Inherited metabolic diseases are common in highly consanguineous populations. They present with a wide range of neurological symptoms, including developmental delays/regression, seizures, acute encephalopathy, hypotonia, neuropsychiatric features, and movement disorders. Epilepsy is common in inherited metabolic diseases. It can present across one's lifespan and constitutes an immense challenge because it is usually refractory to the commonly used antiepileptic medications and impairs the quality of life of such patients. Some of these inherited metabolic diseases, such as vitamin-responsive epilepsies and other metabolic epilepsies, are amenable to specific treatments based on vitamin and cofactor supplementation or diet. Their clinical phenotypes, electroencephalographic (EEG) features, and magnetic resonance imaging (MRI) findings are mostly non-specific, but certain important clues can be obtained. Early diagnosis of an underlying treatable inherited metabolic disease as a cause of epilepsy is crucial since many will require specific management beyond common anti-seizure drugs, either to control seizures or to decrease the risk of brain injury. In this review, we discuss inherited metabolic disorders associated with epilepsy, where early diagnosis and treatment will significantly improve the outcome.

Pathophysiology of epilepsy in inherited metabolic diseases. The mechanisms of seizure generation in inherited metabolic disorders are diverse. They include accumulation of toxic metabolites (e.g., sulfocysteine), cofactor deficiency (e.g., vitamin B6), energy deficiency (e.g., glucose transporter 1/GLUT1), substrate deficiency (e.g., serine biosynthesis deficiency), brain dysgenesis (e.g., pyruvate dehydrogenase deficiency), impaired neuronal function (e.g., storage disorder), disturbance of neurotransmitter systems (e.g., glutamate transaminase deficiency), impaired metabolism and transport (e.g., Menkes disease). Thus, a large proportion of inherited metabolic disorders can present with seizures, either during acute decompensation of the primary metabolic disorder or as a part of the complex phenotype of the inherited metabolic disorder.
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Common treatable inherited metabolic epilepsies. The common treatable inherited metabolic epilepsies are outlined in Table 1.

**Pyridoxine-dependent epilepsy (PDE).** PDE is inherited in an autosomal recessive pattern, and characterized by early-onset seizures refractory to antiseizure medications but responsive to pyridoxine (vitamin B6) supplementation. A variant causes it in the ALDH7A1 gene, which encodes alpha-aminoadipic semialdehyde dehydrogenase, also known as antiquitin, in the cerebral lysine degradation pathway. This leads to the accumulation of toxic metabolites in the central nervous system (alpha-aminoadipic semialdehyde, delta-1-piperideine-6-carboxylate, and pipecolic acid).10,11 Typically, seizures start in the neonatal period or the first few months of life. Multiple types of seizures can be observed, including tonic, partial, myoclonic, and prolonged episodes of status epilepticus. Infantile spasms and tonic seizures may also occur. EEG does not show any notable changes specific to the PDE. It may show diffuse slowing, multifocal discharges, or even burst suppression patterns. Several imaging abnormalities have been reported, such as thinning of the corpus callosum or intracerebral hemorrhage.

Biochemical testing reveals elevated alpha-aminoadipic semialdehyde acid and pipecolic acid in body fluids, but both are non-specific. Molecular genetic testing of the ALDH7A1 gene is essential to confirm the diagnosis. More recently, mutations in PLPBP, a gene encoding a PLP-binding protein, have been reported as a novel finding in a minority of PDE.

Atypical features include late-onset (after the first year of life), prolonged seizure freedom despite being off pyridoxine, and seizures that initially respond to antiepileptic drugs but later become intractable. Affected individuals require life-long supplementation of pyridoxine (20–30 mg/kg/day) divided into 2 doses with a maximum of 500 mg/day as higher doses may cause peripheral neuropathy. Dosage should be doubled during febrile illnesses. Treatment with pyridoxine must be combined with L-arginine or

| Table 1 - Common inherited treatable metabolic epilepsies. |
|-----------------------------------------------------------|
| **IEM** | Genetic causes | Treatments |
|-----------------------------------------------------------|
| Pyridoxine dependent epilepsy | ALDH7A1 | Pyridoxine +/- folinic acid |
| PROSC | Arginine, Lysine restricted diet |
| Pyridox(am)ine 50 -Phosphate oxidase (PNPO) Deficiency | PNPO | PLP +/- Pyridoxine |
| Biotinidase deficiency | BTD | Biotin |
| Glucose transporter 1 deficiency syndrome | SLC2A1 | Ketogenic diet |
| Biotin-thiamine-responsive basal ganglia disease | SLC19A3 | Biotin, Thiamine |
| Serine biosynthesis defects | PHGDH, PSAT1, PSPH | Serine + Glycine |
| Molybdenum cofactor deficiency type - A | MOCS1 | cyclic pyranopterin monophosphate |
| Cobalamin C deficiency | MMACHC | cobalamin, betaine |
| Cerebral folate deficiency | FOLR1 | Folinic acid |
| Creatine deficiency syndromes | GAMT | Creatine, arginine-restricted diet, ornithine |
| | GATM | creatine monohydrate |
| | SLC6A8 | creatine monohydrate |
| Pyruvate dehydrogenase deficiency | PDHA1 | Ketogenic diet |
| | PDHB, DLAT, PDHX, PDP1 | |
| DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome | KCNJ11 | sulfonylurea |
| Hyperinsulinism-Hyperammonemia syndrome | GLUD1 | Diazoxide + protein restriction |
| Tetrahydrobiopterin deficiency (BH4) | | |
| FPHS deficiency | PTS | BH4, L-dopa, 5-HTP |
| DHPR deficiency | QDPR | Low phenylalanine diet, Folinic acid, L-dopa, 5-HTP |
| GTPCH deficiency | GCH1 | |
| PCD | PCBD1 | L-Dopa, 5-HTP |
| SPR deficiency | SPR | |
lysine restriction diet to improve neurological outcomes. Arginine supplementation and a lysine-restricted diet could decrease lysine influx into the central nervous system and subsequently reduce the levels of these toxic intermediates.\textsuperscript{10,11}

**Folinic acid-responsive epilepsy.** Folinic acid-responsive seizures are allelic to PDE and have similar biochemical markers. Starting PDE patients on folinic acid at doses of 3–5 mg/kg/day could have clinical value in improving patients’ conditions.\textsuperscript{12}

**Pyridox(am)ine 50′-phosphate oxidase (PNPO) deficiency.** It is a rare autosomal recessive disorder caused by mutations in the PNPO gene, which leads to PNPO deficiency. This enzyme is essential for converting pyridoxine-5-phosphate and pyridoxamine-5-phosphate into pyridoxal-5′-phosphate (PLP), which is the active form of pyridoxine.\textsuperscript{13} Typically, it is present in the neonatal period with refractory epilepsy similar to PDE, but it shows no or partial response to pyridoxine. Neonates have a wide range of non-neurological manifestations, such as prematurity, failure to thrive, hypoglycemia, lactic acidosis, and normocytic anemia. PNPO deficiency requires lifelong treatment with PLP 20–70 mg/kg/day divided into four doses.\textsuperscript{13}

**Biotinidase deficiency.** It is an autosomal recessive disorder caused by mutations in the BTD gene. Biotinidase is essential for recycling biotin, necessary for biotin-dependent carboxylases to break down fats, proteins, and carbohydrates.

Biotinidase deficiency could be profound when biotinidase activity is reduced to less than 10% of the normal levels, or partial deficiency when biotinidase activity decreases to 10–30% of the normal. Without sufficient biotinidase, biotin cannot be recycled, which

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**Table 2** - Main clinical, EEG, and MRI findings suggesting inherited metabolic epilepsies.

| Features                                                                 |
|--------------------------------------------------------------------------|
| Onset | Early: neonatal, infancy or early childhood |
| Seizure types | Myoclonic, tonic, infantile spasms |
| | Seizures worsening with fasting (GLUT1) or high protein meals (urea cycle defects) |
| | Progressive myoclonic epilepsy phenotype |
| | Seizures refractory to anti-epileptic drugs |
| | Seizures worsening with anti-epileptic drugs |
| Neurological features | Developmental delay/regression |
| | Movement disorders |
| | Fluctuating course of illness |
| Systemic symptoms | Dysmorphic features |
| | Organomegaly |
| | Ophthalmological abnormalities (cataracts, retinitis pigmentosa, cherry red spot, optic nerve atrophy) |
| Family history | Parental consanguinity |
| | Metabolic or unexplained neurological disorder |
| EEG | Burst-suppression, multifocal spike discharges, hysparrhythmia |
| | Comb-like rhythm (maple syrup urine disease) |
| MRI/MRS | Normal/non-specific abnormalities |
| | Corpus callosum dysgenesis (pyruvate dehydrogenase deficiency) |
| | Abnormal MRS in cerebral creatine deficiency or GABA transaminase deficiency |

**Table 3** - Suggested biochemical and genetic testing in early refractory seizures.

| Source | Diagnostic test |
|--------|-----------------|
| Blood | Blood glucose, electrolytes, creatine, ammonia, lactic acid, uric acid, copper, ceruloplasmin, homocysteine, biotinidase assay, VLCFA, transferrin isoelectric focusing, serum amino acids |
| Urine | alpha-aminoadipic semialdehyde acid, pipecolic acid, thiosulfate, xanthine, hypoxanthine, organic acids, guanidinoacetate, creatine, creatinine. |
| CSF | Glucose, lactate, pyruvate, neurotransmitters |
| Genetic testing | Array CGH, next generation sequencing (epilepsy panel, Whole exome sequencing) |
| | VLCFA - very long chain fatty acid |
leads to the accumulation of toxic compounds in the body.\textsuperscript{16}

It can present with various neurological symptoms, including hypotonia, seizures, alopecia, skin rash, visual impairment, and hearing loss. Multiple types of seizures were observed, including tonic, myoclonic, and spasms. EEG is nonspecific. The MRI shows diffuse or patchy signal abnormalities within the cerebral and cerebellar white matter, basal ganglia edema, and global atrophy.

Biotinidase deficiency responds to oral biotin 10–20 mg daily, resolving most of the symptoms, although hearing loss and visual impairment could persist. Screening for biotinidase deficiency is included in the national screening program in Saudi Arabia.\textsuperscript{14,15}

**Glut-1 deficiency.** Glut-1 deficiency is a treatable disorder caused by impaired glucose uptake at the blood-brain barrier. It is caused by the SLC2A1 gene variant, which is essential in synthesizing glucose transporter protein type 1, which affects the glucose transport across the blood-brain barrier, resulting in low cerebrospinal fluid glucose concentration.\textsuperscript{16}

The phenotypes are variable. Typically, patients present with an early onset refractory epilepsy, developmental delay, and progressive microcephaly. SLC2A1 causes multiple seizure phenotypes, including focal seizures, generalized seizures, and infantile spasms, usually associated with irregular eye movements. Other types of epilepsy can be observed, including myoclonic-astatic epilepsy, benign myoclonic epilepsy of infancy, and absence epilepsy. Unusual presentations include late-onset epilepsy and movement disorders.

The biochemical marker of Glut-1 deficiency is low cerebrospinal fluid glucose level (<40 mg/dL), cerebrospinal fluid glucose to blood glucose ratio < 0.4, and low cerebrospinal fluid lactate level.

Prognosis is excellent should early diagnosis is established, and a ketogenic diet is started timely. Certain medications could compete with glucose at GLUT1 and worsen symptoms such as phenobarbital and valproic acid, and it is better to be avoided.\textsuperscript{15,16}

**Biotin-thiamine-responsive basal ganglia disease.** It is an autosomal recessive disease caused by a variant of the SLC19A3 gene, which encodes hTHTR2, a second thiamine transporter. Typically, patients present with subacute encephalopathy, ataxia, opthalmoplegia, extrapyramidal symptoms, and seizures. The phenotype was broadened to include early-onset Leigh-like syndrome, Wernicke-like encephalopathy, and infantile spasms. The brain MRI typically shows bilateral symmetric swelling in the caudate nucleus, putamen, and thalamus during the acute episode. Atrophy, necrosis and gliosis are observed at follow-up. Diagnosis is confirmed by sequencing the SLC19A3 gene.\textsuperscript{17}

Once the diagnosis is suspected, initiate biotin (5 mg/kg/day) and thiamine (up to 1200 mg/day) supplementation as early as possible. Symptoms typically resolve within 2-7 days.\textsuperscript{17}

**Serine biosynthesis defects.** Serine biosynthesis defects result from deficiencies in the 3-phosphoglycerate dehydrogenase, phosphoserine aminotransferase, and phosphoserine phosphatase. Phenotypic presentations range from severe, lethal multiple congenital anomalies (Neu-Laxova syndrome) to milder phenotypes with an intellectual disability or refractory absence seizures in older children.\textsuperscript{15,18} An intermediate form exists wherein patients present with congenital microcephaly and refractory epilepsy in infancy. Early use of serine (400–600 mg/kg/day) and glycine (200–300 mg/kg/day) improves seizure control and psychomotor outcomes.\textsuperscript{18}

**Molybdenum cofactor deficiency type -A (MOCOD).** It is an autosomal recessive inherited disorder caused by mutations in the MOCS1 gene. Affected babies are normal at birth and develop refractory seizures and progressive encephalopathy in the first few weeks. MRI changes resemble those seen in hypoxic-ischemic injuries with cystic encephalomalacia.\textsuperscript{15,19}

The MOCOD phenotypically and radiologically resembles sulfite oxidase deficiency. Biochemically, both show elevated urinary thiosulfate levels, but MOCOD also presents elevated urinary xanthine, hypoxanthine, and low serum uric acid levels. Early treatment with cyclic pyranopterin monophosphate improves patient outcomes.\textsuperscript{19}

**Cobalamin C deficiency.** It is an inherited defect in the MMACHC gene, which results in the dietary vitamin B12 not being converted to the active forms, methylcobalamin, and adenosylcobalamin. This results in the accumulation of methylmalonic acid and homocysteine and decreases methionine synthesis. Symptoms could start at any age. In the early onset, neurological symptoms begin in the 1st year of life with seizures, encephalopathy, hypotonia, and microcephaly. Hematologic, ocular, renal, hepatic, and cardiac symptoms are common. Initiating early treatment with vitamin B12 and betaine will improve outcomes.\textsuperscript{15,20}

**Cerebral folate deficiency.** Cerebral folate deficiency is characterized by low levels of 5-methyltetrahydrofolate in the CSF despite normal folate levels in the plasma and red blood cells. This occurs secondary to FOLR1 gene mutations, autoantibodies against the folate receptor-alpha protein, or other conditions such as Rett syndrome and mitochondrial disorders.\textsuperscript{15,21}
Symptoms typically start in infancy with hypotonia, progressive microcephaly, choreathetoid movements, and seizures. High-dose folinic acid treatment (1–5 mg/kg/day) ameliorates the neurological symptoms.21

**Creatine deficiency syndromes.** It is an inborn error of creatine metabolism which interrupts the synthesis or transportation of creatine, which is essential for sustaining the high energy levels required for muscle and brain development. There are three forms of 2 autosomal recessive biosynthesis defects: guanidoacetate methyltransferase deficiency (GAMT) and arginine: glycine amidinotransferase deficiency (AGAT) and an X-linked creatine transporter deficiency (CTD).15,22 Symptoms include developmental delay, intellectual disability, hypotonia, autistic symptoms, movement disorders, and seizures.

The MR spectroscopy shows depletion of the cerebral creatine in all individuals with GAMT and AGAT deficiency and men with CTD. Biochemical screening is performed by measuring guanidoacetate, creatine, and creatinine in urine and plasma. Diagnosis is confirmed by molecular testing of the 3 genes involved (GAMT, GATM, and SLC6A8). Treatment of patients with AGAT or GAMT deficiency is based on supplementation of creatine monohydrate (350–2000 mg/kg/day). Children with GAMT need to also be placed on an arginine-restricted diet to reduce high levels of neurotoxic guanidoacetate, and also started on ornithine. However, children with CTD are less responsive to therapy.22

The **DEND syndrome (developmental delay, epilepsy, and neonatal diabetes).** DEND syndrome is a rare inherited disorder caused by mutations in the ATP-sensitive potassium channel (KATP channel) subunits, which leads to the inhibition of KATP pathway-dependent insulin release in pancreatic cells and inhibition of neurotransmitter release. Symptoms start early in the neonatal period with neonatal diabetes and dysmorphic features. Neurological features, including hypotonia, developmental delay, and refractory seizures, are common. Different types of seizures can be observed, such as tonic, myoclonic, and infantile spasms. Treatment with oral sulfonylurea blocks the KATP channel restores insulin secretion and improves glycemic control and seizures.23

**“Hyperinsulinism-Hyperammonemia” syndrome.** Hyperinsulinism-hyperammonemia syndrome is a rare inherited condition characterized by excessive insulin secretion, causing repeated episodes of hypoglycemia and abnormal elevation in serum ammonia. It is caused by mutations in the GLUD1 gene, which results in increased activity of the mitochondrial enzyme glutamate dehydrogenase. This leads to increased conversion of glutamate to alpha-ketoglutarate, with subsequent adenosine triphosphate (ATP) generation, leading to KATP-related insulin release and affecting the detoxification of ammonia in the liver. Common neurological symptoms include seizures, behavioral disorders, and developmental delay. Seizures could be secondary to hypoglycemia, but also primarily generalized epilepsy is possible.15,24

Treatment involves starting diazoxide (5–15 mg/kg/day), dietary protein restriction, and intermittent glucagon administration for hypoglycemic crises.24

**Tetrahydrobiopterin (BH4) deficiency.** It is a group of inherited metabolic disorders affecting the biosynthesis and regeneration of BH4, which causes increased serum phenylalanine levels. BH4 is essential for the production of dopamine, epinephrine, norepinephrine, and serotonin. There are 5 main forms of BH4 deficiency, 3 biosynthesis defects; guanosine triphosphate cyclohydrolase I deficiency, 6-pyruvoyl tetrahydrobiopterin synthase (PTPS) deficiency, and sepiapterin reductase (SR) deficiency and 2 regeneration defects; pterin-4-alpha-carbinolamine dehydratase deficiency and dihydropteridine reductase (DHPR) deficiency. PTPS defects are the most common cause. Sepiapterin reductase deficiency is the only one that does not elevate phenylalanine.15,25

Symptoms start in the 1st few months of life with dystonia, abnormal muscle tone, and seizures. Symptoms are progressive, leading to progressive microcephaly, global developmental delay, and intellectual disability. The SR deficiency presents with dystonia, oculogyric crises, and developmental delay mimicking cerebral palsy. The DHPR-related deficiency leads to BH2 accumulation, causing a severe form of the disease and resulting in cerebral folate deficiency and calcifications in the basal ganglia. The neurodevelopmental outcome is correlated with the early initiation of treatment with a low-phenylalanine diet, BH4, L-dopa, and 5-hydroxytryptophan. Starting with carbidopa, monoamine oxidase B, and catechol-O-methyltransferase inhibitors reduce L-dopa’s therapeutic requirements and its peripheral adverse effects.

DHPR deficiency could lead to cerebral folate deficiency; therefore, folinic acid should be administered, and it is better to avoid BH4 since it will augment cerebral folate deficiency.15,25

**Pyruvate dehydrogenase deficiency (PPD).** The PPD is a mitochondrial disorder that affects ATP production and causes the accumulation of lactic acid. It causes progressive neurological symptoms, typically in infancy. Symptoms include abnormal muscle tone,
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developmental delay, abnormal eye movements, and seizures.

Cofactor supplementation with thiamine, carnitine, and lipoic acid stimulates the pyruvate dehydrogenase complex to produce energy. A ketogenic diet (KD) should be started early since it can bypass metabolic defects and control seizures. The KD is effective and safe for controlling seizures during PDD. It should be introduced as early as possible upon diagnosis, as early initiation may prevent further metabolic damage to the brain.  

Succinic semialdehyde dehydrogenase deficiency. It is a rare monogenic disorder caused by a mutation in the ALDH5A1 gene. This will impair the activity of the mitochondrial enzyme succinic semialdehyde dehydrogenase, which will, in turn, affect the GABA metabolism. Clinical manifestations vary significantly and include intellectual disability/developmental delay, autistic symptoms, hypotonia, and seizures. Different types of seizures could be observed, mainly tonic–clonic, atypical absences, and myoclonic seizures. Detection of GABA in urine is a useful screening tool for this disease. A broad spectrum of antiepileptic drugs is required to control seizures, mainly sodium channel blockers, such as lamotrigine and carbamazepine. Other therapies, such as vigabatrin and mTOR inhibitors, are exciting treatment options. Several new therapies are still under investigation, including enzyme replacement therapy, chaperones, read-through drugs, and gene therapy.  

Neuronal ceroid lipofuscinosis type 2. Neuronal ceroid lipofuscinosis type 2 is a rare neurodegenerative lysosomal storage disorder caused by a deficient tripeptidyl peptidase 1 (TPP1) enzyme. It typically manifests between 2 and 4 years of age with seizures, language delay/arrest, and rapid psychomotor regression. Seizures are usually polymorphic, including multiple types of seizures, and resistant to anti-seizures drugs. EEG with low-frequency (1–3 Hz) intermittent photic stimulation shows a characteristic photoparoxysmal response. Diagnosis of neuronal ceroid lipofuscinosis type 2 should be based on genetic testing for mutations in TPP1 and enzyme activity testing of TPP1 protein. Intracerebroventricular administration of cerliponase alfa (rhTPP1 enzyme) stabilizes neuronal ceroid lipofuscinosis type 2 progression, adding this disease to the list of potentially treatable disorders requiring prompt diagnosis.  

Approach to treatable inherited metabolic epilepsies. The presence of any of sign and symptom highlighted in Table 2 should raise suspicion for an underlying metabolic etiology of epilepsy. The expression of the majority of inherited metabolic epilepsies is in the neonatal period or early infancy, although late presentation until adulthood has been reported. Taking a detailed history, paying attention to family history, and performing a thorough clinical examination in all patients presenting with early-onset seizures allows establishing an early diagnosis. Neonates and infants presenting with refractory seizures should be started on pyridoxine, folinic acid, and biotin to avoid therapeutic delay until the biochemical/or genetic workup results for inherited metabolic diseases are available.

The work-up of a patient with a suspected inherited metabolic disease as a cause of epilepsy is based on a combination of EEG, neuroimaging, biochemical and molecular genetic testing (Tables 2 and 3). The presence of specific EEG or brain neuroimaging findings can provide important clues toward the correct diagnosis. EEG helps to clarify the seizure type and type of epileptic encephalopathy. Some inherited metabolic diseases can have characteristic EEG changes, such as the comb-like rhythm seen in patients with maple syrup urine disease. Imaging findings sometimes suggest a particular inherited metabolic disease, as is the case with thiamine-biotin-responsive basal ganglia disease, cerebral creatine deficiency, GABA transaminase deficiency, or molybdenum cofactor deficiency, but more often show non-specific changes (e.g., dysgenesis of the corpus callosum), and normal brain structure and development, which do not exclude an inherited metabolic disease. The laboratory and genetic testing results are outlined in Table 3. Recently, a new LC-MS/MS method, replacing individual metabolite testing assays with a novel “panel-method,” greatly improves the biochemical diagnostic workup of children with early-onset treatable inherited metabolic epilepsies.

Conclusion. A growing number of treatable inherited metabolic disorders associated with epilepsy have been described. Rapid diagnosis and early initiation of appropriate treatment are essential to avoid or minimize irreversible brain damage. Various epilepsy phenotypes can be observed, often refractory to antiepileptic drugs. A high index of suspicion is required to make a diagnosis because the clinical presentation is often non-specific. Early diagnosis and treatment are associated with better outcomes.

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