Metabolic etiologies in West syndrome
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**SUMMARY**

West syndrome (WS) is an early life epileptic encephalopathy associated with infantile spasms, interictal electroencephalography (EEG) abnormalities including high amplitude, disorganized background with multifocal epileptic spikes (hypsarrhythmia), and often neurodevelopmental impairments. Approximately 64% of the patients have structural, metabolic, genetic, or infectious etiologies and, in the rest, the etiology is unknown. Here we review the contribution of etiologies due to various metabolic disorders in the pathology of WS. These may include metabolic errors in organic molecules involved in amino acid and glucose metabolism, fatty acid oxidation, metal metabolism, pyridoxine deficiency or dependency, or acidurias in organelles such as mitochondria and lysosomes. We discuss the biochemical, clinical, and EEG features of these disorders as well as the evidence of how they may be implicated in the pathogenesis and treatment of WS. The early recognition of these etiologies in some cases may permit early interventions that may improve the course of the disease.

**KEY WORDS:** Metabolic disorder, Early onset epileptic encephalopathy, Infantile spasms, Inborn errors of metabolism, Hypsarrhythmia.

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Epileptic encephalopathies are a group of disorders for which epilepsy or epileptic activity plays the main role in disease phenotypes such as severe cognitive and behavioral impairments.\(^1\)-\(^3\) As an early life encephalopathy with an average age of onset of 6 months, West syndrome (WS) is characterized by infantile spasms (IS), hypsarrhythmia, an interictal electroencephalography (EEG) pattern with irregular, high-amplitude slow waves on a chaotic epileptic background, and neurodevelopmental decline; the presence of 2 of these symptoms confirms the diagnosis.\(^4\)-\(^6\) IS is often used to describe the syndrome but can also be used in the literature to describe the characteristic flexion or extension spasms that manifest in this syndrome. More recently, and to also address the patients who have late-onset spasms or continue to have spasms beyond the infantile age, it has been proposed that the term “epileptic spasms” be used when referring to these seizures. In patients with WS, IS disappear over time but are often replaced by various types of seizures. WS may also develop into Lennox-Gastaut syndrome. Many of the infants with IS develop signs of autism spectrum disorders. Indeed, most patients with the disease show poor outcome, with neurodevelopmental or neuropsychiatric symptoms.\(^3,5\)-\(^7\)

The incidence of IS is 2 to 3.5 infants per 10,000 live births, and the majority of affected infants (~64%), have structural, metabolic, infectious, or genetic etiologies, whereas in the remainder, no etiologies can be identified.\(^5,8\)-\(^9\) In a cohort of 251 infants with IS,\(^9\) the breakdown of etiologies, according to the general classification scheme proposed by the International League Against Epilepsy (ILAE),\(^2,10\) included metabolic (4.8%), genetic (14.4%), genetic-structural (10%), structural-congenital (10.8%), structural-acquired (22.4%), and infectious (2%). Genetic examination of 356 trios consisting of parents and probands with IS and Lennox-Gastaut syndrome revealed that 12% of the probands carried de novo genetic alterations.\(^11\)
KEY POINTS

- Disorders with inborn errors of metabolism have been found in approximately 3%-22% of infants with infantile spasms.
- Infantile spasms may be diagnosed in up to 12% of pediatric patients with phenylketonuria.
- Currently, in many cases, diagnosis of infantile spasms may precede the diagnosis of the metabolic disorders.
- Infantile spasms have been associated with numerous metabolic disorders, although the association with many of them can be sporadic.
- Early diagnosis of metabolic disorders may lead to early initiation of appropriate treatment.

However, prognosis is better in infants with IS due to unknown etiology following early treatment compared to those with structural and metabolic etiologies.5,8,12

In this review, we discuss the contribution of metabolic etiologies in the pathology of WS in light of the recent literature. In addition, we describe in vitro and in vivo models of the metabolic disorders included in this review. We have included only articles in English language that were retrieved from PubMed using the search keywords “Infantile Spasms,” “West syndrome,” or “epileptic spasms” to identify relevance to IS. We used keywords “Inborn Errors of Metabolism” or “Metabolic Etiologies” or specific names for each syndrome or gene to retrieve articles on metabolic etiologies of spasms. In our review, we included all etiologies that manifested with IS, recognizing that, for rare diseases, it may be difficult to establish definite causative associations, since these are often based on case reports. Therefore, the level of evidence and strength of association of the various disorders with IS is not the same across these disorders. Articles describing work on both in vivo and in vitro models were accepted for review. Furthermore, separate searches for animal models (“rat” or “mouse” or “mice” or “animal model”) of specific metabolic syndromes were retrieved for review to determine if they produced a phenotype consistent with epilepsy or IS.

Inborn errors of metabolism may include metabolic errors in organic molecules involved in amino acid and glucose metabolism, fatty acid oxidation, metal metabolism, pyridoxine deficiency or dependency, or acidurias in organelles like mitochondria and lysosomes, as well as other rare diseases such as leukodystrophies.13-19 (Table 1). In a Chinese cohort of 60 patients with IS, metabolic disorders were found in 47%, among whom 22% had inborn errors of metabolism.19 In a retrospective study from Saudi Arabia consisting of 80 patients with IS, hereditary neurometabolic disorders were diagnosed in 12.5%, although the high rate of consanguinity (75% among IS patients with metabolic disorders) may have contributed to the high incidence in this population.20 In a larger U.S. cohort (251 infants with IS), metabolic etiologies were identified in 4.8%.9 In the United Kingdom Infantile Spasms Study (UKISS) study, metabolic etiologies were reported in 3.1% of IS patients: 2 newborns with hypoglycemia and 2 infants with pyridoxine dependency or mitochondrial disorder (n = 127 responders).21 The variability in the frequency of such metabolic etiologies may be due partially to the ethnic origin or to the different diagnostic batteries used for detection of such abnormalities. Early diagnosis of certain metabolic etiologies may permit the early initiation of appropriate treatments of WS, which, in certain cases, may ameliorate symptoms or may even lead to the resolution of the disease, such as in phenylketonuria (PKU)22 or cobalamin (vitamin B12) deficiency.23 Such cases emphasize the importance of genetic or metabolic screening of newborns when they are suspected to have metabolic diseases.17-19,24,25

DEFICIENCIES IN AMINO ACID METABOLISM

Phenylketonuria and related disorders

Phenylketonuria (or PKU) is the most prevalent inborn error of metabolism, which is caused by autosomal recessive mutations in the phenylalanine hydroxylase (PAH) gene leading to mental retardation, seizures, and motor deficits if left untreated.26-28 PAH mutations result in defect(s) in oxidation of phenylalanine (Phe) to tyrosine, a precursor of the catecholamines dopamine, norepinephrine, and epinephrine. Excess Phe metabolites inhibit dihydroxyphenylalanine (DOPA) decarboxylase, 5-hydroxytryptophan decarboxylase, and glutamic acid decarboxylase (GAD), and interfere with myelin formation.29,30 Increased Phe levels can be toxic to the brain, and untreated individuals develop irreversible mental dysfunction. A simple blood test can determine Phe levels and therefore PKU diagnosis.31 Although dietary restriction of Phe is the most common treatment for PKU and should be started immediately after its diagnosis, tetrahydrobiopterin (BH4) in mild cases and large neutral amino acids mainly for adult PKU cases are alternative therapies, although they are not as potent as dietary restriction; for review.27,28,32

In an adult population of 3,714 individuals with PKU, the prevalence of epilepsy was 5.2%.33 However, in a comprehensive retrospective study from China evaluating 503 PKU patients that included pediatric patients, seizures were found in 107 PKU patients (21.3%).62 of them (12.3%) had WS with typical (76%) or modified (24%) hypersrrhythmic pattern recognized on EEG.22 Of interest, 82% of those patients manifested WS before PKU diagnosis could have been established. A positive correlation was present between the age of dietary restriction initiation and incidence of WS in...
patients, indicating that early diagnosis and treatment could prevent the evolution of WS. Supporting this, 5 patients receiving combined treatment showed amelioration in myelination on their follow-up magnetic resonance imaging (MRI). Other studies also reported PKU patients presenting with hypsarrhythmic EEG and/or IS.

Another but rare cause of PKU is dihydropteridine reductase (DHPR) deficiency, where decreased or no enzyme activity leads to abnormalities in BH4 generation. DHPR deficiency has been associated with autosomal recessive guanosine triphosphate cyclohydrolase I (GCH1), DHPR, or 6-pyruvoyl tetrahydropterin synthase (PTPS) gene deficits. BH4 is a cofactor of PAH and therefore deficiency of BH4 may lead to elevated Phe, despite normal PAH levels. In such cases, dietary Phe restriction may not suffice to correct the symptoms, and BH4 supplementation is required. BH4 is also involved in the tyrosine and tryptophan hydroxylation, and therefore BH4 deficiency results in reduced norepinephrine, dopamine, and serotonin synthesis, which may further contribute to the neurologic symptoms even if Phe levels are corrected. DHPR deficiency may further reduce the activity of folate. Therefore, the presence of normal PAH levels in patients with elevated Phe or the persistence or progression of neurologic symptoms despite the correction of Phe levels may suggest the need for diagnostic tests for DHPR deficiency. Diagnostic tests may then include DHPR activity levels; analysis of ptetins in urine, blood, or cerebrospinal fluid (CSF); and CSF levels of metabolites of monoamines (homovanilline acid [HVA], 5-hydroxyindoleacetic acid [HIAA]). If DHPR deficiency is documented, consideration of additional specific or supplemental treatments for this disease including BH4, folic acid, or drugs that supplement the monoaminergic deficits should be considered, in addition to Phe dietary restriction.

DHPR deficiency may also lead to IS and hypsarrhythmia, even though this is one of the rare etiologies (Table 2). Phe restriction and neurotransmitter supplement improved a patient’s outcome; however, in a patient with IS, an additional therapy with steroids was needed to control spasms and hypsarrhythmia.

Early neurological sequelae (ie, delayed myelination) may be overlooked depending on the onset of Phe accumulation, since myelination is a continuous process starting from the last days of gestation and reaching through adulthood (for review). The results of the PKU newborn screenings need to be interpreted cautiously, considering that false-positive or, rarely, false-negative results may also be seen.

In vitro and in vivo experimental PKU models have provided significant insights (Table 3). 1-Phe competes both for the glutamate binding region of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, and the glycine-binding site of the N-methyl-d-aspartate (NMDA) receptors in rat neuronal hippocampal cultures, depressing glutamatergic transmission.

| Table 1. Metabolic etiologies in IS |
|------------------------------------|
| **Metabolic errors in organic molecules** |
| Amino acid metabolism |
| Phenylketonuria |
| Glucose metabolism & transport |
| DEND |
| Fatty acid oxidation |
| SCAD deficiency |
| Metal metabolism |
| Menkes disease |
| Vitamin B6-, Pyridoxine dependency, & pyridoxal 5’P deficiency |
| Sulfurylase |
| d-Glyceric Aciduria |
| Homocysteinemia |
| **Metabolic errors in organelles** |
| Mitochondrial disorders |
| PDHC deficiencies |
| Lysosomal storage diseases |
| Hurler syndrome |
| **Other diseases** |
| Leukodystrophies |
| Biotinidase deficiency |
| Molybdenum cofactor deficiency |

CDG, Congenital disorders of glycosylation; (DBP) D-bifunctional protein; DEND, Developmental Delay, Epilepsy, and Neonatal Diabetes; GLUT1, Glucose Transporter 1; PDHC, Pyruvate dehydrogenase complex; SCAD, Short-chain acyl-coenzyme A dehydrogenase enzyme deficiency.
| Metabolic disorder | Mode of inheritance—metabolic or gene defect | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|--------------------|---------------------------------------------|------------------------------------------|----------------|---------------------|------------------------|
| Phenylketonuria (PKU) | AR – PHA26-28 | ↑ Phe22,34,35,37, Mental retardation22,24-36, ↑ Biotin in, ↓ DHR activity41, Hypotonia36,37,41, Developmental delay7,41 | Cerebral atrophy41, Delayed myelination22,41, Lesions in white matter, basal ganglia, cerebellum, brain stem17 | IS with typical or modified hypersrrhythmia has been reported in up to 12% of PKU patients when pediatric population is included22,35,36,41 | Protein restriction: 8/62 cases: trigger IS22, 17/62 cases: effective (with 77.8% relapse)22 |
| Nonketotic hyperglycinemia (NKH) | AR – GLDC, AMT or GCSH52-54,67 | ↑ Glycine,67,68 Mental Retardation,68 Hypotonia,67,68 Abnormal BAEP,66 Abnormal visual responses,66 | Brain atrophy,67 Bilateral subcortical heterotopia,67 Choroid plexus cysts,68 | Case reports with IS, hypsrrhythmia,54,65-68,43 | NTZ & PHT No effect in 2 cases,65 AEDs (unmentioned) No effect in 3 cases67 |
| Glucose metabolism and transport Developmental delay, epilepsy and neonatal diabetes (DEND) | AD - KCNJ177,80-82 | Neonatal Diabetes,77,80-82 Developmental delay77,80-82 | Normal,81 | Case reports of IS & hypsrrhythmia77,80-82 | (1) Insulin, (2) PHB, VGB, PHT, ACT H (3) ACTH and glucocorticosteroids + Sulfonylurea |
Table 2. Continued.

| Metabolic disorder | Mode of inheritance—metabolic or gene defect | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|--------------------|---------------------------------------------|------------------------------------------|-----------------|---------------------|-----------------------|
| Persistent symptomatic hypoglycemia | N/A | Glucose ¹⁰, ²⁰, ³⁴, ³⁸, ⁸⁷, ⁸⁸, ³⁴⁴ | Normal ²⁰, ³⁸, ³⁸, ³⁴⁴ | IS & Typical/modified hypsarrhythmia ²⁰, ³⁸, ³⁸, ³⁴⁴ | 1: No effect, 2: Effect on hypoglycemia, (3) Effect on spasms, (4) continued therapy in 1 case ³⁴⁴ |
| | | Developmental delay ²⁰, ³⁸ | Uni- or bilateral parietooccipital cyst ³⁸, ³⁸ | IS ³⁸ | |
| | | Microcephaly ²⁰ | Abnormal occipital/parietal signal ²⁰, ³⁸ | IS & bilateral epileptic activity ³⁸ | |
| | | Hypotonia ²⁰ | | | |

1: No effect, 2: Effect on hypoglycemia, (3) Effect on spasms, (4) continued therapy in 1 case ³⁴⁴

(1) Diazoxide, chlorothiazide, (2) VGB, ACTH, prednisolone (3) VGB, Lamotrigine
(1) Effect on hypoglycemia, (2) No effect on spasms, (3) controlled seizures in 1 case ³⁴⁴
(1) Diazoxide, (2) VGB, prednisolone (3) VPA, TPR (4) LEV
(1) Effect on hypoglycemia, (2) no effect on spasms (3) reduction in spasms, (4) reduction in seizures in 1 case ³⁸⁷
(1) Diazoxide, chlorothiazide, (2) prednisolone, currently CBZ
(1) Effect on hypoglycemia, (2) reduction in spasms in 1 case ³⁸⁷
(1) Pancreatectomy, (2) ACTH
(1) DM development (2) IS stopped, developmental delay persists in 1 case ³⁸⁷
(1) Pancreatectomy, (2) VGB(1) DM development, (2) N/A ³⁸⁷
VGB
Spasms resolved but focal seizures continued in 1 case, not effective in 1 case ³⁰

3: No effect, 2: Effect on hypoglycemia, (3) Effect on spasms, (4) continued therapy in 1 case ³⁴⁴

(1) Insulin, (2) Pyridoxine, PHB, VGB, TPR, LEV, clobazam, VPA, (3) Sulfonylurea
(1) effective against DM, (2) only transient and partial reduction of the seizures, (3) Effective in 1 case ³⁸⁷
(1) Sulfonylurea
effective in 1 case ³⁸⁷

(1) effective against DM, (2) not effective, (3) effective in 1 case but the patient died after initial amelioration ³⁸⁰

References:
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| Metabolic Errors in West Syndrome | Mode of Inheritance | Main Clinical and Laboratory Abnormalities | Brain Pathology | Association with IS | Treatment Effect on IS |
|----------------------------------|---------------------|------------------------------------------|----------------|-------------------|-----------------------|
| GLUT1 deficiency                 | Deficiency in glucose transporter^{104,106} | ↓ Glucose^{104,111} | Normal^{111,112} | Convulsions, IS^{111} | (1) ACTH, (2) Pyridoxine, biotin folinic acid, (3) Ketogenic diet |
|                                  | SLC2A1 mutation^{112} | ↓ Lactate^{104} | IS-flexion & hypersrrhythmia^{112} | Rare association with IS | 1 & 2: no effect, 3: effect on IS and seizures in 1 case^{111} |
|                                  |                     | ↓ CSF/blood glucose^{104,111,112} | Developmental delay^{111} | IS, with slow and asymmetric background activity with multifocal spikes and slow wave discharges^{115} | Ketogenic diet Effect on seizures, developmental delay persists with slight improvement in 1 case^{112} |
|                                  |                     | Developmental delay^{111} | Abnormal cortical gyri^{117} | IS & hypersrrhythmia^{117} | (1) ACTH, (2) NTZ, TPR, gamma globulin, ZNS (1) partial effect, (2) no effect in 1 case^{117} |
|                                  |                     | ▲ Ethylmalonic acid^{117} | Hypoplastic corpus callosum without splenium and rostrum^{117} | IS, multifocal clonic seizures & Hypersrrhythmia^{123} | (1) Cu-His therapy (2) PHB, primidone, PHT, CZP, VPA (1) Partial effect only initially, (2) Not effective in 1 case^{123} |
| Fatty acid oxidation             | AR-ACADS^{116}      | ▲ Succinyl-CoA {116} | Developmental delay^{117} | IS with/without slow and asymmetric background activity with multifocal spikes and slow wave discharges^{115} | Cu-His, VGB/NTZ Effect on Cu level but only partial effect on IS in 2 cases^{125} |
| SCAD deficiency                  |                     | Developmental delay^{123,129,130} | Ventricular dilatation^{123} | IS & (modified) hypersrrhythmia^{127,129,130} | |
| Metal metabolism                 | XR - ATP7A^{125,127,128,130} | Cu & ↓ Ceruloplasmin^{123,125,128,130} | Abnormal cerebral vessels^{125,128,129} | IS & diffuse irregular slow waves and spike waves^{126} | |
| Menkes disease                   | XR - ATP7A^{125,127,128,130} | Mental retardation^{123,130} | Cortical atrophy^{125,128,129} | IS, partial seizures & hypersrrhythmia^{128} | |
|                                  |                     | Hyponatnia^{123,125,128} | Delayed myelination^{129} | IS, focal seizures & hypersrrhythmia^{129} | |
|                                  |                     | Hypopigmentation in skin^{123,130} | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     | ▲ Fragile hair^{25} | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Ventricular dilatation^{123} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Abnormal cerebral vessels^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Cortical atrophy^{125,128,129} | IS & hypersrrhythmia^{127,129,130} | |
|                                  |                     |                                    | Delayed myelination^{129} | IS & hypersrrhythmia^{127,129,130} | |
| Vitamin B6, pyridoxine deficiency and pyridoxal 5′P deficiency | AR – PNPO^{164,165} | Developmental delay^{165,169} | Atrophy^{165} | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | (1) VGB, (2) ACTH, (3) Pyridoxine (1 & 2) Not effective, (3) effective but |
|                                  | AR – ALDH7A^{166–170} | Mental retardation^{168} | Increased subarachnoidal space^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
|                                  |                     | Tonic-clonic convulsions, myoclonic jerks following pyridoxine withdrawal test^{168} | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
|                                  |                     | ▲ Pipicolic acid^{169} | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
|                                  |                     |                                    | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
|                                  |                     |                                    | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
|                                  |                     |                                    | Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity^{165} | Generalized tonic clonic seizures & Hypersrrhythmia in 3 cases^{168} | |
Table 2. Continued.

| Metabolic disorder | Mode of inheritance—metabolic or gene defect | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|--------------------|---------------------------------------------|-------------------------------------------|----------------|---------------------|------------------------|
| Acidurias          |                                             |                                           |                |                     |                        |
| D-Glyceric aciduria (D-GA) | • AR – GLYCTK<sup>176</sup> | • ↑Glyceric Acid<sup>176–179</sup> | Delayed myelination<sup>179</sup> | • 13% (7/53) of patients with pyridoxine-dependent and/or responsive seizures had IS. 345 | Autism spectrum disorder persists in 1 case<sup>69</sup> |
|                     |                                             | • Hypotonia<sup>179</sup> | Cerebral atrophy<sup>179</sup> | • 64% of late-onset patients with pyridoxine-responsive and/or dependent seizures had IS. 345 | Pyridoxine Effective in 3 cases<sup>169</sup> |
|                     |                                             | • Autistic behavior<sup>179</sup> | Increased T2 signal from mesencephalon, pontine tegmentum, bilateral dentate nuclei, globus pallidus and thalami<sup>179</sup> | • 0.8% (1/127) of patients with IS had pyridoxine dependency.<sup>192</sup> |                        |
|                     |                                             | • Motor and mental retardation<sup>179</sup> | Abnormal signal from 2 globi pallidi<sup>189</sup> | • One case report with IS.<sup>179</sup> |                        |
|                     |                                             |                                           | Abnormal BAEP<sup>19</sup> | • Epileptic fits & multifocal generalized activity with hypsarrhythmia<sup>179</sup> |                        |
| Methylmalonic Aciduria & B12 Deficiency | • AR – MUT<sup>183,186–189</sup> | • ↑MMA<sup>19,189,190</sup> | Abnormal signal from 2 globi pallidi<sup>189</sup> | • IS & hypsarrhythmia<sup>19,23,189,190</sup> | Biotin, L-carnitine, BH4, Vitamin B12, B1 and B2 Not effective in 1 case, partially effective on seizures in 2 cases, effective in 3 cases<sup>19</sup> |
|                     |                                             | • ↓B12<sup>23,190,191</sup> | Developmental delay<sup>19,23,189</sup> | • 10% of IS patients in<sup>19</sup> had methylmalonic aciduria | First 3 treatments are effective on MMA and the rest effective on IS, hypsarrhythmia resolves by time, developmental delay persists in 1 case<sup>189</sup> |
|                     |                                             | • Developmental delay<sup>19,23,189</sup> | Macrocytic anemia<sup>190</sup> | • Pernicious anemia<sup>191</sup> | Cyanocobalamin, PHB, ACTH Effective in 2 cases<sup>23</sup> |
|                     |                                             | • Pernicious anemia<sup>191</sup> | Hypotonia<sup>19,189,190</sup> | • Hypotonia<sup>23,189</sup> | ACTH and Vitamin B12 Effective in 1 case<sup>190</sup> |
|                     |                                             | • Abnormal BAEP<sup>19</sup> | Abnormal BAEP<sup>19</sup> | • Abnormal BAEP<sup>19</sup> | B12 Triggered IS that is responsive to anti-seizure treatment<sup>191</sup> |
| Homocysteinemias    | • AR – MTHFR<sup>200–202,204</sup> | • ↑Homocysteine (maybe also ↓ B12)<sup>200–202,204</sup> | Demyelination<sup>204</sup> | • Case report with IS & hypsarrhythmia and drug resistant epilepsy with episodes of status epilepticus.<sup>204</sup> | Low protein diet, L-carnitine, hydroxycobalamin and VGB, lamotrigine, hydrocortisone Not effective in 1 case<sup>204</sup> |
|                     |                                             | • ↓CS activity<sup>200–202</sup> | Developmental delay<sup>204</sup> | • Case report with IS & hypsarrhythmia and drug resistant epilepsy with episodes of status epilepticus.<sup>204</sup> |                |
|                     |                                             | • Developmental delay<sup>204</sup> | N/A | • Case report with myoclonic seizures & hypsarrhythmia<sup>222</sup> | Betaine, methionine, folic acid, corpus callosotomy, vagal nerve stimulation Not effective in 1 case<sup>204</sup> |
| Propionic Acidemia   | • AR – PCC<sup>215–218</sup> | • Glycinuria<sup>222</sup> | N/A | • Case report with IS & hypsarrhythmia and drug resistant epilepsy with episodes of status epilepticus.<sup>204</sup> |                |
| Metabolic disorder | Mode of inheritance | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|--------------------|---------------------|-------------------------------------------|-----------------|---------------------|----------------------|
| Metabolic errors in organelles | PDHC deficiency | Lactic acidosis | Cortical atrophy | Seizures & hypsarrhythmia | ACTH and later protein restriction Seizures stopped but developmental delay persisted in 1 case |
| Mitochondrial disorders | X-linked-PDHC | Developmental delay | Seizures & hypsarrhythmia | High fat diet, biotin, lipoic acid, thiamine Not effective in 1 case |
| Pyruvate dehydrogenase complex (PDHC) deficiencies | Hydrocephalus | Hypotonia | Hydrocephalus | Thiamine, bicarbonate, biotin, folic acid Not effective in 1 case |
| | Hypotonia | Abnormal facies | Developmental delay | Thiamine + ketogenic diet and Thiamine + DCA Mildly effective in 1 case and effective in the same case, respectively, but developmental delay persists |
| | Microcephaly | Microcephaly | Developmental delay | DCA + Vitamin B1 Effective in 3 cases, not effective in 3 cases |
| Leigh and Leigh-like syndrome | Nuclear (including PDHC) or mitochondrial variants of genes involved in cellular energy production | Developmental delay | Basal ganglia lesions | IS-flexion or extensor & hypsarrhythmia | DCA + Vitamin B1 + Vitamin b6 + ZNS Effective in 1 case |
| | Lactate or pyruvate | Lactate or pyruvate | Thalamus lesions | Clonic convulsions, myoclonic seizures, apneic seizures, hemiconvulsions, opsoclonus-myoclonus | Multiple therapies [Vitamin B6, VPA + CZP, Thiamine, DCA] B6-not effective, the rest-mild effect in 1 case |
| | Sponstics | Hypotonia | SN lesions | Tonic seizures | VGB, + Hydrocortisone or + CZP Effective on IS in 3 cases, developmental delay persisted in ai |
| | Optic atrophy | Lactate | Putamen and brain stem lesions | Tonic-clonic convulsions | VGB Not effective in 1 case |
| | Cardiac problems | Lactate | Cerebral white matter myelination abnormalities | 0.7% (1/141) of IS patients with genetic testing had Leigh disease in | ACTH Effective in 2 cases, not effective in 1 case |
| | Cytochrome c oxidase deficiency | Lactate | | | CZP Effective in 2 cases, Effective only in myoclonus in 1 case |
| | Liver dysfunction | Lactate | | | Vitamin B6 Mildly effective in 1 case |
| | | | | | CBZ and ACTH Effective in seizures in 1 case, developmental delay persists |
| | | | | | VGB, + Hydrocortisone or + CZP Effective on IS in 3 cases, developmental delay persisted in ai |
| | | | | | N/A |
| Metabolic disorder                          | Mode of inheritance—metabolic or gene defect | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|--------------------------------------------|---------------------------------------------|-------------------------------------------|-----------------|---------------------|------------------------|
| Alpers-Huttenlocher disease                | Respiratory chain complex I deficiency       | Mental retardation                        | Generalized, symmetric cortical atrophy | IS, hypsarrhythmia, myoclonic jerks (complex I deficiency) | 27% (3/11) reported patients with FARS2 mutations have IS and hypsarrhythmia, one also had focal seizures | |
| Lysosomal storage diseases                 |                                             |                                           |                 |                     | No known cases of POLG mutations and IS                  |
| Hurler Syndrome                            | Low a-L-iduronidase (IDUA) activity         | ↓ a-L-iduronidase activity (Hurler syndrome) | Dilatation of ventricles | Case reports of IS & hypsarrhythmia | VGB, TPR, Corticotrophin, VPA, surgical intervention |
| Niemann Pick Disease                       | AR - SMPD I                                | ↓ SMPD enzyme (NPD)                      | Hydrocephalus    |                     | No effect in 1 case                                      |
| Other diseases                             |                                             |                                           | Demyelination    | Case reports IS     | VGB                                                   |
| Leukodystrophies                           | Developmental delay                         |                                           | White matter degeneration | IS-flexion & hypsarrhythmia | Effective on IS but development delay and other seizures persist in 1 case |
| Alexander disease                          |                                             |                                           | Spongy vacuolation | IS & convulsions   | ACTH                                                   |
| Krabbe Disease                             |                                             |                                           |                  |                     | Effective only on IS in 1 case but developmental delay persists |
| Biotinidase deficiency                     | AR - BTD                                   | Red skin rashes                          | Case reports IS  |                     | Corticoterpin & PHB                                      |
| D-Bifunctional protein (DBP) deficiency    | AR - HSD I                                 | Lactic aciduria                          | IS & burst suppression pattern       | Only IS and convulsions | Biotin supplement                                      |
|                                           | D-BP activity                              | ↑ alanine                                 |                  |                     | Effective on IS but persisting developmental delay in 1st and 2nd case |
|                                           |                                             | Hypotonia                                 |                  |                     | Corticosterpin                                          |
|                                           |                                             | Alopecia                                  |                  |                     | Partial effect on IS in 2nd case                        |
|                                           |                                             | Opicaputriopathy                          |                  |                     | PHB - VPA                                              |
|                                           |                                             | BAEP abnormalities                        |                  |                     | No effect on convulsions in 2nd case                    |
|                                           |                                             | Developmental delay                      |                  |                     | (1) PHB + VPA, (2) Phenytioin, (3) Biotin + VGB, (4) Biotin + VGB + TPR |
|                                           |                                             |                                           |                  |                     | (1) No effect on IS, (2) effective on IS, (3) Partial effect in 1 case (4) Effective in 1 case, developmental delay persists |

Continued
### Table 2. Continued.

| Metabolic disorder | Mode of inheritance — metabolic or gene defect | Main clinical and laboratory abnormalities | Brain pathology | Association with IS | Treatment effect on IS |
|-------------------|--------------------------------------|------------------------------------------|----------------|---------------------|------------------------|
| **Williams Beuren syndrome (WBS)** | AD, Deletion at WBS area of 7q | Septum pellucidum cyst, Hypoplastic corpus callosum | Case reports of IS & hypsarrhythmia | (1) no effect, (2) no effect, (3) no effect, (4) only reduction in spasms | ACTH, CLZ, VGB, VPA Over 50% effect on IS in first case |
| **Congenital Disorders of Glycosylation (CDG), Molybdenum Cofactor Deficiency (MCD), Primary Carnitine Deficiency (PCD)** | Deficient glycosylation | Abnormal vision, Developmental and motor delay | Case report of IS & hypsarrhythmia | N/A | |
| **Molybdenum cofactor deficiency (MCD)** | AR - MOCS 1 and 2 | Developmental delay | Delayed Myelination | Case report of IS-flexion spasms & hypsarrhythmia | VGB, LEV, VPA Not effective in 1 case |
| **Primary carnitine deficiency (PCD)** | Defective fatty acid oxidation | Developmental delay | Atrophy | Case report of IS-extension spasms & asymmetric hypsarrhythmia, focal seizures | VGB, CLZ, LEV Not effective in 1 case |
| **Isovaleric acidemia** | IVD enzyme deficiency | IVG, Lactic acidosis | Normal | Case report of IS-flexion spasms & hypsarrhythmia | (1) VGB (2) VGB + ACTH (for IS), Protein restricted diet + L-carnitine + hydroxycobalamin supplement (for isovaleric acidemia) (1) Not effective, (2) effective in 1 case |

**ACADS, Acyl-CoA dehydrogenase C-2 to C-3 short chain; ACTH, Adrenocorticotropic hormone; AD, Autosomal dominant; AED, Antiepileptic drug; ALDH7A1, Alpha-aminoadipic semialdehyde dehydrogenase; AR, Autosomal recessive; ATP7A, Adenosine triphosphatase; BAEP, Brainstem auditory evoked potentials; BH4, tetrahydrobiopterin; BTD, Carbamazepine; CDG, Congenital disorders of glycosylation; CS, Cystathionine synthase; CSF, Cerebrospinal fluid; CZP, Clonazepam; CTP, Chloropropamide; DCA, Dichloroacetate; DEND, Developmental Delay, Epilepsy, and Neonatal Diabetes; GA, -Glyceric Aciduria; DM, Diabetes mellitus; FARS2, Phenylalanine-tRNA synthetase; GALC, Galactosylceramidase; GFAP, Glial fibrillary acidic protein; GLUT1, Glucose Transporter 1; GLYCTK, D-Glycerate Kinase; 5-HT, 5-Hydroxytryptamine; IDUA, Alpha-L-iduronidase; IS, Infantile spasms; KCNJ11, Potassium voltage-gated channel subfamily J, member 11; L-DOPA, Levodopa; LEV, Levetiracetam; MCD, Molybdenum cofactor deficiency; MRI, Magnetic resonance imaging; MTHFR, Methylene tetrahydrofolate reductase; MUT, Methylmalonyl mutase; NPD, Niemann-Pick disease; NKKH, Nonketotic hyperglycinemia; NTZ, Nitrazepam; PAH, Phenylalanine hydroxylase; PCC, Propionylcoenzyme A carboxylase; PCD, primary carnitine deficiency; PDHC, Pyruvate dehydrogenase complex; PHB, Phenobarbital; Phe, Phenylalanine; PHN, Phenytoin; PKU, Phenylketonuria; PNPO, Pyridoxine-5'-phosphate oxidase; POLG, Catalytic subunit of mitochondrial DNA polymerase gamma; SCAD, Short-chain acyl-CoA dehydrogenase enzyme deficiency; SLC2A1, Solute carrier family 2 member 1; SMPD1, Sphingomyelin phosphodiesterase 1; SN, Substantia nigra; TPR, Topiramate; TRH, Thyrotropin releasing hormone; VGB, Vigabatrin; VPA, Valproate Acid; WBS, Williams-Beuren syndrome; WS, West Syndrome; ZNS, Zonisamide.**
in the presence of very high Phe levels. This effect may precipitate seizures, in certain situations, when Phe levels are normalized after its dietary restriction reversing the depressed glutamatergic transmission. In vivo models induced by increasing the Phe levels and/or the use of Phe hydroxylase inhibitors have been used but their phenotype resembles more to BH4 deficiency. Therefore, models such as Pahenu mice, which carry chemically induced mutations in the PAH gene, through the administration of ethylnitrosourea (enu), have provided an alternative option to model PKU of genetic etiology. The adult Pahenu2 model mimics the clinical pathology as well as presents with a decreased threshold to audiogenic seizures. Expression studies from these mice also show NMDA receptor subtype–specific changes in glutamate receptors, with increases in NMDA receptor subtype 2A (NR2A) and decreases in NR2B, as well as increased expression of AMPA receptor subunits glutamate receptor 1 (GluR1) and GluR2/3.

Glycine Encephalopathy or Nonketotic Hyperglycinemia

Glycine encephalopathy or nonketotic hyperglycinemia (NKH) is caused by autosomal recessive mutations in mostly P-protein (a pyridoxal phosphate-dependent glycine decarboxylase, GLDC) and/or T protein (a tetrahydrofolate-requiring enzyme, aminomethyltransferase, AMT) and very rarely H-protein (hydrogen carrier protein, GCSH), which are components of the mitochondrial glycine cleavage system (GCS). As a result, glycine levels increase. Glycine is an inhibitory neurotransmitter, especially in the spinal cord, but also acts as a positive regulator of NMDA receptors in central neurons, and is shown to increase excitability and lead to neurotoxicity in cultured hippocampal rat slices, as well as to enhance transmitter release in rat auditory brainstem slices. Mutational screening of NKH-related genes in 69 families with NKH patients identified mutations in GLDC and AMT genes in 75% to 83% individuals with neonatal or infantile onset NKH but in none of those with late-onset NKH.

NKH symptoms may start to appear in neonatal, infantile, or a later period, with a better prognosis in the latter. Transient NKH was also reported with a good prognosis. The affected individuals show elevated plasma and CSF glycine levels, and present with hypotonia, seizures, and developmental delay. In a retrospective study reporting on the natural history of 65 patients with NKH, seizures were reported in ~90% of patients, most (68%) of whom had neonatal-onset seizures. Among the patients with NKH who manifested seizures, 29% had burst suppression on EEG and 5% had hypersarrhythmia. Most of the literature on IS in NKH is in the format of case reports, with very few reports on larger cohorts of patients with NKH. In general, expert reviews of the clinical course of neonatal NKH and a cohort of 56 families with neonatal NKH described the emergence of IS and/or hypersarrhythmia as a common feature of NKH among infants who survive beyond the neonatal period.

NKH patients manifesting with WS have been reported (Table 2). Because the prognosis is very poor in neonatal-onset NKH, Korman et al. treated, immediately after birth, a prenatally diagnosed male newborn carrier of a GLDC mutation with sodium benzoate and ketogenic (NMDA receptor antagonist; Table 2). Although the treatment prevented the neonatal hypotonia and apnea it did not ameliorate the long-term epilepsy and neurocognitive outcomes.

To create a model for NKH, Pai et al. used mice with 95% decreased Gldc expression with dramatically reduced GCS activity that led to neural tube defects in homozygote mice (Table 3). Similar defects are also reported from use of mice lacking GCS activity through deletions in the Amt gene. However, neither report mentions any seizure phenotype. On the other hand, in a model of mild-type glycine encephalopathy, mice with 29% reduced GCS activity (low GCS) show a longer duration of tonic or clonic seizures induced by electroshock, and higher locomotor activity and anxiety-related behavior, which can be partially reversed by NMDA antagonists specific to the glycine-binding site of the receptor. Likewise, after focal cerebral ischemia, mice with low GCS activity demonstrate greater neuronal injury compared to wild-type (WT) animals.

The glycine transporter 1 (Glyt1) knockout (KO) mice have been used to model features of glycine encephalopathy. Homozygous mutations in solute carrier family 6 member 9 (Slc6A9) encoding Glyt1 are lethal within the first postnatal day (PN), mostly due to respiratory deficits, but strychnine, a glycine receptor antagonist, reverses the abnormal respiratory activity in brainstem slices from these mice. An association between NKH and GLYT1 was suspected in a patient with no GCS abnormality but absence of glycine transport system on autopsy. A homozygous Slc6A9 mutation has recently been identified in an atypical NKH patient, a 15-month-old girl presenting with normal EEG and most of the disease symptoms except encephalopathy.

Deficiencies in glucose metabolism and transport

Developmental delay, epilepsy, and neonatal diabetes

Permanent neonatal diabetes mellitus has been associated with autosomal–dominant mutations in the potassium voltage-gated channel subfamily J, member 11 (KCNJ11) gene encoding the pore-forming subunit (Kc,6.2) of the adenosine triphosphate (ATP)–sensitive inward-rectifier potassium channels (KATP). In the presence of ATP, KATP channels close and trigger insulin secretion from pancreatic beta cells. Closure of these channels leads to membrane depolarization and opening of t-type voltage-dependent calcium (Ca2+) channels that subsequently increase intracellular Ca2+ and therefore insulin exocytosis. Some of the diabetic
neonates present also with developmental delay and epilepsy.7,7 a syndrome that is known as DEND (developmental delay, epilepsy, neonatal diabetes).78–82 Hypsarrhythmia has been reported in a total of 4 DEND patients77,80–82 (Table 2), 3 of whom presented with IS and one with tonic–clonic seizures.80–82 Sulfonylurea therapy (acting by binding to the sulfonylurea receptor part of the KATP and closing them—leading to insulin secretion) mitigated neurologic symptoms and psychomotor development in these patients.80–82 However, one patient died following initial amelioration.80

KATP channels are expressed not only in pancreas but also in skeletal muscle, cardiac muscle, and brain tissue (for review: ref 83). Therefore, epilepsy, including IS when present, was suggested to be linked to the genetic defect in DEND syndrome, rather than the outcome of neonatal diabetes.77,79,80 The rarity of reported cases of IS in DEND and the lack of cohorts exploring the incidence of IS in patients with DEND do not allow for strong arguments that there is a specific association of this syndrome with IS rather than epilepsy in general. However, not all patients carrying mutations have neurologic features.79 Despite the fact that the location of Kα6.2 mutations has a strong influence on the severity of symptoms,78 DEND is a rare disease and more information is needed to confirm these findings.

In vitro functional analyses of different mutations leading to neonatal diabetes and DEND using Xenopus oocytes indicate that although a mutation (R201C) in KCNJ11 directly acts on ATP sensitivity of KATP,2 other mutations linked with DEND (Q52R and V59G) lead to conformational change that keeps channels in an open state and therefore interferes with the sulfonylurea efficacy (Table 3).78 In vivo EEG and electromyography (EMG) recordings from Kα6.2 KO mice show myoclonic jerks, severe tonic convulsions, and death when challenged with hypoxia, whereas WT animals recover normally.84 In vitro recordings from SNr neurons from the same model displayed no difference in firing rates of the neurons compared to the neurons from WT animals; however, the firing rates increased during hypoxia in the former, whereas they decreased in slices from WT animals, indicating the inhibitory effect of these channels in SNr.84 Likewise, overexpression of the other subunit of KATP channels, sulfonylurea 1 (Sur1), in mice protects against kainic acid–induced seizures and the neuronal damage.85 Although the protective role of these channels in different parts of the brain during hypoxia is known,86 there are no known reports of spontaneous seizures in these models.

**Persistent symptomatic hypoglycemia**

Patients with persistent neonatal hypoglycemia and specific syndromic etiology such as those that may require pancreatectomy for persistent hyperinsulinemia may develop IS following variable latent time.87,88 In earlier studies, neonatal hypoglycemia (low blood glucose levels, <2.6 mmol/L) was reported in some of the IS patients in 2 long-term population studies in Finland.89,90 However, at the time these studies were carried out, there were limited diagnostic tools to determine the reason behind the persistent hypoglycemia while limited treatment options existed, such as since diazoxide administration and pancreatectomy were developed later. In almost all cases in which IS occurred, there were structural brain abnormalities, indicating that the abnormal MRI finding was the entry criterion in the available retrospective study91 (Table 2).

Increased awareness of the significance of identifying the causes of hypoglycemia and the institution of targeted treatments helped to decrease the incidence of persistent symptomatic hypoglycemia as an etiologic factor in IS.89,92

Hypoglycemia may have profound effects on the brain where it is used as a primary energy source, even though the exact mechanism leading to IS has yet to be discovered. The effects may include but are not limited to mitochondrial energy deficiencies and increased susceptibility to hypoxic-ischemic brain injuries,88,93 and may interfere with any of the proposed mechanisms of IS/WS development.7 The effects of hypoglycemia may be age specific. Experimental data from immature rats and dogs point out that immature animals are more resistant to induced hypoglycemia if there are no other underlying abnormalities, owing to their decreased energy dependence, higher endogenous carbohydrate storage and use of alternative energy sources, as well as compensatory mechanisms such as increased cerebral blood flow and glucose transport into the brain. However, hypoglycemia in the presence of hypoxia-ischemia may be detrimental (for review84).

A number of models, both in vitro and in vivo, that mimic the hypoglycemic condition are studied in different animals (Table 3).95 Results of one of the studies that evaluated insulin-induced hypoglycemia in rats indicate that neuronal damage is triggered when EEG becomes isoelectric, regardless of the glucose level.96 The damage is correlated with the duration of the isoelectric time, in that the longer the time spent in the isoelectric state, the greater the brain injury.96 In an attempt to establish an animal model for brain injury caused by neonatal hypoglycemia, Zhou et al.97 later showed that immature rats exposed to prolonged insulin-induced hypoglycemia had neuronal death and that the damage was seen mainly in cortex, dentate gyrus (DG), thalamus, and hypothalamus but not in the CA1 and CA3 regions of the hippocampus. In contrast, a previous study that used mature animals showed damage in the hippocampus, caudate nucleus, spinal cord, and cerebellar Purkinje cells.96 These findings underscore the impact of age when animals are exposed to hypoglycemia on both neuronal injury and its location.98 In addition, the ketogenic diet provides the brain with an alternative energy source in the absence of glucose, and decreases the neuronal injury when started at the

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Table 3. In vivo and in vitro models of metabolic diseases associated with WS

| Metabolic disease                  | Disease model and main features                                                                 | Spontaneous seizures or spasms |
|-----------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------|
| Phenylketonuria (PKU)             | • Rat hippocampal neuronal cultures exposed to high Phe depression of glutamatergic transmission\(^{47}\) | NR                            |
|                                   | • Pah\(^{100}\) mice                                                                                                                                   | NR                            |
|                                   | ↓ threshold to audiogenic seizures\(^{46,49,50}\)                                                                                                  |                               |
|                                   | ↑ expression of NR2A&B, GluR1&2/3\(^{48}\)                                                                                                       |                               |
| Nonketotic hyperglycinemia (NKH)  | • Glycine on cultured hippocampal rat slices                                                                                                      | NR                            |
|                                   | ↑ excitability & neurotoxicity\(^{55}\)                                                                                                           |                               |
|                                   | • Glycine on auditory brain stem rat slices                                                                                                       | NR                            |
|                                   | ↑ transmitter release\(^{56}\)                                                                                                                      |                               |
|                                   | • 95% ↓ Gcs mice & Ant deletion in mice                                                                                                          | NR                            |
|                                   | Neural tube defects\(^{69,70}\)                                                                                                                      |                               |
|                                   | • 29% ↓ GCS mice                                                                                                                                  | NR                            |
|                                   | Longer electroshock induced tonic–clonic seizures\(^{71}\)                                                                                       |                               |
|                                   | High locomotor activity and anxiety behavior\(^{71}\)                                                                                             |                               |
|                                   | Severe neuronal injury after focal cerebral ischemia\(^{72}\)                                                                                     |                               |
|                                   | • Glyt1 KO mice                                                                                                                                  | NR                            |
|                                   | abnormal respiration reversed by strychnine\(^{73}\)                                                                                             |                               |
| DEND                              | • Expression of KCNJ11 mutations in Xenopus oocytes                                                                                               | NR                            |
|                                   | Interfere with K\(_{ATP}\) sensitivity or sulfonylurea efficacy\(^{78}\)                                                                       |                               |
|                                   | • Kir\(_{6.2}\) KO mice                                                                                                                            | NR                            |
|                                   | Myoclonic jerks, tonic convulsions, & death in response to hypoxia\(^{84}\)                                                                     |                               |
|                                   | SNr firing rates increase during hypoxia in vitro\(^{84}\)                                                                                       |                               |
|                                   | • Overexpression of SUR1 in mice                                                                                                                     | NR                            |
|                                   | Protective against kainic acid–induced seizures\(^{85}\)                                                                                           |                               |
| Symptomatic hypoglycemia          | • Insulin-induced hypoglycemia in rats                                                                                                              | NR                            |
|                                   | Neuronal damage in the hippocampus, caudate nucleus, spinal cord, and cerebellar Purkinje cells\(^{86}\)                                             |                               |
|                                   | In immature rats: neuronal damage in cortex, DG, thalamus, and hypothalamus\(^{97}\)                                                           |                               |
|                                   | In PN25 rats ketogenic diet protects against neuronal damage if started at PN21\(^{99}\)                                                        |                               |
|                                   | In fasting rats: decreased latency to seizures\(^{103}\)                                                                                           |                               |
|                                   | • Insulin & SEZ-induced hypoglycemia in juvenile rats\(^{100}\)                                                                                  | seizures                      |
|                                   | Seizures responsive to NMDA & non-NMDA antagonists & midazolam, decreased synaptic transmission, spreading depolarizations\(^{101}\)     |                               |
|                                   | • Slices from developing rats exposed to repetitive hypoglycemia decreased LTP\(^{102}\)                                                          |                               |
| GLUT1 deficiency                  | • Heterozygous Glut1 mice                                                                                                                          | Seizures                      |
|                                   | Generalized/focal onset electrographic seizures, rhythmic or polyspikes, SWDs, no behavioral change\(^{113}\)                                   |                               |
|                                   | Behavioral arrests during fasting\(^{113}\)                                                                                                       |                               |
|                                   | • Expression of SLC2A1 variants in Xenopus oocytes                                                                                               | NR                            |
|                                   | Mild to dramatic glucose transport changes\(^{115}\)                                                                                              |                               |
| SCAD deficiency                   | • BALB/cByJ mice                                                                                                                                | NR                            |
|                                   | impaired thermoregulation in cold\(^{121}\)                                                                                                      |                               |
|                                   | • Slices from BALB/cByJ mice                                                                                                                       | NR                            |
|                                   | Cerebral edema, astrocytic swelling, neuronal mitochondrial injury\(^{120}\)                                                                       |                               |
|                                   | • Slices from ethylmalonic acid–administered rats                                                                                                 | NR                            |
|                                   | Deficient redox homeostasis & ↓ Na\(^{+}/K\(^{+}\)ATPase activity\(^{122}\)                                                                       |                               |
| Menkes disease                    | • Mo\(^{14}\) mice                                                                                                                               | NR                            |
|                                   | impaired axonal development & synaptogenesis in the cerebral cortex and the                                                                         |                               |

Continued
| Metabolic disease | Disease model and main features | Spontaneous seizures or spasms |
|-------------------|---------------------------------|-----------------------------|
| Spontaneous seizures or spasms | hippocampus, ↓ peptidylglycine alpha-amidating monooxygenase activity in slices | NR |
|                      | Phenotype partially reversed by human Menkes transgene | NR |
|                      | • Inhibition of atp7a expression in Drosophila cell -specific amidation impairments | NR |
| Vitamin B6-, Pyridoxine dependency & pyridoxal-5’-phosphate deficiency | • TNAP KO mice seizures, ↑ PLP, ↓ GABA that are reversible by PLP but not pyridoxine depending on the mice background | Seizures |
|                      | • TNAP+/+ and heterozygous mice Pyridoxine-deficient diet-induced seizures | Seizures |
| α-Glyceric aciduria (DGA) | • Rats with high fructose & fat diet type II diabetes | NR |
|                      | • Glyctk KO mice | NR |
| Methylmalonic aciduria & B12 deficiency | • Intrastrital MMA injection in rats Clonic & tonic – clonic seizures, ↓ duration of seizures with preadministration of MK-801, alpha-tocopherol or ascorbic acid | Seizures |
|                      | • ICV MMA in rats clonic convulsions that can be reduced by pyridoxine, baclofen, and muscimol; ↓ GAD activity that can be prevented by pyridoxine & MK-801 | Seizures |
|                      | • CD320/TCbIR KO mice cognitive deficits & anxiety | NR |
|                      | • Membrane preparations from MMA-treated rat cortex/brain homogenates preincubated with MMA ↓ Na+/K+ATPase activity, prevented by glutathione | No |
| Homocysteinemias | • Heterozygous Mthfr KO mice Impaired short-term memory in WT animals born to this phenotype & apoptosis in the hippocampus | NR |
|                      | • Systemic administration homocysteine in rats & mice convulsive seizures | Seizures |
|                      | • Intraperitoneal homocysteine injection status epilepticus & flexion seizures in immature rats | Seizures |
|                      | • ICV application of homocysteic acid in PN12 rats Generalized tonic – clonic seizures, prevented by pre-NBQX & AP7 application | Seizures |
|                      | • Subcutaneous chronic homocysteine injection in rats ↓ Na+/K+ATPase activity in hippocampal synaptic membrane preparations | NR |
|                      | • Homocysteine application on rat organotypic cortical & hippocampal slice cultures Excitotoxicity | NR |
| Propionic acidemia | • ICV propionic acid injection in adult rats Dystonia, hyperactivity, caudate spiking, ↑ severity of kindling-induced seizures | NR |
|                      | • Oral propionic acid application in PN 21 rats ↓ glutathione & glutathione peroxidase activity, ↑ IL6, TNFα, HSP70 & caspase 3, DNA fragmentation, ↓ GABA, serotonin & dopamine | NR |
| PDHC deficiency | • PDHC E1 α null mutation in mice Low PDC activity, reduced litter size | NR |
|                      | All males die & 50% females survive after only brain-targeted mutation, females show ↓ neuronal density & neuropil fibers, abnormal neuronal localization in | NR |

Continued
| Metabolic disease | Disease model and main features | Spontaneous seizures or spasms |
|------------------|---------------------------------|-------------------------------|
| Spontaneous seizures or spasms | the gray matter, lipid synthesis & irregular myelination, adult females have neurological deficits<sup>239</sup> | NR |
| PDHC E<sub>1</sub>α knockdown in striatum & SN in rats | abnormal amphetamine-induced rotation<sup>240</sup> | NR |
| Systemic deletion of exon 8 from PDHC E<sub>1</sub>α | ↓brain weight, de novo lipid synthesis, ↓proliferation, differentiation and migration of newly generated neuronal precursor cells in cerebellum, impaired dendritic development of Purkinje cells ex vivo | NR |
| Impaired acoustic startle reflex<sup>242</sup> | Ketoconazole diet reversed abnormal vision, lactic acidosis & lethargy<sup>243</sup> | NR |
| ND2 deletion in zebrafish | Rapamycin increases the life span but leads to fat storage impairments<sup>258</sup> | NR |
| Alpers-Huttenlocher disease | D257A knockin mice <small>(PolyA<sup>mut</sup>/*)</small> | NR |
| Early aging, ↓body size & weight, death<sup>264,265</sup> | Early lethality & mtDNA depletion if KO at preimplantation stage<sup>267</sup> | NR |
| Polg<sup>−/−</sup> zebrafish | larvae survive till juvenile age<sup>266</sup> | NR |
| Lysosomal storage diseases | Idua KO mice | NR |
| High glycosaminoglycan in urine, flat face, abnormal lysosomal storage in glial cells, vacuolation in Purkinje cells, neurons in the cortex, no behavioral alterations<sup>272</sup> | Human IDUA injection into putamen reverses brain pathology<sup>273</sup> | NR |
| ICV human IDUA injection prevents brain pathology & spatial learning deficits<sup>274</sup> | ASM KO mice | NR |
| High sphingomyelin, no ASM activity, ↓body weight & death<sup>272</sup> | Mutations expressed in this background show high level of expression in brain & higher residual ASM activity than ASM KOs<sup>272</sup> | NR |
| Leukodystrophies | Mice carrying WT+I mutated hGFAP | NR |
| No Rosenthal fibers<sup>286</sup> | | |
| Mice carrying WT + multiple mutated hGFAP | Rosenthal fibers in adult age, severe convulsions & high mortality rate when challenged with kainate<sup>286</sup> | NR |
| Mice with hGFAP | Hyperthermic astrocytes, Rosenthal fiber-like inclusions, upregulation of small HSPs<sup>287</sup> | NR |
| BTD deficiency | Rats fed with biotin-deficient diet | NR |
| Alopecia of lower back, delayed growth, longer BAEP latency<sup>295</sup> | BTD KO mice fed with biotin-deficient diet | NR |
| Hypotonia, demyelination, axonal degeneration, impaired motor neuron function, lethargy, limping, ventriculomegaly, slow growth, weight loss reversed with biotin supplement<sup>296,297</sup> | | |
| DBP deficiency | MFP2 KO mice | NR |
| Failure to thrive, astrogliosis & microglial activation in gray matter, death<sup>300,303</sup> | | |

Continued...
weaning age (PN21) in rats exposed to insulin-induced hypoglycemia at PN25.99 In juvenile rats with insulin- and streptozotocin- (SEZ, an antibiotic that is toxic to the pancreatic beta cells) induced hypoglycemia, seizures and neuronal damage were found to be similar to that in nondiabetic rats treated with only insulin, indicating the

| Metabolic disease                          | Disease model and main features                                                                 | Spontaneous seizures or spasms |
|------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------|
| Nestin-Mfp2-/- mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.                   | NR                             |
| dbp knockdown in zebrafish                | Rescue by murine Dbp                                                                      | NR                             |
| Williams-Beuren syndrome (WBS)            | Fzd9 deletions in mice                                                                      | NR                             |
|                                          | Both heterozygous & homozygous deletions lead to ↓ threshold of pentylenetetrazole-induced seizures & abnormalities in hippocampal structure, only homozygous deletions lead to spatial learning impairments.  |
|                                          | WBS distal deletions in mice                                                                | NR                             |
|                                          | Cognitive impairment                                                                       | NR                             |
|                                          | WBS distal & proximal deletions in mice                                                    | NR                             |
|                                          | Heterozygous WBS complete deletions in mice                                                | NR                             |
|                                          | ↓ brain weight, dendritic length & spine density in the hippocampus, GFAP↑ in amygdala, ↑ immature cells in DG, craniofacial and cardiac abnormalities, spatial learning deficits. |
|                                          | Slices from these mice show unstable LTP in CA1, ↑ BDNF in CA1-CA3.                         | NR                             |
| Nestin-Mfp2/C0 mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2/+/C0 mice                     | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2−/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2 mice                          | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2C0 mice                        | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/C0 mice                      | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2−/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2C0 mice                        | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/C0 mice                      | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2−/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2C0 mice                        | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/C0 mice                      | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2−/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2C0 mice                        | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/C0 mice                      | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2−/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2+/− mice                       | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |
| Nestin-Mfp2C0 mice                        | Mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits.               | NR                             |

AMT, Aminomethyltransferase; AP7, 2-amino-7-phosphonooctanesoic acid; ASM, acid sphingomyelinase; ATP7A, Adenosine triphosphatase; BAEP, Brainstem auditory evoked potentials; BNDF, Brain-derived neurotrophic factor; BTD, Biotinidase; DG, Dentate gyrus; Fzd9, Frizzled 9; GABA, Gamma-aminobutyric acid; GAD, Glutamic acid decarboxylase; GFAP, Glial fibrillary acidic protein; GLYT1, Glycine transporter 1; GLYCTK, D-Glycerate Kinase; GCSH, Glycine cleavage system H protein; Heat shock protein; ICV, Intracerebroventricular; IDUA, Alpha-L-iduronidase; IL6, Interleukin 6; IVG, Isovalerylglycine; KATP, Adenosine triphosphate (ATP)-sensitive inward-rectifier potassium channels; KCNJ11, Potassium voltage-gated channel subfamily J, member 11; Kir, Inward rectifier potassium channel; KO, Knockout; MOFS, multifunctional protein-2; Mga2, Mannosyl (Alpha-1,6)-Glycoprotein Beta-1,2-N-Acetylgalactosaminyltransferase; MGA, Methylmalonic acid; Moblo, Mobr and Modp, Murine motilin, motilin-related peptides, motilin-like peptide; MOC51 and MOC52, Molybdenum cofactor/Methylmalonyl-CoA mutase; MOCS1 and MOCS2, Molybdenum cofactor/Methylmalonyl-CoA mutase; MSN, Motile neuron; MTHFR, Methylene tetrahydrofolate reductase; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzoquinoxaline-2,3-dione; ND2, NADH dehydrogenase 2; NDUF54, NADH ubiquinone oxidoreductase subunit S4; NMDA, N-methyl D-aspartate; NRZ2 and NRZ2B, NMDA receptor subtype 2A and 2B; LTP, Long-term potentiation; PHA, Phenylalanine hydroxylase; PDHC, Pyruvate dehydrogenase complex; Phe, Phenylalanine; PLP, Pyridoxal phosphate; POLG, Catalytic subunit of mitochondrial DNA polymerase gamma; PN, Postnatal day; SEZ, Streptozotocin; SLCA1, Solute carrier family 1, member 1; SLC6A9, Solute carrier family 6 member 9; SN, Substantia nigra; SNr, Substantia nigra pars reticulata; SUR1, Sulfonflylurea 1; SWDs, Slow wave discharges; CD320/TCblR, Transcobalamin II receptor; TNP, Tissue non-specific alkaline phosphatase; TNF, Tumor Necrosis Factor; WBS, Williams-Beuren Syndrome; WT, Wild type.

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Glucose transporter 1 deficiency

Deficiency of glucose transporter 1 GLUT1, the primary transporter in the blood–brain barrier allowing glucose entrance to the brain, was first reported by De Vivo et al.\textsuperscript{104} in 2 infants having drug-resistant epilepsy, developmental delay, hypoglycorrhachia (a very low CSF glucose level), and low lactate level. No genetic analysis is performed but western blot analysis of erythrocytic glucose transporters (EGTs) showed decreased interaction with cytochalasin B, a mycotoxin that binds to GLUTs and inhibits glucose transport. EGTs show close homology to brain vascular endothelial cell GLUTs and are therefore suggested to represent the activity of brain GLUTs.\textsuperscript{105} Mutations in GLUT1 (SLC2A1, solute carrier family 2 member 1) underlie the pathology of the GLUT1 deficiency syndrome, which comprises infantile-onset epilepsy, developmental delay, movement disorders, and acquired microcephaly.\textsuperscript{106–108} Various seizure types may occur, including generalized tonic or clonic, atypical absences, atonic, myoclonic, myoclonic atactic, or focal.\textsuperscript{108–110} GLUT1 deficiency syndrome has rarely been reported in IS patients who responded to the ketogenic diet fully or partially,\textsuperscript{110–112} including a patient with a missense mutation in SLC2A1\textsuperscript{112} (Table 2).

Heterozygous haploinsufficiency of the Glut1 gene in mice (heterozygous Glut1 mice) mimics most of the clinical phenotype of GLUT1 deficiency without the histopathological changes, whereas homozygous deletion of the gene is lethal during embryonic development (Table 3).\textsuperscript{113} In heterozygous Glut1 mice, generalized or focal-onset electrographic seizures with rhythmic spikes or polyspikes and slow wave discharges or bursts of 2-3 Hz spike and slow-wave discharges (SWDs) were noted with no apparent disruption of the animal’s behavior. During fasting, however, 1-4 seconds of 6 Hz SWDs associated with behavioral arrests were also seen.\textsuperscript{113} The authors conclude that lactate deprivation is the main reason for pathology in the presence of GLUT1 deficiency,\textsuperscript{113} since glucose is used mainly by astrocytes to maintain the glutamate-glycine cycle and is converted into lactate, which is in turn used by the neurons as a main energy source.\textsuperscript{114} In X. oocytes, functional testing of 7 variants in the SLC2A1 gene, which is also associated with 1% of the genetic generalized epilepsies, shows mild to dramatic glucose transport changes that are not always correlated with the phenotypes seen in the patients, indicating that in some cases, modifier genes and environmental factors also play a role in GLUT1 deficiency.\textsuperscript{115} These models have already shown a predisposition to spontaneous seizures, even though no IS have been reported, and the possible presence of disease modifiers.

Deficiencies in fatty acid oxidation

Short-chain acyl-coenzyme A dehydrogenase enzyme deficiency

Short-chain acyl-coenzyme A (CoA) dehydrogenase enzyme deficiency (SCAD) is an autosomal recessive disorder with mutations in the acyl-CoA dehydrogenase C-2 to C-3 short chain (ACADS) gene wherein infants’ increased levels of butyrylcarnitine and urinary ethylmalonic acid are accompanied by heterogeneous clinical symptoms such as hypotonia, hypoglycemia, and lethargy, and later in life by developmental delay and seizures.\textsuperscript{116} To our knowledge, there is one WS case with SCAD resistant to treatment in the literature\textsuperscript{117} (Table 2).

The BALB/cByJ mouse is described as a model for human SCAD during routine screening of mutated mice for metabolic disorders (Table 3).\textsuperscript{118,119} Histopathologically, cerebral edema, astrocytic swelling, and neuronal mitochondrial injury,\textsuperscript{120} and clinically, impaired thermoregulation in cold conditions are reported;\textsuperscript{121} however, no seizure phenotype is mentioned. Because it was known that the ethylmalonic acid accumulates in SCAD deficiency, a study investigated the effects of its direct administration into striatum in young rats and found that striatal slices from these rats have deficient redox homeostasis and decreased sodium potassium ATPase (Na\textsuperscript+K\textsuperscript+ATPase) activity, both of which may lead to neuronal impairment in neurotransmission.\textsuperscript{122}

Deficiencies in metal metabolism

Menkes disease

IS have been commonly reported in patients presenting with Menkes disease\textsuperscript{123–130} (Table 2). Bahi-Buisson et al.\textsuperscript{126} reported that IS manifested during the intermediate stage of Menkes disease in all their patients. Menkes disease is an X-linked recessive disease with low serum copper (Cu) levels due to mutations in an adenosine triphosphatase (ATP7A) gene encoding P-type ATPase, which transports nutritional Cu into organelles.\textsuperscript{131–133} In the absence of Cu, dysfunctional Cu-dependent enzymes involved in blood clotting, superoxide removal, myelin, and dopamine/melanin and norepinephrine synthesis (ie, blood clotting factors
V and VII, superoxide dismutase and ceramide galactosyl transferase, lysyl oxidase, and dopamine beta hydroxylase) lead to variable outcomes such as anemia, vessel abnormalities, muscle weakness, and neurologic effects.\textsuperscript{127,134} Nevertheless, Cu supplementation is insufficient as a therapy in Menkes disease.\textsuperscript{125,126} Even when the disease was first described in 1962, severe neurological symptoms and seizures were observed in 5 related patients.\textsuperscript{133} However, the main mechanism leading to IS is still unknown (for review\textsuperscript{135}).

Variations in the murine mottled (blotchy and dappled, \textit{Mo}\textsuperscript{blo} and \textit{Mo}\textsuperscript{dp}) locus are suggested to be the homolog of the human Menkes disease–causing \textit{ATP7A} gene.\textsuperscript{136,137} Neurological aspects of Menkes disease, including seizures, are reflected at most by the brindled mottled mouse (\textit{Mo}\textsuperscript{blo}), although no spasms were reported (Table 3).\textsuperscript{137} In these mice, axonal development and synaptogenesis are impaired in the cerebral cortex and the hippocampus, and in addition, peptidylglycine alpha-amidating monooxygenase activity is reduced, indicating an impaired amidation that is important for functioning of neuropeptides as glycine, cholecystokinin, and neuropeptide \textit{Y}.\textsuperscript{137,138} Some of these changes in the brindled \textit{Mo} can be rescued by the human Menkes transgene, although the Cu concentrations are not fully reversed to normal.\textsuperscript{139} In addition, recently, non-mammalian models of Menkes disease have also been established. The normal brain expression of \textit{atp7a} in a zebrafish model is very low,\textsuperscript{140} whereas amidation impairments in a \textit{Drosophila} model are similar to the murine model.\textsuperscript{141} These findings from animal models already indicate the global alterations that lead to the Menkes disease phenotype and pathology similarities in different organisms.

**Vitamin B\textsubscript{6}, pyridoxine dependency, and pyridoxal-5'-phosphate deficiency**

Reports of nervous system symptoms, epileptiform activities, or seizures induced by pyridoxine (vitamin B\textsubscript{6}) deficiency and of the seizure-suppressing effect of pyridoxine have been described for rats and humans.\textsuperscript{142–146} A Japanese study testing pyridoxal phosphate (PLP, active form of pyridoxine) as a treatment in WS showed efficacy in 12.7\% of patients including the ones with no underlying metabolic defect, prompting a treatment trial with high-dose PLP in all WS infants.\textsuperscript{147} Similarly, Ohta-hara et al.\textsuperscript{148} and Pietz et al.\textsuperscript{149} report successful use of PLP in 11.8\% of WS patients and of high-dose pyridoxine in 30\% of IS patients, respectively, regardless of the prenatal etiology (ie, tuberous sclerosis complex [TSC], chromosome abnormalities, or brain malformations; symptomatic or idiopathic). Pyridoxine is still one of the first treatment choices in WS in Japan due to its safety and because of the side effects of other treatments.\textsuperscript{150–152} However, new reports implement the use of first-line treatments (eg, adrenocorticotropic hormone [ACTH] or vigabatrin [VGB]), as there is no significant difference in efficacy of pyridoxine treatment compared to other medications.\textsuperscript{153}

The exact mechanisms of pyridoxine or PLP deficiency and vitamin B\textsubscript{6} dependency, as well as therapeutic action of these compounds, are still unknown in seizure generation considering that even in certain patients with unknown etiology epilepsy,\textsuperscript{146} pyridoxine or PLP treatment can be effective. Vitamin B\textsubscript{6} is converted into pyridoxine and its active coenzyme form, PLP, which is a cofactor of a number of enzymes including GAD catalyzing the conversion of glutamate to \gama-amino butyric acid (GABA).\textsuperscript{154} Low GABA levels are seen in some patients with neonatal seizures that were responsive to vitamin B6 and pyridoxine.\textsuperscript{155,156} GABA is the main inhibitory neurotransmitter in the central nervous system (CNS), but also plays a role in oxidative energy metabolism.\textsuperscript{157} Due to this relation, seizures are attributed to functional deficiencies in GAD1 and GAD2 genes and GABA synthesis,\textsuperscript{158–160} but no significant linkage has been found in affected families.\textsuperscript{161–165}

Autosomal recessive mutations in the pyridoxine-5'-phosphate oxidase (\textit{PNPO}) gene that expresses the enzyme that converts pyridoxine and pyridoxamine to active PLP underlie PLP-responsive (but pyridoxine-unresponsive) neonatal epileptic encephalopathy in 5 patients.\textsuperscript{164} A patient with IS of unknown etiology who had normal CSF pyridoxal-5'-phosphate, carried a \textit{PNPO} mutation that resided in a conserved sequence with damaging effects, as determined by 2 functional online analysis programs, polymorphism phenotyping v2 (PolyPhen) and sorting tolerant from intolerant (SIFT).\textsuperscript{165} DNA sequencing from 13 individuals between 17 months and 15 years of age who had pyridoxine-dependent seizures revealed mutations in the \alpha-aminoacidic semialdehyde dehydrogenase (ALDH7A1) gene that encodes antiquitin which is involved in lysine catabolism.\textsuperscript{166} The location of the mutations in the \textit{ALDH7A1} gene contributes to the phenotype of the patients.\textsuperscript{167} In addition, unlike patients carrying \textit{PNPO} mutations or having \textit{PNPO} deficiency, in patients with ALDH deficiency, no increases in threonine or glycine in serum or CSF are found.

There are patients with \textit{ALDH7A1} mutations and IS although there is a patient with antiquitin dysfunction but without a mutation suggesting an unknown mechanism in this deficiency\textsuperscript{168,169} (Table 2). Of interest, patients with folinic acid deficiency, also a known but rare cause of seizures, may carry \textit{ALDH7A1} mutations.\textsuperscript{170} Although this condition is seen mostly with neonatal seizures, urine antiquitin measurement is advised when no underlying cause is present for IS.\textsuperscript{171}

KO mice for tissue-nonspecific alkaline phosphatase (TNAP) show seizures, elevated PLP and reduced levels of GABA all of which can be reversed by the application of PLP but not pyridoxine (Table 3).\textsuperscript{172} Interestingly, pyridoxal treatment is influenced by the genetic background of the mice, being effective fully
hyperglyceric aciduria. Autosomal recessive mutations in tal retardation, but also with hyperglyceric acidemia and nary glycine, myoclonic jerks, and motor and development. A 6-month-old boy having symptoms similar to NKH such as high urination glycine and hyperglyceric aciduria.175 Autosomal recessive mutations in the 5-glycerate kinase (GLYCTK) gene were identified in 3 patients including the 5GA patient first described.176 Regardless of the high urinary 5-glyceric acid content, individuals that are fully healthy or present with only mildly affected fructose metabolism have been reported.176–178

A 6-month-old boy with healthy sisters from first-degree, consanguineous parents was diagnosed with WS and was followed until 3 years of age (Table 2). A fructose-free diet provided partial amelioration, with decreases in autonomic behavior and resolution of abnormal signal intensity in mesencephalon, thalami, and globus pallidum on MRI; however, it is not clear how defects in fructose metabolism led to neuronal symptoms, and particularly WS. No seizures are reported in rats that are exposed to a high-fructose and high-fat diet (Table 3). Glyctk KOs that are created by the clustered regularly interspaced short palindromic repeats (CRISPR) and Glyctk small interfering RNAs (siRNAs) to silence the gene are available; however, no model with a seizure phenotype has been identified to date.

Methylmalonic aciduria and cobalamin (B12) deficiencies

Deficient methylmalonyl CoA mutase (MUT) that converts propionyl-CoA from amino and fatty acids into a Krebs cycle component, succinyl-CoA, leads to accumulation of methylmalonic acid (MMA) and its derivatives. These derivatives are toxic to kidneys and brain where they affect particularly the basal ganglia.5–Deoxynadinosylcobalamin is a cofactor of MUT; therefore its absence or deficient synthesis may also result in methylmalonic aciduria. The disease progression, and treatment options and their success may differ depending on the location of autosomal recessive mutations affecting either the synthetization of the apoenzyme or the cofactor. IS due to MMA accumulation or B12 deficiency is reported in several patients with various responses to vitamin supplements (Table 2). In bigger cohorts, the frequency of methylmalonic aciduria among the reported underlying etiologies in infants with IS varies between 0 and 10%.9,19,192

Rats show clonic and tonic–clonic seizures after intrastratal MMA injection, and the duration of these seizures are reduced by preadministration of MK–801, alpha–tocopherol, or ascorbic acid, indicating the possible role of NMDA receptors and free radicals in the MMA-induced phenotype (Table 3).193,194 Membrane preparations from both cerebral cortex of the subcutaneously MMA-treated rats and brain homogenates of untreated rats that are preincubated with MMA indicate decreased Na+/K+ ATPase activity, which is prevented by ex vivo simultaneous glutathione application. On the other hand, intracerebroventricular (ICV) injection of MMA leads to clonic convulsions and lower GAD activity in rats, and although the duration of convulsions can be reduced by pyridoxine, baclofen, and muscimol, decrease in GAD activity can be prevented by pyridoxine and MK–801.196

Of the few mice models that mimic cobalamin deficiency, transcobalamin receptor (CD320/TcblR) KOs present with neurological impairments that are similar to the human cobalamin deficiency.197–199 These mice show cognitive deficits and anxiety behaviorally, whereas in vitro examination indicates smaller pyramidal cells and impaired in the CA1 region of the hippocampus together with lower GluR1 expression, indicating an AMPA receptor–mediated LTP deficit. However, seizures have not been observed.

Homocysteinemia

Increased levels of homocysteine in blood and urine in patients presenting with neurological symptoms were reported to be due to cystathionine synthase (CS) deficiency or decreased activity of methylene tetrahydrofolate reductase (MTHFR) enzyme due to autosomal-recessive MTHFR mutations. Insufficiency of cobalamin (or vitamin B12), a cofactor of MTHFR, may also result in homocysteinemia. When homocysteine is not converted to cystathione via CS or not reduced to methionine via MTHFR, it accumulates in many tissues and interacts with a number of molecules including cytochrome C, hemoglobin, and immune mediators. Therefore, homocysteine affects a range of functions including energy metabolism, oxidative reactions, and immunity (for review see). Although the direct link between homocysteinemia and seizures or spasms is not clear, it is known that systemic administration of homocysteine leads to convulsive seizures in adult rats and adult mice and excitotoxicity in organotypic cortical and hippocampal slice cultures from rat brain. In addition, homocysteine accumulation is associated with vascular and neurodegenerative diseases, and also with epilepsy (for review). Folic acid and cobalamin supplements are known to decrease blood homocysteine levels.209

A 14-month-old girl from a nonconsanguineous parents presenting with IS, hyspsarrhythmia, and developmental
delay was shown to have MTHFR deficiency. None of the interventions including betaine, methionine, vitamin supplements, various antiseizure drug combinations, corpus callosotomy, and vagus nerve stimulator implantation blocked her seizures\textsuperscript{205} (Table 2).

Intraperitoneal homocysteine injection of rats of different age groups ranging between 7 and 90 days show age-specific seizures (Table 3).\textsuperscript{210} In immature rats, status epilepticus and flexion seizures are apparent, whereas in adult rats, spikes and spike waves without a behavioral correlation are observed. Intracerebroventricular administration of homocysteic acid in 12-day-old rats leads to generalized tonic–clonic seizures that are completely prevented when NMDA nonselective and selective 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzoquinoxaline-2,3-dione (NBQX) and 2-amino-7-phosphonoheptanoic acid (AP7), respectively, are administered before homocysteic acid.\textsuperscript{211} Likewise, subcutaneous chronic injection of homocysteine in rats from PN6 to PN28 decreases Na\textsuperscript{+}/K\textsuperscript{+}ATPase activity in the synaptic membrane preparations from the hippocampus ex vivo.\textsuperscript{212} Few animal models present with homocysteinemia but the Mthfr KO mouse is the closest phenotype to the one seen in humans.\textsuperscript{197} Heterozygote mice show a moderate increase in homocysteine, whereas homozygotes have a 10-fold increase and they have developmental retardation.\textsuperscript{213} Of interest, WT animals from heterozygote hyperhomocysteinemic mothers show impaired short-term memory assessed by a behavioral test, and slices from these mice indicate apoptosis in the hippocampus.\textsuperscript{214}

**Propionic acidemia**

Autosomal recessively inherited mutations in propionyl-coenzyme A carboxylase (PCC) genes resulted in PCC deficiencies, leading to deficient catabolism of various amino and fatty acids and cholesterol.\textsuperscript{215–218} Due to the resulting accumulation of propionyl-CoA, secondary hypoglycemia, hyperammonemia, and hyperglycinemia, it is considered as a form of ketotic hyperglycinemia\textsuperscript{216} but can also manifest without metabolic symptoms.\textsuperscript{219} Patients are presenting with failure to thrive, vomiting, ketoacidosis, lethargy, and neurological symptoms ranging from developmental delay to seizures and stroke-like episodes. Treatment involves protein-restricted diet and carnitine load to help propionyl-carnitine excretion, although interventions may not prevent or reverse all the neurological symptoms.\textsuperscript{220,221}

In a 4-month-old girl with hypsarrhythmia and propionic acidemia associated with deficient PCC activity in her leukocytes and cultured skin fibroblasts, ACTH treatment stopped her seizures and normalized her EEG. Dietary protein restriction also was reported as beneficial, but she developed ketoacidosis triggered by poor feeding at 11 months of age and developmental delay\textsuperscript{222} (Table 2).

ICV administration of propionic acid in adult rats led to dystonia, hyperactivity, spiking in the caudate, and worsening of kindling-induced seizures; in vitro analysis showed increased oxidative stress and reduced glutathione and glutathione peroxidase activity along with neuroinflammation (Table 3).\textsuperscript{223} Of interest, the authors suggest that this model may serve as a model for autism spectrum disorder (ASD), as it shows impairments of social behavior, social cognition, and sensorimotor ability.\textsuperscript{224,225} In addition, in vitro evaluation of the brains from 21-day-old rats that received oral propionic acid show decreased glutathione and glutathione peroxidase activity, elevated levels of neuroinflammatory markers, interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-\textalpha{}), interferon gamma (IFN-\gamma{}), and heat shock protein 70 (HSP17), and proapoptotic marker caspase 3, along with DNA fragmentation as well as decreased levels of GABA, serotonin, and dopamine.\textsuperscript{226} Despite the fact that IS, especially due to symptomatic origin, is also a known risk factor for ASD,\textsuperscript{5,227} no seizures are reported in this model.

**METABOLIC ERRORS IN ORGANELLES**

**Mitochondrial disorders**

**Pyruvate dehydrogenase complex deficiency**

Pyruvate dehydrogenase complex (PDHC) comprises multiple enzymes that catalyze oxidative decarboxylation of pyruvate to acetyl-CoA, an irreversible and rate-limiting reaction in the aerobic glucose metabolism in mitochondria.\textsuperscript{228} PDHC enzymes are expressed in many cell types, and deficiency of the enzymes leads to lactic acidemia as well as neurological complications, since the brain is a highly energy dependent organ.\textsuperscript{228,229} Lactic acidosis was found to be due to the mutations in the pyrophosphate-dependent pyruvate dehydrogenase (E1) \( \alpha \) subunit of the PDHC,\textsuperscript{230} and these mutations were shown to be the most prominent ones in patients with mild to severe neurological symptoms.\textsuperscript{229,231} Depending on the genomic localization of the mutations on the X chromosome and also the random X inactivation in different tissues, PDHC E1 \( \alpha \) subunit deficiency may have variable effects on tissues with sexually dimorphic features.\textsuperscript{229,231,232}

There are several reports of patients presenting both PDHC deficiency and WS with variable responses to treatment\textsuperscript{231,233–236} (Table 2). A preference for female patients with PDHC to develop WS has been reported.\textsuperscript{234} Genotype-phenotype variability has been observed in patients with PDHC deficiency receiving similar treatments, which could be due to different genetic substrates or variable developmental effects of PDHC deficiency and its treatments.\textsuperscript{237}

Mice with a null mutation of PDHC E1 \( \alpha \) subunit, which removed exon 8 \( (Pdha1 (Deltaex8)) \) from the gene globally, have low PDC activity and reduced litter size, whereas developmental delay was reported in the mice that had the
**Pdh1 (Deltaeα8)** allele predominantly (Table 3). When the same mutation was targeted only to the developing nervous system, using a nestin-cre promoter, male mice died prenatally and only 50% of female mice survived. These female mice had decreased neuronal density and neuropil fibers, abnormal localization of the neurons in the gray matter, reduced lipid synthesis, and irregular myelination. Of interest, the affected female mice survived into adulthood without discernible neurological deficits. Knockdown of the PDHC E1 α subunit via the delivery of siRNAs into striatum and substantia nigra of rats led to abnormal amphetamine-induced rotation, indicating degenerative changes in the nigrostriatal system. A recent investigation of a systemic deletion of exon 8 from PDHC E1 α subunit in mice showed general decrease in brain weight, de novo lipid synthesis, reduced proliferation, differentiation, and migration of newly generated neuronal precursor cells in prenatal and postnatal periods in cerebellum and impaired dendritic development of Purkinje cells. The locomotor activity was normal in these mice; however, they had impaired acoustic startle reflex indicating mild motor abnormalities. In a zebrafish model of PDH deficiency via the impairment of the E2 subunit, ketogenic diet reversed the abnormal vision, lactic acidosis, and lethargic swimming behavior.

**Leigh syndrome (subacute necrotizing encephalomyopathy)**

Leigh syndrome was first described in 1951 based on the autopsy findings of focal, bilateral subacute necrotic white matter lesions in a boy presenting with somnolence, deafness, blindness, and spastic limbs. The lesions are now known to include basal ganglia, thalamus, cerebellum, and brainstem; the symptoms and signs include hypotonia, feeding problems, and psychomotor delay. Mutations leading to this phenotype can be autosomal or X-linked, as in the case of mitochondrial PDHC or respiratory chain mutations, although patients without these mutations were also reported.

Leigh and Leigh-like syndromes presenting with IS/WS were described in several patients due to PDHC mutations (Table 2). Of interest, Tsuji et al. reported 2 sisters with Leigh syndrome, where only one developed WS and in another family both brothers with Leigh syndrome had WS later, adding further to the complexity of pathology in Leigh syndrome with WS patients.

Because mutations in the NADH:ubiquinone oxidoreductase subunit S4 (NDUFS4), encoding a mitochondrial complex I protein, are also related to Leigh and Leigh-like syndromes, Ndufs4 KO mice were generated (Table 3). These mice were behaviorally normal during the first 4 postnatal weeks but their growth was delayed; they progressively became lethargic, ataxic, and blind; lost their startle response; and died by week 7. Selective KO of Ndufs4 in neurons and glia present with similar phenotype as complete KO; however, slices from these mice also showed gliosis and microglial activation in brainstem and cerebellum. Of interest, hypoxia (11% O2) reversed neurodegenerative changes and increased the life span of Ndufs4 KO mice. In addition, rapamycin (an inhibitor of mechanistic target of rapamycin [mTOR]) extended the life span, prevented brain injury, increased the low levels of GABA, dopamine, and free fatty acids, and decreased the glycolytic intermediates without having an effect on oxidative stress markers in Ndufs4 KO mice. Likewise, rapamycin also increased the life span of animals but led to fat storage impairments in a Drosophila model of Leigh syndrome via the complex I subunit NADH dehydrogenase 2 (ND2) deletion. Alterations in glycolytic intermediates and fat storage in these models suggest that rapamycin exerts its effects via the changing metabolism, a hypothesis that is yet to be proven.

**Alpers-Huttenlocher disease**

Alpers-Huttenlocher disease is a rare disorder characterized by microcephaly, refractory seizures, and liver dysfunction that may result from deficiencies in the PDH enzyme in citric acid cycle or respiratory chain or mutations in mitochondrial DNA polymerase gamma (POLG) or FARS2 gene (Phe-tRNA synthetase 2). Three patients with Alpers-Huttenlocher disease and WS were identified in a study examining the etiological factors in 20 patients with mitochondrial dysfunction confirmed by biochemical and morphologic examinations (Table 2). Despite all 3 Alpers-Huttenlocher disease patients having mitochondrial complex I deficiency, it was not inherited in any of them. Among 11 reported cases with FARS2 mutations, 3 (27%) had WS and hypsarrhythmia. No reports of patients with POLG mutations and IS are known to the authors.

The mitochondrial mutator mice, carrying a D257A knockin mutation at the catalytic subunit A of the Polg gene that removes the proofreading ability of the enzyme, show instability of the mitochondrial DNA (mtDNA) with increased mutation rate and deletions in the mitochondrial DNA (mtDNA), leading to early aging (Table 3). Homozygous Polgmut/mut mice manifest reduced body size and weight around the 20th week, prematurely age at around 48 weeks, and die by 61 weeks of life. Heterozygous Polgmut/wt mice do not show abnormalities in aging. A zebrafish model was developed where Polg--/-- larvae survived until juvenile age (4 weeks after fertilization). A different study suggested that early KO of PolgA at the preimplantation stage results in early lethality by embryonic day 11 and depletion of mtDNA in mice.

**Lysosomal storage diseases**

Lysosomal storage diseases comprise a group of disorders including neuronal ceroid lipofuscinosis (NCL), Gaucher disease, Tay-Sachs disease, Hurler syndrome, Niemann-Pick disease, and a few others resulting from deficiencies in lysosomal metabolic enzyme(s) (for...
Autopsy investigations of brain specimens from patients with IS and cognitive dysfunction show spongy dystrophies or leukodystrophies.20,277–280 Some patients with Alexander and Krabbe disease were reported to have IS/WS.281,282 (Table 2). Autosomal dominant mutations in glial fibrillary acidic protein (GFAP) resulting in build-up of Rosenthal fibers in astrocytes may be associated with Alexander disease,283 whereas autosomal recessive mutations in galactosylceramidase gene (GALC) leading to lysosomal glycosphingolipid accumulation was shown to lead to Krabbe disease.284,285

Mice expressing WT and only one copy of the human GFAP (hGFAP) mutation (R239H) causing Alexander disease showed no Rosenthal fiber formation (Table 3).286 However, mice expressing WT and multiple copies of the transgene do show Rosenthal fibers only in adult age, have severe convulsions and a high mortality rate when challenged with kainate but show no spontaneous seizures and leukodystrophy.286 Hypertrophic astrocytes, Rosenthal fiber-like inclusions, and upregulation of small HSPs are seen in mice carrying the hGFAP transgene without mutations but overexpressed GFAP.287 In a similar model, microarray analysis showed increased immune and stress response, neuronal death, and dysfunction.288

Biotinidase deficiency

As an inherited disorder in an autosomal recessive manner, biotinidase (BTD) enzyme deficiency leads to abnormalities in the recycling of the vitamin biotin, which is an important cofactor of carboxylase enzymes that help in the catabolism of complex organic acids, fatty acid synthesis, and gluconeogenesis.289–291 The resulting metabolic dysfunction clinically presents with red skin rash, lactic aciduria, hearing loss, hypotonia, seizures, and developmental delay, and biotin supplements can be used to treat the symptoms.290,292

Three patients with full or partial BTD deficiency and IS partially responsive to biotin supplement have been reported; however, mild to moderate developmental delay persisted in all patients.293,294 (Table 2). Rats fed with a biotin-deficient diet have alopecia of the lower back, delayed growth, and longer latencies in brainstem auditory evoked potentials (BAEPs), indicating an alteration in the auditory system (Table 3).295 BTD KO mice, fed with a biotin-deficient diet show hypotonia, demyelination, axonal degeneration, impaired motor neuron function, lethargy, limping, and ventriculomegaly, in addition to slower growth and weight loss, and these symptoms are reversed with biotin supplement.296,297

D-bifunctional protein deficiency

D-bifunctional protein (DBP) deficiency is one of the peroxisomal disorders with poor prognosis, leading to defective oxidation of fatty acids and synthesis of bile salts due to mutations in the DBP gene also known as paroxysmal
multifunctional enzyme type 2 (HSD17B4) or multifunctional protein-2 (MFP-2). High levels of very long chain fatty acids in the plasma and cultured fibroblasts, hypotonia, facial dysmorphism, neuronal migration defects, demyelination, developmental delay, and seizures may be present (for review). A patient with drug-resistant WS having DBP deficiency has been reported (within Table 2).

Multifunctional protein (MFP2) KO mice mimic the metabolic disturbances at birth leading to failure to thrive and death, but they are not hypotonic and do not show any neuronal migration defects (within Table 3). The surviving MFP2 KO mice, however, have astrogliosis and microglial activation in the gray matter, which is not seen in humans.

In mice, the selective MFP2 deletion either from all neuronal cells (Nestin-Mfp2−/−) or only from oligodendrocytes (Cnp-Mfp2−/−) lead to mild neuroinflammation and axonal impairments in Purkinje cells correlated with motor deficits only in Nestin-Mfp2−/− mice, indicating no oligodendrocytic involvement in this brain pathology. Complete MFP2 KO mice also show severe proneuroinflammatory activation. More recently, morphological impairments, delayed growth, and abnormal neuronal development in the dbp knockdown zebrafish model is rescued by murine Dbp, indicating the benefit of modeling the disease in different organisms.

Williams-Beuren syndrome

Williams-Beuren syndrome (WBS) also known as Williams syndrome is due to variable microdeletions within the WBS area on the long arm of chromosome 7 containing 26 to 28 genes such as, Elastin (ELN) and Syntaxin 1A (STX1A), and may present with various features as hypercalcemia, hypothyroidism, impaired glucose tolerance, growth abnormalities, characteristic facial appearance, mental retardation, and cardiac anomalies. The exact contribution of the involved deleted genes to the WBS phenotype is yet to be elucidated. Treatment is only symptomatic, directed toward the specific clinical presentation of the disease.

In WBS, due to deletions in the WBS area of the 7th chromosome, WS has been reported in 3 children whose spasms were fully or partially treated with ACTH and anti-seizure drugs, although the developmental impairment is progressive (within Table 2). Of interest, the deletions in the membrane-associated guanylate kinase inverted-2 (MAGI2) gene in the very same region of chromosome 7 were previously shown to be associated with IS. The scaffolding protein encoded by MAGI2 is also associated with Stargazin protein. MAGI2 mutations are the cause of epilepsy in the stargazer epilepsy model, which presents with generalized cortical spike and wave discharges accompanied by behavioral arrest and complex bilateral neocortical discharges. A recent study evaluating the candidate genes residing on chromosome 7 in a zebrafish knockdown model reported haploinsufficiency of wagg gene, residing in the telomeric region of the chromosome and encoding 14-3-3 protein gamma, and related this gene with IS and cardiomegaly seen in WBS patients. Because the WBS area encompasses a number of genes, the first experiments focused on both heterozygous and homozygous single gene deletions in this region to elucidate the contribution of each gene to the phenotype (for review). Of these modeled genes, both heterozygous and homozygous deletions of one of the Wnt receptor-coding frizzled 9 (Fzd9) gene, involving in the neurotrophic processes, led to decreased pentyletetrazole-induced seizure threshold and abnormalities in hippocampal structure, whereas the homozygous deletions also result in spatial learning impairments in mice (within Table 2). The large-scale deletions in proximal and/or distal regions in the mouse WBS area present with cognitive impairments in distal deletions and defective motor skills in double, heterozygotes (proximal and distal deletions), showing a closer relation to the human phenotype. Heterozygous, almost-complete deletions of the WBS region in mice reduce brain weight and dendritic length and spine density in the hippocampus and GFAP-positive cells in the amygdala; increase the number of immature cells in the DG; and lead to craniofacial and cardiac abnormalities. In addition, complete deletion mice show spatial learning deficits, and slices from these mice indicate unstable LTP with no changes in presynaptic function or AMPA and NMDA receptor activity in CA1 but low brain-derived neurotrophic factor (BDNF) levels in CA1-CA3 regions.

Congenital disorders of glycosylation, molybdenum cofactor deficiency, and primary carnitine deficiency

Several disorders such as congenital disorders of glycosylation (CDG), molybdenum cofactor deficiency (MCD), primary carnitine deficiency (PCD), and isovaleric acidemia (IVA) were also reported in patients with WS. CDG is a group of disorders with deficient glycosylation of proteins and lipids, leading to their abnormal folding, transport, stability, and activity. A patient with abnormal vision, IS, hypsarrhythmia, abnormal myelination, reduced white matter, and developmental and motor delay was shown to have a deficient glycosylation, classified as CDG-li, as investigated by serum transferrin isoelectric focusing (within Table 2). This defect impairs the transfer of mannosyl residues at the cytosolic side of endoplasmic reticulum, leading to deficient oligosaccharide biosynthesis. Mouse models for 2 different groups of CDGs (CDGI and CDG II) are currently available (for review). However, transient paralysis and tremors that resemble the epileptic seizures are reported only from 20% of mannosyl (alpha-1,6)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase (Mgat2)–null mice modeling the CDG type IIA (within Table 3). A further evaluation is needed to understand the pathology in this model. MCD and PCD were reported.
in 2 different WS patients in a study that investigated the metabolic etiologies in 80 children.20 Both patients were nonresponsive to antiseizure drugs and showed severe developmental delay (Table 2).

Molybdenum is a cofactor of xanthine dehydrogenase, sulfite oxidase, and aldehyde oxidase and in the absence of it, all these enzymes are affected leading mainly to toxic accumulation of sulfite.17 Carnitine is involved in the transport of long-chain fatty acids and peroxisomal oxidation products, such as acetyl-CoA, into mitochondria for oxidation. Deficiency in carnitine transport leads to PCD with defective fatty acid oxidation and fatty acid accumulation.

Because few mutations in molybdenum cofactor synthesis protein 1 and 2 (MOCS1 and MOCS2) genes and one mutation in gephyrin (GPHN) gene leading to MCD are reported, several animal KO models are described (for review324). MOcs1 KO mice survive 1 to 11 days with no convulsions, ataxia, or structural changes in the brain (Table 3).325 Systemic injection of adenoviruses carrying human MOCS1 cDNA increases the life span of the MOcs1 KO mice that are treated via hepatic injections of cyclic pyranopterin monophosphate (ePMP), a precursor in the molybdenum cofactor synthesis, until they are old enough to get a systemic injection.326 MOcs2 KO mice also survive for 11 days on average; pathological and biochemical studies show apoptosis in the hippocampus, cortex, and brainstem; inactivation of all molybdenum cofactor-dependent enzymes; and accumulation of hypoxanthine, xanthine, and S-sulfocysteine.327

Dietary restriction of carnitine in rats leads to 50% of reduction in its physiological levels, indicating an ongoing endogenous synthesis but induces no major anatomical or behavioral changes (Table 3).328 Dietary restriction, together with supplement of butyrobetaine hydroxylase inhibitor that blocks the last step of the carnitine synthesis results in carnitine deficiency within 3 weeks in rats; however, only liver anomalies are reported.329 Of interest, when combined with acyl-CoA, acylcarnitines, including acetyl-L-carnitine, have neuroprotective effects in various disorders such as330 Alzheimer’s disease331 and ischemia-hypoxia–induced brain injury332 (for review333). Carnitine deficiency may result in loss of these protective effects. In addition, the link between PCD and autism is investigated.334

Isovaleric acidemia due to deficient isovaleryl-CoA dehydrogenase (or IVD) enzyme was confirmed in cultured fibroblasts from a boy in presenting with vomiting, lethargy, and WS335 (Table 2). IVD is involved in the catabolism of leucine, and in IVD deficiency, this amino acid cannot be degraded, leading to excess excretion of isovalerylglucose (IVG).336 To our knowledge, currently there is no model mimicking isovaleric acidemia; however, application of isovaleric acid or IVG onto cortical homogenates of 30-day-old rats indicates no changes in citric acid cycle or creatine kinase activity, whereas synaptic membrane preparations from these homogenates show that IA decreases Na+/K+ ATPase activity via peroxide radicals (Table 3).337 In a similar in vitro experiment using brain homogenates and mitochondrial preparations, IVG but not IA leads to lipid peroxidation and reduced GSH levels in a mitochondria-independent way. On the other hand, IA triggers protein oxidation.338 Despite the fact that no other phenotype is defined in these experiments, in vitro alterations are suggestive of neurodegenerative transformations.

**Diagnosis of metabolic etiologies**

As discussed earlier, the frequency of metabolic disorders in the diagnostic evaluation of infants with IS varies among studies, ranging between 3% and 47%, depending on the cohort, the type, and extent of diagnostic investigation for such causes, and the criteria used in each study to distinguish “metabolic disorders” from “genetic etiologies” or “inborn errors of metabolism.”9,19,20 In infants with IS, metabolic disorders for which we have more evidence for a higher association with IS include PKU, NKH, Menkes disease, pyridoxine responsive or dependent seizures, methylmalonic aciduria, and mitochondrial disorders (Table 2). In general, such diagnostic tests may include routine clinical chemistry (eg, electrolytes, glucose, ammonia, lactate, liver function, or creatine kinase), amino acids, monoamines, or organic acids in blood, urine, or cerebrospinal fluid, specific assays for the activity of certain enzymes, genetic testing for nuclear or mitochondrial DNA defects, or biopsy. Especially newborn screenings from a basic biochemical test to rapid tandem mass spectrometry or genetic tests if indicated may lead to early detection of these abnormalities even before the appearance of the symptoms.339,340 Early identification may also assist in the fast clearance of toxic metabolites (ie, hyperammonemia) and could improve the course of the disease, as in PKU,22 cobalamin deficiency,20,23,339–341 or pyridoxine-responsive seizures. It is beyond the scope of this review to detail the diagnostic workup indicated for each condition or provide guidelines for the physician. The clinical suspicion for an underlying metabolic or genetic etiology plays a significant role in initiating the specific workup, particularly in regions where cost and availability may be a prohibiting factor, which could also affect the reported incidence of such etiologies. Clinicians are therefore guided by other features, symptoms, or signs of these disorders, including neuroimaging findings or expected rate of specific metabolic disorders in the relevant population to direct the diagnostic workup by assessing the cost-benefit relationship of each test before ordering extensive diagnostic metabolic
workups. We refer the readers to textbooks or specific reviews that address the diagnostic features and findings of such disorders. MRI or routine metabolic studies, including glucose and lactate/pyruvate, or organic and amino acids analysis, may help guide further diagnostic decisions. Genetic testing with specific epilepsy panels or whole-exome sequencing, which may also identify defects in certain neurometabolic genes, are increasingly available. More specific diagnostic tests for metabolic disorders may be requested based on clinical suspicion and available diagnostic workup.

Associated features that may help the diagnostic evaluation include the neurological exam (eg, hypertonia or hyporeflexia) or presence of movement disorders (Table 2). Clinical examination may give hints such as dysmorphic features and neonatal diabetes (eg, DEND), skin hypopigmentation (eg, Menkes disease), facial elfin appearance (eg, Williams-Beuren syndrome), abnormal facies (eg, PDHC deficiencies), alopecia (eg, biotinidase deficiency), abnormal visual responses (eg, NKH), or alterations in auditory-evoked potentials (eg, NKH, methylmalonic aciduria, and biotinidase deficiency), optic atrophy (eg, Leigh syndrome and biotinidase deficiency). Biochemical screening is typically the first approach to diagnose the metabolic abnormalities. In blood—increased Phe (PKU), glycine (NKH, propionic acidemia), homocysteine (homocysteinemia), propionate (propionic acidemia), lactate (Leigh syndrome, biotinidase deficiency, isovaleric acidemia), ammonia (PCD, isovaleric acidemia) or lactate; or decreased glucose (GLUT1 deficiency), Cu and ceruloplasmin (Menkes disease), B12 (B12 deficiency), carnitine (PCD); in urine—increased ethylmalonic acid (SCAD deficiency), glyceric acid (D-GA), methylmalonic acid (methylmalonic aciduria), propionate (slightly propionic acidemia), sulfocysteine or decreased uric acid (GLUT1 deficiency), or alterations in auditory-evoked potentials (eg, NKH, methylmalonic aciduria, and biotinidase deficiency), or decreased lactate (Leigh syndrome, biotinidase deficiency), or increased pyridoxine dependency give hints about the respective diseases. Decreased DHPR (DHPR deficiency), cystathionine synthase (homocysteinemia), alpha-L-iduronidase (Hurler syndrome), SMPD (Niemann-Pick disease) or abnormal propionyl CoA (propionic acidemia), cytochrome c oxidase (Leigh syndrome), and enzymatic activities can also be used as confirmatory analyses. Anemia (B12 deficiency) and neonatal diabetes (DEND), cardiac problems (Leigh syndrome, Williams-Beuren disease), and liver dysfunction (Alpers-Huttenlocher disease) are also some symptoms of the respective diseases (Table 2).

MRI findings may be normal in some cases as DEND, GLUT1 deficiency, or isovaleric acidemia, or provide either nonspecific features (atrophy, delayed myelination, white matter abnormalities) or specific alterations such as in acidurias (abnormal signals from globus pallidi) or Leigh syndrome (basal ganglia and SN lesions) (Table 2). Dysgenesis of corpus callosum and gyral abnormalities may also be present in certain patients with NKH.

CONCLUSIONS

Metabolic etiologies are one of the major contributors to the evolution of WS pathology. Because WS presents in early ages when most of the developmental changes are occurring, where both temporal and spatial coherence are critical, especially for the brain maturation, the presentation and progression of the symptoms and responses to the treatment are variable in patients having inborn errors of metabolism together with WS. The IS/WS phenotype has not been reported yet in several of the existing experimental models for metabolic diseases; nevertheless, these models provide invaluable information about putative pathogenesis and prevention as well as development and fine tuning of newer and better models. Despite the lack of knowledge in the exact pathology of many metabolic errors leading to IS/WS, diagnosis of the metabolic deficiency may decelerate the progression of WS, ameliorate patients’ symptoms, and in some cases even treat WS patients. Therefore, screening for disorders of inborn metabolic pathways including physical and neurological examination, biochemical and/or genetic investigations, and MRI (where possible), are helpful in diagnosis. The development of animal models is critical not only for diagnosis but also for improving our knowledge about the pathways involved in WS generation.

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CONFLICT OF INTEREST

S.S. has no conflicts of interest. S.L.M. has no conflicts of interest with regard to this review. He is serving as Associate Editor of Neurobiology of Disease and is on the editorial boards of Brain and Development, Pediatric Neurology, and Physiological Research. He receives from Elsevier an annual compensation for his work as Associate Editor on Neurobiology of Disease and royalties from 2 books that he coedited. He received a consultant fee from UCB for participation in a Data Safety Monitoring Board. He has also received honorarium for participation in an advisory board meeting of Mallinckrodt, but there is no conflict of interest with regard to the

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