy with a marked decrease in white matter are evident on brain MRI [46]. Some infants also present with congenital cataracts, hypogonadism, adducted thumbs, inguinal and umbilical hernias, and megaloblastic anemia [47]. A mild juvenile form of the disorder was described in two siblings who presented with absence seizures and moderate developmental delays [48]. L-serine plays a major role in the development of the central nervous system and acts as a precursor for phospholipids, glycolipids, and the neurotransmitters glycine and D-serine [47]. Its deficiency is caused by mutations in any of its biosynthetic enzymes 3-phosphoglycerate dehydrogenase (3-PGDH), phosphoserine aminotransferase, and phosphoserine phosphatase, with autosomal recessive mutations in the first being the most common [45]. Defects in the other two enzymes are reported in a handful of cases including one with a Williams syndrome phenotype [45].

Plasma L-serine levels are strongly influenced by food intake and might be only marginally lower than the reference ranges, which leads to underdiagnoses in the milder forms. It is advisable when this condition is suspected, to perform CSF amino acid analysis, followed by confirmatory genetic testing [49]. Treatment consists of supplementation with L-serine (200–600 mg/kg/day) and glycine (200–300 mg/kg/day) [44]. With treatment, seizures disappear, or at the very least improve. Myelination, spasticity, feeding, and behavior improve as well [46, 50]. Psychomotor developmental problems already present in symptomatic patients are nonreversible [51]. If treatment is initiated before symptoms appear, developmental problems may be completely avoided, as evidenced when an affected fetus was treated with intrauterine L-serine supplementation [50].

Tetrahydrobiopterin deficiency

Tetrahydrobiopterin (BH_4) disorders are characterized by a varying degree of combined deficiencies in monoamine neurotransmitters resulting in psychomotor delay, and a constellation of symptoms including parkinsonism, dystonia, hypertonia, hypersalivation, oculogyric crises, irritability, disturbed sleep, and temperature dysregulation [52]. The condition is caused by defects in the BH_4 recycling enzyme, DHPRP, or in biosynthetic enzymes, GTP cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), and

sepiapterin reductase (SR) [52]. Except for SR-related BH_4 deficiency, all forms of this condition are associated with hyperphenylalaninemia (HPA), detectable by the phenylketonuria (PKU) newborn screening test. Pterins in blood or urine, and plasma dihydropteridine reductase (DHPR) activity can be performed to differentiate between PKU and the various forms of BH_4 deficiency associated with HPA. CSF biogenic amines, pterins, and folates must be evaluated to determine the specific type of BH_4 disorder [53].

Defects in PTPS are the most common cause of BH_4 deficiency. It is associated with early gestational age, low birth weight, microcephaly, axial hypotonia with appendicular spasticity, a movement disorder, and predominantly myoclonic seizures, though convulsions may occur [53, 54]. GTPCH-deficient patients also have hypotonia and movement disorders with seizures occurring in less than 20% of the cases, and, less commonly, vegetative symptoms and hypertonicity [53]. Both PTPS and GTPCH deficiencies may be associated with intellectual disability. In addition to administering BH_4 (5–10 mg/kg/day orally), neurotransmitter deficiencies require supplementation with L-dopa (1–3 mg/kg/day in the newborn; 4–7 mg/kg/day for the 1–2-year-old infants; 8–15 mg/kg/day for children above 2 years of age) and 5-hydroxytryptophan (5-HTP) (1–2 mg/kg/day in the newborn; 5–10 mg/kg/day for older infants) [44]. Concurrent administration of carbidopa (10–25% of the L-dopa dose), monoamine oxidase B (MAO-B) or catechol-*O*-methyltransferase (COMT) inhibitors reduce the therapeutic requirements of L-dopa and related peripheral adverse effects [44]. Early supplementation results in neurological improvement and seizure suppression.

Infants and children with SR defects present with nonspecific symptoms that mimic cerebral palsy with dystonia and oculogyric crises with diurnal fluctuations [55]. They do not have HPA, and are not detected by PKU newborn screening. Instead, early diagnosis must rely on clinical suspicion and CSF analysis. Recently, elevated urine sepiapterin levels were reported as helpful [56••]. SR deficiency is usually very severe, likely due to accumulation of dihydrobiopterin (BH_2) which further impairs activity of neurotransmitter synthetic enzymes [57]. Patients are treated with L-dopa, 5-HTP, and carbidopa.

DHPR-related deficiency leads to BH_2 accumulation, and thus a severe form of the disease similar to SR deficiency. Unlike the other forms, defects in DHPR also lead to cerebral folate deficiency and calcifications in the basal ganglia. Therefore, in addition to L-dopa and 5-HTP, treatment must include folinic acid (15–20 mg/day) and BH_4 is typically not administered to avoid inducing further folate deficiency [44]. If started early, basal ganglia calcification can be reversed [58]. With treatment, neurological symptoms may improve, but some patients may still need anti-seizure drugs. A low-phenylalanine diet is recommended to prevent HPA [44].

Cerebral folate deficiency

Cerebral folate deficiency (CFD) presents with a variety of clinical features that encompass intractable epilepsy, developmental delay, regression, dyskinesia, and prominent autistic features in infancy and childhood, as well as schizophrenia and catatonia in adolescence [59, 60]. CFD is characterized by a low level of CSF 5-methyltetrahydrofolate (5MTHF) in the face of normal plasma

folate levels. 5MTHF, a cofactor in the synthesis of neurotransmitters and amino acids, is transported into the CSF via folate receptor alpha (FRα)-dependent endocytosis [59]. While autoantibodies to FRα [61] and mutations in the FOLR1 gene encoding it [60, 62] are the primary causes of CFD, there seem to be a number of secondary causes, the exact mechanism of which remains elusive. Nevertheless, CFD likely represents a final common pathway because of a multitude of etiologically heterogeneous pathological mechanisms disrupting folate transport into CSF, including, among others, mitochondrial encephalomyopathies such as Kearns-Sayre syndrome, Alpers disease, 3-PGDH-related serine deficiency syndrome, and the DHPR-related BH_4 deficiency discussed above [59].Treatment should be initiated with folinic acid supplementation (0.5–1 mg/kg/day, or 2–5/mg/kg/day in cases of FOLR1 mutations) [59]. Folinic acid ameliorates the symptoms and controls seizures in some patients, including those with secondary etiologies. Even mitochondrial encephalomyopathy-related hypomyelination improves with folinic acid treatment [63].

Biotinidase deficiency

Biotinidase (BTD) deficiency is characterized by seizures and other neurological, ophthalmological, and cutaneous manifestations. The condition usually presents weeks to months after birth, once prenatal biotin stores are depleted and recycling becomes essential, but sometimes earlier in the presence of a stressor such as an infection [64]. In addition, late-onset BTD deficiency has been described in a number of older children and adolescents who present with spasticity, limb weakness, and vision loss, mimicking multiple sclerosis and related conditions [65, 66]. Seizures include myoclonic types, in addition to infantile spasms [67]. Patients can manifest developmental delay, conjunctivitis, optic atrophy, sensorineural hearing loss, alopecia, and a perioral rash [64]. EEG may show multifocal spikes, burst suppression, hypsarrhythmia, or background slowing [64, 67]. Common neuroimaging findings include brain atrophy, decreased white matter, enlarged ventricles, and basal ganglia abnormalities [64].Biotin is a cofactor required for several important carboxylation reactions. Its deficiency results in increases in plasma lactate levels, and in several urinary organic acids, especially 3-hydroxyisovalerate [44]. BTD deficiency responds to biotin supplementation (5–20 mg/day) with seizure control, reversal of neuroimaging abnormalities, and, potentially, a complete prevention of neurological complications. Some of the cognitive problems, visual and hearing loss, may, however, persist [64].

Nonketotic hyperglycinemia

Nonketotic hyperglycinemia (NKH), or glycine encephalopathy, presents with three levels of severity (severe, attenuated, and late onset), and phenotypically manifests with varying degrees of neurodevelopmental delay, hypotonia, and seizures. Severe NKH presents in the neonatal period, and, occasionally, in infancy, with axial hypotonia, limb spasticity, intractable seizures (often myoclonic), transient apnea, and lethargy progressing to coma with a neonatal mortality of 30% [68, 69]. It may be accompanied by club feet, cleft lip/palate,

and congenital hernias [68, 69]. Abnormal EEG patterns are nonspecific, and include the electroclinical phenotypes of EMEI and West syndrome [68, 69]. Brain malformations include corpus callosum hypoplasia, brain atrophy, hydrocephalus, and posterior fossa cysts. They occur in 50% of the cases and are associated with the worst prognosis [69]. Patients with attenuated NKH also present during the neonatal period or infancy, but have a milder phenotype and no congenital malformations. They may develop hyperactivity, chorea, and varying degrees of intellectual disability [69]. While they have seizures, these are usually not refractory [69]. Late-onset NKH is rare, and presents after 2 years of age with cognitive decline and behavioral problems. Seizures are uncommon, and progressive spinocerebellar symptoms and fluctuating choreoathetosis have been described [70, 71].

Glycine accumulation is caused by autosomal recessive mutations in the glycine cleavage system [72]. Intractable seizures result from glycine-mediated overstimulation of *N*-methyl-D-aspartate (NMDA) receptors in the brain, whereas stimulation of the inhibitory glycine receptors in the brain stem and spinal cord may be responsible for hypotonia, neonatal apnea, and hiccups [69]. An increase in CSF and plasma glycine levels, and in the CSF to plasma glycine ratio are suggestive of NKH [68]. Diagnosis is confirmed by genetic testing. The condition is treated with benzoate supplementation which ameliorates seizure control and alertness, and may improve neurodevelopmental outcomes if started early [44]. Benzoate toxicity includes gastritis, renal dysfunction, glycosuria, hypokalemia, hypocalcaemia, and can be fatal [73]. It is hence important to monitor glycine and benzoate levels if available, and to start with a low dose (500–750 mg/kg/day for the severe form; 250–500 mg/kg/day for the attenuated form) with a gradual upward titration by 50 mg/kg/day increments until optimal glycine levels are reached [73]. In addition, benzoate requirements can be reduced by restricting the dietary intake of glycine in severe NKH [73]. Carnitine level monitoring and supplementation may also be needed to circumvent the secondary hypocarnitinemia [69]. Treatment with dextromethorphan (5–10 mg/kg/day), an NMDA receptor blocker, may be helpful [44]. In addition, standard anti-seizure medications are needed, but valproate should be avoided as it further impairs the enzymatic defect [44].

Conclusions

The number of genetic epilepsies that is amenable to treatment will hopefully continue to expand with the increased availability of genetic testing, and the accompanying research-driven enhanced understanding of their pathophysiology. While certain seizure types such as myoclonus tend to be the most common accompaniment of the syndromes described previously, the epileptic seizures and EEG findings are not specific, and at times might even overlap with those seen in the nonlesional genetic benign epilepsy syndromes (so-called idiopathic) such as CAE. Any digression from the typical age-specific maturational switches at which such benign syndromes occur, or from the relatively normal development and good response to standard anti-seizure medications implied by the term "benign," should trigger a search for an underlying treatable metabolic etiology. When a metabolic epilepsy is suspected, certain electroclinical phenotypes such as MAE, EMEI, or those overlapping with CAE may help in narrowing down the diagnostic possibilities, but diagnoses cannot be made solely on electroclinical grounds. Structural brain

imaging findings are also diagnostically nonspecific and, when present, are often diffuse and symmetrical reflecting processes such as neuronal loss and hypomyelination. Occasionally, malformative lesions may also be seen (such as in NKH and PDE). Even when structural abnormalities are present, they may fail to explain the entire electroclinical phenotype, and should not conclude the diagnostic workup as these are not considered the culprit "epileptogenic lesions" in the epilepsy lexicon [74]. These should not deter the diagnostician from pursuing further testing to fully elucidate the cause of epilepsy and promptly explore potentially treatable metabolic etiologies. The clinical context and biochemical testing, including CSF studies, may lead to a preliminary diagnosis of a treatable genetic metabolic epilepsy, which is then confirmed with genetic testing. With prompt detection and treatment, seizure suppression and reversal, at times complete, of many neurological aspects of these conditions is gratifying and calls for their early consideration when formulating a differential diagnosis, despite their relative rarity.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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