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Treatable inherited metabolic epilepsies

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ABSTRACT

Inherited metabolic epilepsies (IMEs) represent inherited metabolic disorders predominately presenting with seizures. While most IMEs are currently managed with symptomatic and supportive therapies, some are amenable to disorder-specific targeted treatments. In most cases, these treatments are effective only if given in a narrow time window early in the lives of affected patients. Hence, prompt recognition of treatable inherited metabolic epilepsies at an early age and as soon as symptoms appear has paramount importance. Herein, we provide an overview of inherited metabolic epilepsies, which presently have established targeted treatments showing clinical efficacy in reducing seizure burden and improving neurodevelopmental outcomes. These therapeutic modalities range from specific diets, vitamins, and supplementation of organic compounds to synthetic pharmacological agents and novel genetic-based therapies that alter the biochemical pathways of these disorders at the cellular or molecular level, steering them to their normal function.

1. Introduction

It is a special pleasure and honor to contribute to this volume celebrating the legacy of Michael Duchowny, M.D., a towering figure in pediatric epilepsy who set the standard for pediatric epilepsy surgery, kind and effective clinical care, and masterful education for epilepsy fellows. His reputation was soaring throughout his career and lasting impact profound.

Of the ~1450 known inherited metabolic disorders (IMDs), in approximately 250, seizures are a prominent clinical manifestation and a primary determinant of the overall clinical outcome [1]. These conditions represent the inherited metabolic epilepsies (IMEs). A broad range of pathomechanisms affecting molecular biochemical pathways can result in epileptogenesis. These pathomechanisms serve as the basis of the IME classification [2]. They include deficiency or accumulation of low-molecular-weight compounds leading to neurotoxicity (for example, in amino and organic acidemias and urea cycle disorders), poorly created or converted large-molecular-weight compounds (for example, in lysosomal and peroxisomal-related disorders, and congenital disorders of glycosylation), defects in cellular energy [such as glucose transporter type I (Glut-1) deficiency, mitochondrial diseases, and fatty acid oxidation disorders], deficiency of fundamental trace minerals, enzyme cofactors, and vitamins (such as in pyridoxine-dependent epilepsy, biotinidase deficiency, and cerebral folate deficiency), and improper neurotransmission (such as in succinic semialdehyde dehydrogenase deficiency) [3].

An estimated 20 % of the IMEs are amenable to specific therapies correcting molecular elements of their biochemical pathways, which leads to different degrees of clinical improvement [1]. These therapies may not only reduce seizure burden but also positively affect development, the degree of encephalopathy, and other neurological deficits [4]. An important aspect concerning many of their therapies is that they should be introduced in a limited time window to maximize clinical effectiveness [5]. Hence, it is imperative that healthcare providers

Abbreviations: AADC, Aromatic L-amino acid decarboxylase; AAV, Adenovirus-associated vector; AGAT, Arginine:glycine amidinotransferase; ARG1, Recombinant arginase 1; ASLD, Argininosuccinate lyase deficiency; ASSD, Argininosuccinate synthetase deficiency; ATP, Adenosine triphosphate; BH4, Tetrahydrobiopterin; CAD, Carbamoyl phosphate synthetase, aspartate transcarbamylase, dihydroorotase; CLN2, Ceroid lipofuscinosis type 2; cPMP, Cyclic pyranopterin monophosphate; CPS1D, Carbamoyl phosphate synthetase 1 deficiency; CSF, Cerebrospinal fluid; CoA, Coenzyme A; ERT, Enzyme replacement therapy; GAMT, N-methyltransferase; Glut-1, Glucose transporter type I; IESS, Infantile epileptic spasms syndrome; IMD, Inherited metabolic disorder; IME, Inherited metabolic epilepsy; MOCOD, Molybdenum Cofactor Deficiency; NAGSD, N-acetylglutamate synthetase deficiency; NMDA, N-methyl-D-aspartate; OCTD, Ornithine transcarbamylase deficiency; PAL, Phenylalanine ammonia-lyase; PKU, Phenylketonuria; P5P, Pyridoxal-5-phosphate; PLPBP, Pyridoxal 5′-phosphate binding protein; PNPO, Pyridoxamine-5′-phosphate oxidase; PROSC, Proline synthesis co-transcribed; TPP1, Tripeptidyl peptidase 1; UCDs, Urea cycle disorders.

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diagnose and manage them promptly and as early as possible. This review provides an overview of the IMEs with established disorder-specific treatments proven beneficial for reducing seizure intensity and ameliorating neurodevelopmental outcomes (Table 1). The disorders are presented according to their pathomechanism-related group, and the treatment modalities described correspond with the different pathomechanistic defects. Some are simple, accessible, and affordable, such as disorder-specific diets and vitamins, and some are complex and costly, such as specific synthetic agents and gene-based therapies.

2. Small molecule disorders

2.1. Glutaric aciduria type I

Caused by a deficiency of glutaryl-CoA dehydrogenase, glutaric aciduria type I commonly presents in the early childhood years, with dystonia derived from striatal injury that occurs following metabolic decompensation, usually associated with acute childhood illnesses. Seizures are not the salient symptom of this disorder but can be seen in addition to dystonia and encephalopathy [6]. Early diagnosis of the disease via screening and treatment with a lysine-reduced diet and supplementation of carnitine and riboflavin may prevent irreversible striatal injury [6].

2.2. Phenylketonuria and 6-pyruvoyl-tetrahydropterin synthase deficiency

Phenylketonuria (PKU), a condition screened by most neonatal screening programs worldwide, is primarily caused by the deficiency of phenylalanine hydroxylase activity and secondarily by the deficiency of the cofactor tetrahydrobiopterin (BH4). Untreated, it results in neurotoxicity precipitated by phenylalanine accumulation [7], presenting clinically with progressive encephalopathy and different seizure types. Individuals with PKU for whom there is early initiation of a modified low-phenylalanine, low-protein diet, and tyrosine supplementation may develop normally and be seizure-free. Sepiapterin may be offered to patients with BH4-responsive PKU [8]. Notably, reduction of phenylalanine levels may also be achieved by the nonmammalian enzyme phenylalanine ammonia-lyase (PAL), which converts phenylalanine to transcinnamic acid, a harmless compound, or by pegvaliase, which prevents the breakdown of the enzyme [9].

2.3. Serine synthesis defects

Serine is a nonessential amino crucial for neurotransmitter (e.g., glycine) and myelin formation, and serves as a precursor for many other metabolic compounds and pathways [10]. Defects in its biosynthesis or transport lead to variable degrees of encephalopathy, the most severe including epilepsies such as infantile epileptic spasms syndrome (IESS), progressing later into Lennox-Gastaut syndrome. Administering L-serine to individuals with these disorders (predominately those caused by biosynthesis defects), including in-utero exposure to pregnant women with the benefit of a prenatal diagnosis, has been shown to prevent or improve neurodevelopmental symptoms and seizures [11].

2.4. Glycine encephalopathy

Glycine is a neurotransmitter with inhibitory properties in the brainstem and excitatory properties in the cortex. Glycine encephalopathy is caused by various pathomechanisms resulting in the cerebral accumulation of glycine. The most commonly identified are defects in the multienzyme complex amenable for glycine cleavage, but pathogenic variants in genes not relating to glycine cleavage such as *LIAS*, *GLYT1*, *LYT2*, *BOLA3*, and *GLRX5,* have also been implicated [12,13]. Most individuals with glycine encephalopathy present in the first days of life with lethargy, breathing problems, and seizures, which lie on the myoclonic-spasms spectrum [14], part of an early infantile developmental epileptic encephalopathy that may later evolve into IESS and Lennox-Gastaut syndromes [14]. The disorder may also present in milder forms at later ages. A disorder-remitting treatment for glycine encephalopathy is currently unavailable. However, early treatment with the N-methyl-D-aspartate (NMDA) antagonist dextromethorphan and benzoate, which reduce serum glycine levels, has proven to improve seizure control and ameliorate developmental decline. If benzoate is given, carnitine is also recommended to replenish its benzoate-related depletion. Notably, the antiseizure medication valproic acid should not be given to individuals with glycine encephalopathy as it can facilitate further hyperglycinemia.

Table 1
The presently treatable inherited metabolic epilepsies.

Disorder Group	Disorder	Therapeutic method	Treatment
Small molecule disorders	Glutaric aciduria type I	Dietary; organic compounds	Low protein diet; carnitine supplementation; lysine restriction
	Phenylketonuria	Dietary; nonmammalian enzyme	Phenylalanine-restricted diet; phenylalanine ammonia-lyase or pegvaliase
	6-pyruvoyl-tetrahydropterin synthase deficiency	Pharmacologic organic compounds	Sepiapterin
	Serine synthesis defects	Amino acids	L-serine
	Glycine encephalopathy	Pharmacologic organic compounds; synthetic compounds	Sodium benzoate; NMDA receptor antagonists (dextromethorphan)
	Urea cycle disorders	Pharmacologic organic compounds	Arginine or citrulline Sodium phenylbutyrate; sodium benzoate; glycerol phenylbutyrate
Large molecule disorders	CAD deficiency	Pyrimidine	Uridine supplementation
	CLN2 disease	Enzyme replacement therapy	Cerliponase alfa
Disorders of Energy Production	Creatine synthesis defects	Pharmacologic organic compounds; dietary	Creatine, sodium benzoate, ornithine, and dietary arginine restriction
	Glut-1 transporter defects	Dietary	Ketogenic diet
Vitamin and trace mineral related disorders	Biotinidase deficiency	Vitamins	Biotin
	Molybdenum cofactor deficiency type A	Pharmacologic organic compounds	Fosdenopterin (cyclic pyranopterin monophosphate)
	Pyridoxine dependent epilepsy	Vitamins	Pyridoxine
	PNPO deficiency	Vitamins	Pyridoxal-5-phosphate
	Cerebral folate deficiency	Vitamins	dl-folinic acid, levo-folinic acid, or levo-5-methyl-tetrahydrofolate

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.

2.5. Urea cycle disorders

Urea cycle disorders (UCDs) result from partial or complete deficiencies of a collection of enzymes accountable for nitrogen removal. The manifestations of these disorders, including seizures, are hyperammonemia-related. Treatment of acute hyperammonemia consists of nitrogen-scavenging agents such as sodium benzoate, sodium phenylacetate, sodium phenylbutyrate, and glycerol phenylbutyrate. Hemo- or peritoneal dialysis can be performed in refractory cases. L-arginine and L-citrulline (its precursor) are also important since L-arginine synthesis is insufficient in all of these disorders apart from arginase 1 (ARG1) deficiency [15]. The chronic treatment approach for urea cycle disorders comprises a low-protein diet and urea cycle intermediate supplementation [15]. Uncontrolled cases have also been treated by liver transplantation [16]. Currently, the newborn screening programs of only a selected number of countries include the proximal urea cycle disorders [the most common UCD- ornithine transcarbamylase deficiency (OTCD), carbamoyl phosphate synthetase 1 deficiency (CPS1D), and N-acetylglutamate synthetase deficiency (NAGSD)] and even fewer countries screen neonates for the distal UCDs [argininosuccinate synthetase deficiency (ASSD) and argininosuccinate lyase deficiency (ASLD)]. If any of these conditions are diagnosed in a pre-symptomatic state, their chronic treatment should be initiated.

3. Large molecule disorders

3.1. Carbamoyl phosphate synthetase, aspartate transcarbamylase, and dihydroorotase (CAD) deficiency

The trifunctional protein acronymized as CAD has an essential role in the catalysis of the first three out of the six steps involved in pyrimidine synthesis. Patients may present in the first year of life with generalized seizures and epileptic encephalopathy, in addition to anisopoikilocytosis and anemia. Treatment with uridine, a pyrimidine, leads to a reduction in seizures and improvement of the other developmental and hematological symptoms [17].

3.2. Ceroid lipofuscinosis 2 (CLN2 disease, or tripeptidyl-peptidase 1 deficiency)

Ceroid lipofuscinosis 2 (CLN2) is a lysosomal storage disease ensuing from pathogenic variants in the *TPP1* gene, which encodes for the tripeptidyl peptidase 1 enzyme. Clinical presentation typically occurs between two to four years of age and consists of refractory myoclonic seizures, retinopathy, and neurodevelopmental decline. A recombinant human TPP1 proto-enzyme, cerliponase alfa, administered intraventricularly, has proven to stabilize the protean manifestations of this disorder [18].

4. Disorders of energy production

4.1. Creatine synthesis defects

Creatine is an essential component of adenosine triphosphate (ATP) regeneration and energy production. A lack of creatine can be caused by either a deficiency of one of two enzymes responsible for its formation-arginine:glycine amidinotransferase (AGAT) and N-methyltransferase (GAMT), or defects in the transporter accountable for its intracellular transfer, caused by pathogenic variants in the *SLC6A8* gene [19]. Regardless of the cause, a shortage of creatine may lead to all seizure types and encephalopathy that typically progresses during childhood. While defects of the creatine transporter are less responsive to creatine treatment, the provision of creative, along with sodium benzoate, ornithine, and dietary arginine restriction, has been shown to improve developmental trajectories and reduce seizures [20].

4.2. Glut-1 transporter defects

Deficiency or loss of function of Glut-1 results in decreased cerebral glucose availability. Depending on the degree to which transporter function is lost, seizures may develop in the neonatal period to later stages in life. Seizure types are varied and may be atypical absence seizures as well as generalized, focal, myoclonic, and astatic seizures. Other prominent manifestations include hypotonia, developmental delays, head bobbing, and characteristic horizontal roving eye movements [21]. The disorder is classically diagnosed by demonstrating cerebrospinal fluid (CSF)-to-blood glucose ratio lower than 0.4 (and typically an absolute CSF glucose lower than 40 mg/dL) via a lumbar puncture performed after 4–6 h of fasting. Diagnostic confirmation can be achieved in most cases by genetic tests indicating pathogenic variants in the *SLC2A1* gene [22]. Ketogenic diet is the primary treatment modality for Glut-1 deficiency. It works by replenishing cerebral energy, and this has proven to be significantly beneficial for eliminating seizures and arresting the developmental and neurological decline associated with the disorder [23].

5. Vitamin, trace minerals, and neurotransmitter-related disorders

5.1. Biotinidase deficiency

Biotinidase deficiency is included as part of an expanded newborn screen implemented by selected countries worldwide. Undiagnosed cases typically present in the first six months of life. Seizures, which occur in more than 50 % of patients, are the first presenting manifestation in 40 % of cases, the others being developmental delay, hypotonia, and dermatological manifestations such as dermatitis and alopecia [24]. Later, optic atrophy, sensorineural hearing loss, and ataxia may ensue [25]. Seizure types range from generalized, focal, and epileptic spasms, and the EEG will commonly show burst suppression, poorly established awake and sleep features, and frequent epileptiform patterns [25]. The signs and symptoms of biotinidase deficiency can be successfully managed or avoided by treatment with biotin, although once established, sensorineural hearing or vision loss persist [26].

5.2. Cerebral folate deficiency

Reductions in cerebral folate can result from primary causes such as a pathogenic sequence variant in the folate transporter gene *FOLR1* or secondarily due to the inability to absorb folate for various systemic and metabolic reasons [27]. Irrespective of the pathomechanism, a deficiency of cerebral folate leads to progressive encephalopathy with intractable seizures. The mainstay treatment is a high dose of dl-folinic acid, levo-folinic acid, or levo-5-methyl-tetrahydrofolate. Treatment can improve neurodevelopmental outcomes and seizures. Yet, the correct subtype-specific folate form is crucial for clinical efficacy, and depending on the cause of a secondary cerebral folate deficiency, other treatment measures may be necessary [28–30].

5.3. Molybdenum cofactor deficiency (MOCOD) and sulfite oxidase deficiency

Molybdenum Cofactor is a necessary component of three enzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Its deficiency can be caused by pathogenic sequence variants in *MOCS1, MOCS2,* or *MOCS3*, all of which are crucial for its biosynthesis [31]. The deficiency of sulfite oxidase is derived from pathogenic variants in *SUOX* [32].

Presentation of both disorders typically occurs in the neonatal period or early infancy and consists of drug-resistant myoclonic and focal seizures, diffuse encephalopathy, and findings that may mimic those of hypoxic-ischemic encephalopathy. Other systemic manifestations, such

as lens dislocation and hepatopathy, may also develop [33]. Diagnostic distinction between these disorders is possible, as urinary purines and pyrimidines (xanthine and hypoxanthine) are increased only in MOCOD. Treatment for the underlying metabolic defect of sulfite oxidase deficiency is not available. However, early-initiated treatment of MOCOD type A caused by pathogenic *MOCS1* variants with Fosdenopterin [cyclic pyranopterin monophosphate (cPMP)] was reported to restore the activity of the deficient molybdenum cofactor-dependent enzyme and lead to seizure reduction and neurodevelopmental gains [34].

5.4. Pyridoxine dependent epilepsy

Pyridoxine dependency represents a collection of disorders including the most known *ALDH7A1* (antiquitin) deficiency [35], but also pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency [36], proline synthesis co-transcribed (PROSC) gene or pyridoxal 5′-phosphate binding protein (PLPBP) deficiency [37], and congenital hypophosphatasia [38]. Patients affected by any of these conditions may present early as the neonatal period with intractable myoclonic, generalized, and focal seizures, as well as epileptic spasms. The seizures of individuals with antiquitin deficiency may respond to pyridoxine, and improvement of other encephalopathy-related symptoms coincides with the timing of treatment initiation [39,40]. Recent evidence also supports the clinical utility of early-initiated lysine-restricted diet therapy to improve neurodevelopmental outcomes [41]. PNPO deficiency, which may have a partial or lack of response to pyridoxine, is treated with pyridoxal-5-phosphate (P5P) [42].

5.5. Aromatic L-amino acid decarboxylase (AADC) deficiency

Deficiency of aromatic L-amino acid decarboxylase (AADC) leads to decreased synthesis of dopamine and serotonin, two of the most important neurotransmitters. Their reduction or absence is manifested by significant extrapyramidal symptoms, including dystonia, oculogyric crises, and hypotonia, as well as cognitive, mood, and autonomic signs. Seizures are reported in a minority of affected patients, and at times, the extrapyramidal symptoms are misinterpreted as seizures. This pediatric neurotransmitter-related disorder is included here, however, due to its novel targeted therapy of intraparenchymal gene replacement. Adeno-associated virus vector (AAV)-based gene therapy administered directly into the putamen or substantia nigra has demonstrated safety and efficacy in normalizing AADC activity and affecting clinical responsiveness [43,44].

6. Conclusions

Despite the rarity of individual treatable inherited metabolic epilepsies, their combined prevalence serves as a significant challenge for clinicians, including epileptologists. Prompt diagnosis of these unique disorders is critical since early initiation of their targeted therapies may significantly reduce seizure burden and improve neurodevelopmental outcomes. However, seizures of individuals affected by these disorders are often indistinct, and not all of them are included in neonatal screening programs. Hence, clinicians should be cognizant of their specific clinical characteristics and have a high level of suspicion for a metabolic-related pathomechanism for seizures for which the etiology is otherwise unexplained. In this review, we highlight those inherited metabolic epilepsies for which targeted therapies have been indispensable to yield clinical benefits for epilepsy and neurodevelopmental disorder independent of traditional antiseizure medicines. These disorder-specific treatments range from simple and affordable therapies to complex targeted gene-based interventions. While only selected inherited metabolic epilepsies are currently treatable, there are ongoing efforts to expand treatment options of others. These efforts include revamping dietary, cofactor, and vitamin-based therapies, developing novel pharmaceutical agents aimed at stabilizing flawed biochemical pathways, and targeted gene editing and replacement that offer burgeoning opportunities for transformational therapies.

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Itay Tokatly Latzer: Writing – review & editing, Writing – original draft, Conceptualization. **Phillip L. Pearl:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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