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CRITICAL REVIEW AND INVITED COMMENTARY

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.

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]

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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]

METABOLIC ERRORS IN ORGANIC MOLECULES

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%) hypsarrhythmic 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

Table 1. Metabolic etiologies in IS

Metabolic errors in organic molecules		
Amino acid metabolism		
Phenylketonuria	Nonketotic hyperglycinemia	
Glucose metabolism & transport		
DEND	Persistent symptomatic hypoglycemia (specific syndromes)	GLUT1 deficiency
Fatty acid oxidation		
SCAD deficiency		
Metal metabolism		
Menkes disease		
Vitamin B6-, Pyridoxine dependency, & pyridoxal 5′P deficiency		
Acidurias		
D-Glyceric Aciduria	Methylmalonic acid & cobalamin deficiencies	
Homocysteinemia	Propionic acidemia	
Metabolic errors in organelles		
Mitochondrial disorders		
PDHC deficiencies	Leigh syndrome	Alpers-Huttenlocher disease
Lysosomal storage diseases		
Hurler syndrome	Niemann-Pick disease	
Other diseases		
Leukodystrophies	Biotinidase deficiency	DBP deficiency
Biotinidase deficiency	Williams-Beuren Syndrome	CDG
Molybdenum cofactor deficiency	Primary carnitine deficiency	Isovaleric acidemia

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.

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).[22] Other studies also reported PKU patients presenting with hypsarrhythmic EEG and/or IS[34–37] (Table 2).

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 (GCHI)*, *DHPR*, or *6-pyruvoyl tetrahydropterin synthase (PTPS)* gene deficits.[38] 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.[38–40] DHPR deficiency may further reduce the activity of folate.[38] 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 pterins in urine, blood, or cerebrospinal fluid (CSF); and CSF levels of metabolites of monoamines (homovallinic acid [HVA], 5-hydroxyindoleacetic acid [HIAA]).[38] If DHPR deficiency is documented, consideration of additional specific or supplemental treatments for this disease including BH4, folinic acid, or drugs that supplement the monoaminergic deficits should be considered, in addition to Phe dietary restriction.[38]

DHPR deficiency may also lead to IS and hypsarrhythmia, even though this is one of the rare etiologies[41] (Table 2). Phe restriction and neurotransmitter supplement improved a patient's outcome[42]; however, in a patient with IS, an additional therapy with steroids was needed to control spasms and hypsarrhythmia.[41]

Early neurological sequelae (ie, delayed myelination) may be overlooked depending on the onset of Phe accumulation,[37] since myelination is a continuous process starting from the last days of gestation and reaching through adulthood (for review[43]). In addition, 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.[37,44,45]

In vitro and in vivo experimental PKU models have provided significant insights (Table 3).[46–51] L-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 2. Disorders of inborn errors in metabolism: clinicopathological findings and association with WS

Metabolic errors in West syndrome

Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
Metabolic errors in organic molecules					
Amino acid metabolism					
Phenylketonuria (PKU)	• AR – PAH[26–28] • AR - DHPR Deficiency[39,40]	• ↑ Phe[22,34,35,37] • Mental retardation[22,34–36] • *↑ Biopterin, ↓ DHPR activity[41] • Hypotonia[36,37,41] • Developmental delay[37,41]	• Cerebral atrophy[41] • Delayed myelination[22,41] • Lesions in white matter, basal ganglia, cerebellum, brain stem[37]	• IS with typical or modified hypsarrhythmia has been reported in up to 12% of PKU patients when pediatric population is included.[22,35,36,41] • In a study, 82% of patients with PKU were diagnosed with IS prior to the diagnosis of PKU.[22] • 30.4% (7/23) of patients with PKU had hypsarrhythmia and 5 of them reported IS in.[35]	• Protein restriction: 8/62 cases: trigger IS[22] 17/62 cases: effective (with 77.8% relapse)[22] • Protein restriction + VPA and/or NTZ: 11/62: effective (18.2% relapse)[22] • Protein restriction effective in 2 cases, reduction in spasms in 1 case, not effective in 1 case[35] • (1) Corticotropin, (2) corticotropin + protein restriction (1) only reduction in spasms, (2) effective in 1 case[36] • Protein restriction, VGB, VPA, Benzodiazepines and prednisolone: no effect in 1 case[37] • (1) Protein restriction, L-DOPA, 5-HT, (2) Protein restriction, CZP (3) Protein restriction, hydrocortisone and neurotransmitter support (1) No effect, (2) Partial effect on myoclonus (3) effective in 1 case[41]
Nonketotic hyperglycinemia (NKH)	• AR - GLDC, AMT or GCSH[52–54,67]	• ↑ 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, hypsarrhythmia[54,65–68,343] • IS/hypsarrhythmia are considered common among neonatal NKH survivors beyond neonatal age.[17,54,64] • 0.7% (1/134) of IS patients with metabolic screening in[9] had NKH.	• NTZ & PHT No effect in 2 cases[65] • AEDs (unmentioned) No effect in 3 cases[67] • Sodium benzoate, ketamine, dextromethorphan, VGB, PHB, PHT, CZP, diazepam, ACTH Only reduction in seizures, developmental delay persists in 1 case[68] Case reports of vigabatrin-induced acute encephalopathy reported in two infants with NKH[343]
Glucose metabolism and transport					
Developmental delay, epilepsy and neonatal diabetes (DEND)	• AD - KCNJ11[77,80–82]	• Neonatal Diabetes[77,80–82] • Developmental delay[77,80–82]	• Normal[81]	• Case reports of IS & hypsarrhythmia[77,80–82]	• (1) Insulin, (2) PHB, VGB, PHT, ACTH (3) ACTH and glucocorticosteroids + Sulfonylurea

Continued

Table 2. Continued.

Metabolic errors in West syndrome					
Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
		• Hypotonia[77,80,81] • Ptosis[77,80] • Dysmorphic features[77,80]			(1) effective against DM, (2) not effective, (3) effective in 1 case but the patient died after initial amelioration[80] • (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[81] • Sulfonylurea effective in 1 case[82]
Persistent symptomatic hypoglycemia probably associated with several underlying etiologies that may have contributed to the outcome	N/A	• ↓Glucose[20,87,88,344] • Developmental delay[20,87] • Microcephaly[20] • Hypotonia[20]	• Normal[20,87,88] • Uni- or bilateral parietooccipital cyst[87,88] • Abnormal occipital/parietal signal[20,88]	• IS & Typical/modified hypsarrhythmia[20,87,88,344] • IS[87] • IS & bilateral epileptic activity[87]	• (1) Glucose infusion and prednisolone, (2) +diazoxide and nifedipine, (3) +ACTH, (4) no effect ACTH, positive effect with PHB 1: No effect, 2: Effect on hypoglycemia, (3) Effect on spasms, (4) continued therapy in 1 case[344] • (1) Diazoxide, chlorothiazide, (2) +VPA, ACTH, prednisolone (3) VGB, Lamotrigine (1) Effect on hypoglycemia, (2) No effect on spasms, (3) controlled seizures in 1 case[87] • (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[87] • (1) Diazoxide, chlorothiazide, (2) prednisolone, currently CBZ (1) Effect on hypoglycemia, (2) reduction in spasms in 1 case[87] • (1) Pancreatectomy, (2) ACTH (1) DM development (2) IS stopped, developmental delay persists in 1 case[87] • (1) Pancreatectomy, (2) VGB(1) DM development, (2) N/A[87] • VGB Spasms resolved but focal seizures continued in 1 case, not effective in 1 case[20]

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Table 2. Continued.

Metabolic errors in West syndrome

Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
GLUT1 deficiency	• Deficiency in glucose transporter[104,106] • SLC2A1 mutation[112]	• ↓Glucose[104,111] • ↓Lactate[104] • ↓ CSF/blood glucose[104,111,112] • Developmental delay[111] • Microcephaly[111]	• Normal[111,112]	• Convulsions, IS[111] • IS-flexion & hypsarrhythmia[112] • Rare association with IS	• (1) ACTH, (2) Pyridoxine, biotin folinic acid, (3) Ketogenic diet 1&2: no effect, 3: effect on IS and seizures in 1 case[111] • Ketogenic diet Effect on seizures, developmental delay persists with slight improvement in 1 case[112]
Fatty acid oxidation					
SCAD deficiency	• AR-ACADS[116]	• ↑ Ethylmalonic acid[117] • Developmental delay[117]	• Hypoplastic corpus callosum without splenium and rostrum[117] • Abnormal cortical gyri[117]	• One case report with generalized tonic-clonic seizures, IS & hypsarrhythmia[117]	• (1) ACTH, (2) NTZ, TPR, gamma globulin, ZNS (1) partial effect, (2) no effect in 1 case[117]
Metal metabolism					
Menkes disease	• XR - ATP7A[125,127,128,130–133]	• ↓ Cu & ↓ Ceruloplasmin[123,125,128,130] • Developmental delay[123,130] • Mental retardation[123,130] • Hypotonia[123,125,128] • Hypopigmentation in skin[123,130] • Fragile hair[125]	• Ventricular dilatation[123] • Abnormal cerebral vessels[125,128,129] • Cortical atrophy[125,128,129] • Delayed myelination[129]	• IS are common in Menkes disease; all infants with Menkes disease had IS in[126] • IS, multifocal clonic seizures & Hypsarrhythmia[123] • IS with/out slow and asymmetric background activity with multifocal spikes and slow wave discharges[125] • IS & (modified) hypsarrhythmia[127,129,130] • IS & diffuse irregular slow waves and spike waves[126] • IS, partial seizures & hypsarrhythmia[128] • IS, focal seizures & hypsarrhythmia[129]	• (1) Cu-His therapy (2) PHB, primidone, PHT, CZP, VPA (1) Partial effect only initially, (2) Not effective in 1 case[123] • Cu-His, VGB/NTZ Effect on Cu level but only partial effect on IS in 2 cases[125]
Vitamin B6, pyridoxine dependency and pyridoxal 5′P deficiency					
Vitamin B6, Pyridoxine dependency and Pyridoxal 5′P deficiency	• AR – PNPO[164,165] • AR - ALDH7A1[166–170]	• Developmental delay[165,169] • Mental retardation[168] • Tonic-clonic convulsions, myoclonic jerks following pyridoxine withdrawal test[168] • ↑ Pipecolic acid[169]	• Atrophy[165] • Increased subarachnoidal space[165]	• Myoclonic, multifocal seizures, IS-flexion & suppression-burst activity[165] • Generalized tonic clonic seizures & hypsarrhythmia in 3 cases[168] • IS, hypsarrhythmia[169]	• 13% (7/53) of patients with pyridoxine-dependent and/or responsive seizures had IS.[345] • Pyridoxine, benzodiazepine, VGB, TPR, ACTH, PHB, CZP, VPA, clobazam, pyridoxine, ketogenic diet No effect in 1 case (PLP-never tried)[165] • (1) VGB, (2) ACTH, (3) Pyridoxine (1 & 2) Not effective, (3) effective but

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Table 2. Continued.

Metabolic errors in West syndrome					
Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
				• 13% (7/53) of patients with pyridoxine-dependent and/or responsive seizures had IS.[345] • 64% of late-onset patients with pyridoxine-responsive and/or dependent seizures had IS.[345] • 0.8% (1/127) of patients with IS had pyridoxine dependency.[192]	autism spectrum disorder persists in 1 case[169] • Pyridoxine Effective in 3 cases[169]
Acidurias					
D-Glyceric aciduria (D-GA)	• AR – GLYCTK[176]	• ↑ Glyceric Acid[176–179] • Hypotonia[179] • Autistic behavior[179] • Motor and mental retardation[179]	• Delayed myelination[179] • Cerebral atrophy[179] • Increased T2 signal from mesencephalon, pontine tegmentum, bilateral dentate nuclei, globus pallidus and thalami[179]	• One case report with IS.[179] • Epileptic fits & multifocal generalized activity with hypsarrhythmia[179]	• (1) VGB, (2) ACTH, (3) fructose-restricted diet + VGB + diazepam (1) Not effective, (2 & 3) partially effective, dietary restriction resolve MRI abnormalities in mesencephalon, thalami and globus pallidus, in 1 case[179]
Methylmalonic Aciduria & B12 Deficiency	• AR – MUT[183,186–189]	• ↑ MMA[19,189,190] • ↓ B12[23,190,191] • Developmental delay[19,23,189] • Macrocytic anemia[190] • Pernicious anemia[191] • Hypotonia[23,189,190] • Abnormal BAEP[19]	• Abnormal signal from 2 globi pallidi[189] • Cerebral atrophy[191] • Delayed myelination[191]	• IS & hypsarrhythmia[19,23,189,190] • 10% of IS patients in[19] had methylmalonic aciduria • 0.7% (1/134) of IS patients with metabolic screening in[9] had methylmalonic aciduria	• 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[19] • Low protein diet, L-carnitine, hydroxycobalamin and VGB, lamotrigine, hydrocortisone First 3 treatments are effective on MMA and the rest effective on IS, hypsarrhythmia resolves by time, developmental delay persists in 1 case[189] • Cyanocobalamin, PHB, ACTH Effective in 2 cases[23] • ACTH and Vitamin B12 Effective in 1 case[190] • B12 Triggered IS that is responsive to anti-seizure treatment[191]
Homocysteinemias	• AR –MTHFR[200–202,204]	• ↑Homocysteine (maybe also ↓ B12)[200–202,204] • ↓ CS activity[200–202] • Developmental delay[204]	• Demyelination[204]	• Case report with IS & hypsarrhythmia and drug resistant epilepsy with episodes of status epilepticus.[204]	• Betaine, methionine, folic acid, corpus callosotomy, vagal nerve stimulation Not effective in 1 case[204]
Propionic Acidemia	• AR – PCC[215–218]	• Glycinuria[222] • Propionic academia[222]	N/A	• Case report with myoclonic seizures & hypsarrhythmia[222]	

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Table 2. Continued.

Metabolic errors in West syndrome

Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
		• Deficient propionyl CoA activity[222]			• ACTH and later protein restriction Seizures stopped but developmental delay persisted in 1 case[222]
Metabolic errors in organelles					
Mitochondrial disorders					
Pyruvate dehydrogenase complex (PDHC) deficiencies	• PDHC deficiency • X-linked-PDHC E1α[1,229–236]	• Lactic acidosis[233–236] • Developmental delay[231,233,235,236] • Hydrocephalus[231] • Hypotonia[231,233,235,236] • Abnormal facies[231,235,236] • Microcephaly[231,233,235,236]	• Cortical atrophy[231,233]	• Seizures & hypsarrhythmia[231] • IS & hypsarrhythmia[233–235] • IS-flexion & multiple spike and slow wave discharges[236] • 30% (9/30) of female patients with PDHC had WS.[234] • 3% (1/30) of male patients with PDHC had WS.[234]	• High fat diet, biotin, lipoic acid, thiamine Not effective in 1 case[231] • Thiamine, bicarbonate, biotin, folic acid Not effective in 1 case[231] • Thiamine + ketogenic diet and Thiamine + DCA Mildly effective in 1 case and effective in the same case, respectively, but developmental delay persists[233] • DCA + Vitamin B1 Effective in 3 cases, not effective in 3 cases[234] • DCA + Vitamin B1 + Vitamin b6 + ZNS Effective in 1 case[234] • Multiple therapies [Vitamin B6, VPA + CZP, Thiamine, DCA] B6-not effective, the rest-mild effect in 1 case[235]
Leigh and Leigh-like syndrome	• Nuclear (including PDHC) or mitochondrial variants of genes involved in cellular energy production[20,245–251]	• Developmental delay[20,246,248–251] • ↑ Lactate or pyruvate[20,246,250,251] • Hypotonia[20,246,251] • Spasticity[246] • Optic atrophy/ retinopathy[246,251] • Cardiac problems[246] • Cytochrome c oxidase deficiency[250] • Liver dysfunction[259–261]	• Basal ganglia lesions [80%][246,251] • Thalamus lesions [40%][246,250] • SN lesions [40%][246,249] • Putamen and brain stem lesions[248–250] • Cerebral white matter myelination abnormalities[249,250]	• IS-flexion or extensor & hypsarrhythmia[20,246,248–251] • Clonic convulsions, myoclonic seizures, apneic seizures, hemiconvulsions, opsoclonus-myoclonus[246,251] • Tonic seizures[249] • Tonic-clonic convulsions[250] • 0.7% (1/141) of IS patients with genetic testing had Leigh disease in[9] • 2/80 (2.5%) of patients with IS had clinical Leigh-like syndrome in[20]	• VGB Not effective in 1 case[20] • ACTH Effective in 2 cases, not effective in 1 case[246] • CZP Effective in 2 cases,[250] Effective only in myoclonus in 1 case[251] • Vitamin B6 Mildly effective in 1 case[249] • CBZ and ACTH Effective in seizures in 1 case, developmental delay persists[250] • VGB, +Hydrocortisone or +CZP Effective on IS in 3 cases, developmental delay persisted in all[251] N/A

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Table 2. Continued.

Metabolic errors in West syndrome					
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[260] • FARS2[262,263] • POLG mutations[259–261]	• Mental retardation[260] • Spasticity[260]	• Generalized, symmetric cortical atrophy[260]	• IS, hypsarrhythmia, myoclonic jerks (complex I deficiency)[260] • 27% (3/11) reported patients with FARS2 mutations have IS and hypsarrhythmia, one also had focal seizures[262,263] • No known cases of POLG mutations and IS	
Lysosomal storage diseases					
Hurler Syndrome Niemann Pick Disease	• Low a-L-iduronidase (IDUA) activity)[269] • AR – SMPD I[270]	• ↓α-L-iduronidase activity (Hurler syndrome)[269] • ↓ SMPD enzyme (NPD)[270] • Psychomotor retardation[269] • Opaque cornea[269] • Diminished bone density[269]	• Dilatation of ventricles[269] • Hydrocephalus[269]	• Case reports of IS & hypsarrhythmia[269,270]	• VGB, TPR, Corticotrophin, VPA, surgical intervention No effect in 1 case[269]
Other diseases					
Leukodystrophies Alexander disease Krabbe Disease	• AD - GFAP[282,283] • AR - GALC[284,285]	• Developmental delay[282,283]	• Demyelination[282] • White matter degeneration[277–280] • Spongy vacuolation[277–280]	• Case reports IS • IS-flexion & hysparrhythmia[282] • IS & convulsions[283]	• VGB Effective on IS but developmental delay and other seizures persist in 1 case[282] • ACTH Effective only on IS in 1 case but developmental delay persists[283]
Biotinidase deficiency	• AR - BTD[291,294] • ↓ BTD activity[289–294]	• Red skin rashes[290,292] • Lactic aciduria[290,292] • ↑ alanine[293] • Hypotonia[293,294] • Alopecia[293,294] • Optic atrophy[293] • BAEP abnormalities[293,294] • Developmental delay[293,294]	• Normal[293] • Atrophy[294]	• Case reports IS • IS & burst suppression pattern[293] • Only IS and convulsions[293] • IS-flexion spasms &hypsarrhythmia[294]	• Corticotropin & PHB Partially effective on IS in 1st case[293] • Biotin supplement Effective on IS but persisting developmental delay in 1st and 2nd case[293] • Corticotropin Partial effect on IS in 2nd case[293] • PHB +VPA No effect on convulsions in 2nd case[293] • (1) PHB +VPA, (2) Phenytoin, (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[294]
D-Bifunctional protein (DBP) deficiency	• AR - HSD17B4[298–300] • ↓ DBP activity[298–302]	• Hypotonia[302]	• Abnormal periventricular white matter[302]	• Case report of IS & modified hypsarrhythmia[302]	• (1) Pyridoxine, (2) Clordemetildiazepam, (3) VPA, Clobazam, lamotrigine (4) VGB

Continued

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Table 2. Continued.

Metabolic errors in West syndrome

Metabolic disorder	Mode of inheritance—metabolic or gene defect	Main clinical and laboratory abnormalities	Brain pathology	Association with IS	Treatment effect on IS
			• Septum pellucidum cyst[302] • Hypoplastic corpus callosum[302]		(1) no effect, (2) no effect, (3) no effect, (4) only reduction in spasms[302]
Williams Beuren syndrome (WBS)	• AD, Deletion at WBS area of 7q[307–310]	• Facial elfin appearance[310,311] • Cardiac anomalies[310,311] • Developmental delay[310,311]	• Normal[310,311]	• Case reports of IS & hypsarrhythmia[310,311]	• ACTH, CLZ, VGB, VPA Over 50% effect on IS in first case[310] • ACTH, VPA Effect on IS in second case[310] • (1) Pyridoxine, VPA, (2) ACTH (3) ZNS, NTZ, PB (4) TRH (5) PHB, ZNS (1) No effect (2) effective for IS, but progressive ventricular hypertrophy, (3 & 4) partially effective, effect only on IS in 1 case[311]
Congenital Disorders of Glycosylation (CDG), Molybdenum Cofactor Deficiency (MCD), Primary Carnitine Deficiency (PCD)					
Congenital Disorders of Glycosylation (CDG)	• Deficient glycosylation[319,320]	• Abnormal vision[319] • Developmental and motor delay[319]	• ↓white matter[319] • abnormal myelination[319]	• Case report of IS & hypsarrhythmia[319]	N/A
Molybdenum cofactor deficiency (MCD)	• AR - MOCS 1 and 2[324] • AR-GPHN[324] • Toxic sulfite accumulation[324]	• Developmental delay[20] • Hypotonia[20] • Microcephaly[20] • ↑sulfocysteine[20] • ↓uric acid[20]	• Delayed Myelination[20]	• Case report of IS-flexion spasms & hypsarrhythmia[20]	• VGB, LEV, VPA Not effective in 1 case[20]
Primary carnitine deficiency (PCD)	• Defective fatty acid oxidation[323]	• Developmental delay[20] • Hypotonia[20] • ↓carnitine[20] • ↑ammonia[20]	• Atrophy[20]	• Case report of IS-extension spasms & asymmetric hypsarrhythmia, focal seizures[20]	• VGB, CLZ, LEV Not effective in 1 case[20]
Isovaleric acidemia	• IVD enzyme deficiency[335,336]	• ↑IVG[335,336] • Lactic acidosis[335] • Hyperammonemia[336]	• Normal[335]	• Case report of IS-flexion spasms & hypsarrhythmia[335]	• (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[335]

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, Biotinidase; CBZ, Carbamazepine; CDG, Congenital disorders of glycosylation; CS, Cystathionine synthase; CSF, Cerebrospinal fluid; CZP, Clonazepam; 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; NKH, Nonketotic hyperglycinemia; NTZ, Nitrazepam; PAH, Phenylalanine hydroxylase; PCC, Propionyl-coenzyme A carboxylase; PCD, primary carnitine deficiency; PDHC, Pyruvate dehydrogenase complex; PHB, Phenobarbital; Phe, Phenylalanine; PHT, Phenytoin; PKU, Phenylketonuria; PNPO, Pyridoxine-5'-phosphate oxidase; POLG, catalytic subunit of mitochondrial DNA polymerase gamma; SCAD, Short-chain acyl-coenzyme A 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, Valproic Acid; WBS, Williams-Beuren syndrome; WS, West Syndrome; ZNS, Zonisamide.

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in the presence of very high Phe levels.[47] This effect may precipitate seizures, in certain situations, when Phe levels are normalized after its dietary restriction reversing the depressed glutamatergic transmission.[47,49] 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 *Pah*^{enu2} 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.[46,50,51] The adult *Pah*^{enu2} model mimics the clinical pathology as well as presents with a decreased threshold to audiogenic seizures.[46,49,50] 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.[48]

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).[52–54] 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,[55] as well as to enhance transmitter release in rat auditory brainstem slices.[56] 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.[54]

NKH symptoms may start to appear in neonatal, infantile, or a later period, with a better prognosis in the latter.[53,54] Transient NKH was also reported with a good prognosis.[57–59] The affected individuals show elevated plasma and CSF glycine levels, and present with hypotonia, seizures, and developmental delay.[60–62] 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.[63] Among the patients with NKH who manifested seizures, 29% had burst suppression on EEG and 5% had hypsarrhythmia.[63] 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 hypsarrhythmia as a common feature of NKH among infants who survive beyond the neonatal period.[17,54,64]

NKH patients manifesting with WS have been reported[54,65–68] (Table 2). Because the prognosis is very poor in neonatal-onset NKH, Korman et al.[68] treated, immediately after birth, a prenatally diagnosed male newborn carrier of a *GLDC* mutation with sodium benzoate and ketamine (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.[69] 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.[70] 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.[71] Likewise, after focal cerebral ischemia, mice with low GCS activity demonstrate greater neuronal injury compared to wild-type (WT) animals.[72]

The glycine transporter 1 (*Glyt1*) knockout (KO) mice have been used to model features of glycine encephalopathy.[73,74] 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.[73] An association between NKH and GLYT1 was suspected in a patient with no GCS abnormality but absence of glycine transport system on autopsy.[75] 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.[76]

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 ($K_{ir}6.2$) of the adenosine triphosphate (ATP)–sensitive inward-rectifier potassium channels (K_{ATP}). In the presence of ATP, K_{ATP} channels close and trigger insulin secretion from pancreatic beta cells.[77] Closure of these channels leads to membrane depolarization and opening of L-type voltage-dependent calcium (Ca^{2+}) channels that subsequently increase intracellular Ca^{2+} and therefore insulin exocytosis. Some of the diabetic

neonates present also with developmental delay and epilepsy,[77] a syndrome that is known as DEND (developmental delay, epilepsy, neonatal diabetes).[78–82] Hypsarrhythmia has been reported in a total of 4 DEND patients[77,80–82] (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 K_{ATP} and closing them—leading to insulin secretion) mitigated neurological symptoms and psychomotor development in these patients.[80–82] However, one patient died following initial amelioration.[80]

K_{ATP} 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 *K_{ir}6.2* 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 K_{ATP}, 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 *K_{ir}6.2* 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 K_{ATP} 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 study[91] (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 review[94]).

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 EEG, 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

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^{enu} mice ↓ threshold to audiogenic seizures[46,49,50] ↑expression of NR2A&B, GluR1&2/3[48]	NR
Nonketotic hyperglycinemia (NKH)	• Glycine on cultured hippocampal rat slices ↑ excitability & neurotoxicity[55]	NR
	• Glycine on auditory brain stem rat slices ↑ transmitter release[56]	NR
	• 95% ↓ Gcs mice & *Amt* deletion in mice Neural tube defects[69,70]	NR
	• 29% ↓ GCS mice Longer electroshock induced tonic–clonic seizures[71] High locomotor activity and anxiety behavior[71] Severe neuronal injury after focal cerebral ischemia[72]	NR
	• Glyt1 KO mice abnormal respiration reversed by strychnine[73]	NR
DEND	• Expression of KCNJ11 mutations in Xenopus oocytes Interfere with K_{ATP} sensitivity or sulfonylurea efficacy[78]	NR
	• $Kir_{6.2}$ KO mice Myoclonic jerks, tonic convulsions, & death in response to hypoxia[84] SNr firing rates increase during hypoxia in vitro[84]	NR
	• Overexpression of SUR1 in mice Protective against kainic acid–induced seizures[85]	NR
Symptomatic hypoglycemia	• Insulin-induced hypoglycemia in rats Neuronal damage in the hippocampus, caudate nucleus, spinal cord, and cerebellar Purkinje cells[96] 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]	NR
	• Insulin & SEZ-induced hypoglycemia in juvenile ratsSeizures[100]	seizures
	• Hypoglycemia in hippocampal slices from juvenile miceSeizures responsive to NMDA & non-NMDA antagonists & midazolam, decreased synaptic transmission, spreading depolarizations[101]	seizures
	• Slices from developing rats exposed to repetitive hypoglycemia decreased LTP[102]	
GLUT1 deficiency	• Heterozygous Glut1 mice Generalized/focal onset electrographic seizures, rhythmic or polyspikes, SWDs, no behavioral change[113] Behavioral arrests during fasting[113]	Seizures
	• Expression of SLC2A1 variants in Xenopus oocytes Mild to dramatic glucose transport changes[115]	NR
SCAD deficiency	• BALB/cByJ mice impaired thermoregulation in cold[121]	NR
	• Slices from BALB/cByJ mice Cerebral edema, astrocytic swelling, neuronal mitochondrial injury[120]	NR
	• Strial slices from ethylmalonic acid–administered rats Deficient redox homeostasis & ↓ Na^+/K^+ATPase activity[122]	NR
Menkes disease	• Mo^{br} mice impaired axonal development & synaptogenesis in the cerebral cortex and the	NR

Continued

Table 3. Continued.

Metabolic disease	Disease model and main features	Spontaneous seizures or spasms
	hippocampus, ↓ peptidylglycine alpha-amidating monooxygenase activity in slices[137] Phenotype partially reversed by human Menkes transgene[139]	
	• Inhibition of atp7a expression in *Drosophila* cell–specific amidation impairments[141]	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[172]	Seizures
	• TNAP+/+ and heterozygous mice Pyridoxine-deficient diet-induced seizures[173]	Seizures
D-Glyceric aciduria (DGA)	• Rats with high fructose & fat diet type II diabetes[180]	NR
	• Glyctk KO mice	NR
Methylmalonic aciduria & B12 deficiency	• Intrastriatal MMA injection in rats Clonic & tonic–clonic seizures, ↓duration of seizures with preadministration of MK-801, alpha-tocopherol or ascorbic acid[193,194]	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[196]	Seizures
	• CD320/TCblR KO mice cognitive deficits & anxiety[198] smaller pyramidal cells, impaired LTP in CA1, ↓ GluR1[198]	NR
	• Membrane preparations from MMA-treated rat cortex/brain homogenates preincubated with MMA ↓Na^+/K^+ATPase activity, prevented by glutathione[195]	No
Homocysteinemias	• Heterozygous Mthfr KO mice Impaired short-term memory in WT animals born to this phenotype & apoptosis in the hippocampus[213,214]	NR
	• Systemic administration homocyteine in rats & mice convulsive seizures[205,206]	Seizures
	• Intraperitoneal homocysteine injection status epilepticus & flexion seizures in immature rats[210] Spikes & spike waves without behavioral correlation in adults rats[210]	Seizures
	• ICV application of homocysteic acid in PN12 rats Generalized tonic–clonic seizures, prevented by pre-NBQX & AP7 application[211]	Seizures
	• Subcutaneous chronic homocysteine injection in rats ↓ Na+/K+ATPase activity in hippocampal synaptic membrane preparations[212]	NR
	• Homocysteine application on rat organotypic cortical & hippocampal slice cultures Excitotoxicity[207]	NR
Propionic acidemia	• ICV propionic acid injection in adult rats Dystonia, hyperactivity, caudate spiking, ↑ severity of kindling-induced seizures[223] ↑ oxidative stress, ↓glutathione & glutathione peroxidase activity & neuroinflammation ex vivo[223]	NR
	• Oral propionic acid application in PN 21 rats ↓ glutathione & glutathione peroxidase activity, ↑ IL6, TNFα, HSP70 & caspase 3, DNA fragmentation, ↓GABA, serotonin & dopamine[226]	NR
PDHC deficiency	• PDHC E1 α null mutation in mice Low PDC activity, reduced litter size[238] All males die & 50% females survive after only brain-targeted mutation, females show ↓neuronal density & neuropil fibers, abnormal neuronal localization in	NR

Continued

Table 3. Continued.

Metabolic disease	Disease model and main features	Spontaneous seizures or spasms
	the gray matter, ↓lipid synthesis & irregular myelination, adult females have neurological deficits[239]	
	• PDHC E1 α knockdown in striatum & SN in rats abnormal amphetamine-induced rotation[240]	NR
	• Systemic deletion of exon 8 from PDHC E1 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 Impaired acoustic startle reflex[242]	NR
	• E2 impairment in zebrafish Ketogenic diet reversed abnormal vision, lactic acidosis & lethargy[243]	NR
Leigh syndrome	• Ndufs4 KO mice Delayed growth, progressive lethargy, ataxia, blindness, progressive loss of startle response & death at week 7 due to systemic KO, hypoxia reversed neurodegenerative changes & ↑ life span, rapamycin also extended life span, prevented brain injury, ↑ GABA, dopamine and free fatty acid levels, ↓glycolytic intermediates[254,256,257] Similar outcome as in the systemic knockout, in addition, gliosis & microglial activation due to KO only in glial cells and neurons[255]	NR
	• ND2 deletion in *Drosophila* Rapamycin increases the life span but leads to fat storage impairments[258]	NR
Alpers-Huttenlocher disease	• D257A knockin mice (PolyA$^{mut/mut}$) Early aging, ↓ body size & weight, death[264,265] Early lethality & mtDNA depletion if KO at preimplantation stage[267]	NR
	• Polg−/− zebrafish larvae survive till juvenile age[266]	NR
Lysosomal storage diseases	• Idua KO mice High glycosaminoglycan in urine, flat face, abnormal lysosomal storage in glial cells, vacuolation in Purkinje cells, neurons in the cortex, no behavioral alterations[272] Human IDUA injection into putamen reverses brain pathology[273]	NR
	ICV human IDUA injection prevents brain pathology & spatial learning deficits[274]	NR
	• ASM KO mice High sphingomyelin, no ASM activity, ↓body weight & death[272] Mutations expressed in this background show high level of expression in brain & higher residual ASM activity than ASM KOs[272]	
Leukodystrophies	• Mice carrying WT+1 mutated hGFAP No Rosenthal fibers[286]	NR
	• Mice carrying WT + multiple mutated hGFAP Rosenthal fibers in adult age, severe convulsions & high mortality rate when challenged with kainate[286]	NR
	• Mice with hGFAP Hypertrophic astrocytes, Rosenthal fiber-like inclusions, upregulation of small HSPs[287]	NR
BTD deficiency	• Rats fed with biotin-deficient diet Alopecia of lower back, delayed growth, longer BAEP latency[295]	NR
	• BTD KO mice fed with biotin-deficient diet Hypotonia, demyelination, axonal degeneration, impaired motor neuron function, lethargy, limping, ventriculomegaly, slow growth, weight loss reversed with biotin supplement[296,297]	NR
DBP deficiency	• MFP2 KO mice Failure to thrive, astrogliosis & microglial activation in gray matter, death[300,303]	NR

Continued

Table 3. Continued.

Metabolic disease	Disease model and main features	Spontaneous seizures or spasms
	• Nestin-Mfp2−/− mice mild neuroinflammation & axonal impairments in Purkinje cells, motor deficits[305]	NR
	• dbp knockdown in zebrafish Rescue by murine Dbp[306]	NR
Williams-Beuren syndrome (WBS)	• Fzd9 deletions in mice both heterozygous & homozygous deletions lead to ↓ threshold of pentylenetetrazole-induced seizures & abnormalities in hippocampal structure, only homozygous deletions lead to spatial learning impairments[315]	NR
	• WBS distal deletions in mice cognitive impairment[316]	NR
	• WBS distal & proximal deletions in mice defective motor skills[316]	NR
	• Heterozygous WBS complete deletions in mice ↓ brain weight, dendritic length & spine density in the hippocampus, GFAP+ cells in amygdala, ↑ immature cells in DG, craniofacial and cardiac abnormalities, spatial learning deficits[317] Slices from these mice show unstable LTP in CA1, ↓ BDNF in CA1-CA3[318]	NR
Congenital disorder of glycosylation (CDG)	• Mgat2-null mice 20% of the animals show transient paralysis & tremors resembling epileptic seizures[322]	Seizure mimics
Molybdenum cofactor deficiency (MCD)	• Mocs1 KO mice survival 1 to 11 days, human MOCS1 & cPMP injections ↑life span[325,326]	NR
	• Mocs2 KO mice Survival for 11 days, apoptosis in the hippocampus[327] Cortex & brainstem, inactivation of all molybdenum cofactor-dependent enzymes, accumulation of hypoxanthine, xanthine & S-sulfocysteine ex vivo[327]	NR
Primary carnitine deficiency (PCD)	• Dietary restriction of carnitine in rats 50% reduction of carnitine, no other changes[328]	NR
	• Dietary restriction of carnitine with butyrobetaine hydroxylase inhibitor in rats Liver anomalies[329]	NR
Isovaleric acidemia	• Isovaleric acid application onto rat cortical synaptic membrane preparations ↓ Na^+/K^+ ATPase activity[337]	NR
	• Isovaleric acid application onto rat brain homogenates & mitochondrial preparations ↑ protein oxidation[338]	NR
	• IVG application onto rat brain homogenates & mitochondrial preparations Lipid peroxidation & ↓GSH levels[338]	NR

AMT, Aminomethyltransferase; AP7, 2-amino-7 phosphonoheptanoic 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-aminobutryric acid; GAD, Glutamic acid decarboxylase; GFAP, Glial fibrillary acidic protein; GLYT1, Glycine transporter 1; GCS, Glycine cleavage system; GluR1,2,3, AMPA receptor subunits glutamate receptor 1,2,3; GLUT1, Glucose Transporter 1; GLYCTK, D-Glycerate Kinase; GCSH, Glycine cleavage system H protein; HSP, 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; MFP-2, multifunctional protein-2; Mgat2, Mannosyl (Alpha-1,6)-Glycoprotein Beta-1,2-N-Acetylglucosaminyltransferase; MMA, Methylmalonic acid; Moblo , Mobr and Modp, Murine mottled blotchy, brindled and dappled; MOCS1 and MOCS2, Molybdenum cofactor synthesis protein 1 and 2; mtDNA, Mitochondrial DNA; MTHFR, Methylene tetrahydrofolate reductase; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzoquinoxaline-2,3-dione; ND2, NADH dehydrogenease 2; NDUFS4, NADH : ubiquinone oxidoreductase subunit S4; NMDA, N-methyl D-aspartate; NR2A and NR2B, NMDA receptor subtype 2A and 2B; LTP, Long-term potentiation; PAH, Phenylalanine hydroxylase; PDHC, Pyruvate dehydrogenase complex; Phe, Phenylalanine; PLP, Pyridoxal phosphate; POLG, catalytic subunit of mitochondrial DNA polymerase gamma; PN, Postnatal day; SEZ, Streptozotocin; SLC2A1, Solute carrier family 2 member 1; SLC6A9, Solute carrier family 6 member 9; SN, Substantia nigra; SNr, Substantia nigra pars reticulata; SUR1, Sulfonylurea 1; SWDs, Slow wave discharges; CD320/TCblR, Transcobalamin II receptor; TNAP, Tissue non-specific alkaline phosphatase; TNF ,Tumor Necrosis Factor ; WBS, Williams-Beuren syndrome; WT, Wild type.

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

relation of seizures to decreased levels of glucose.[100] Slices from juvenile mice exposed to hypoglycemia showed seizures and subsequent decline in synaptic transmission that were accompanied by spreading depolarizations in the hippocampus, and only seizures could be abolished by NMDA and non-NMDA-receptor antagonists and midazolam.[101] Likewise, following repetitive hypoglycemia, slices from developing rats showed decreased long-term potentiation (LTP) in the hippocampus, suggesting a cognitive impairment, even though the basal synaptic transmission was intact in these animals.[102] On the other hand, adult rats that had free or limited access to food 14–16 h before the insulin-induced hypoglycemia, had decreased latency to seizure development in the fasting group, although this effect was related to the reduced expression of K_{ATP} channels in SNr due to fasting.[103]

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.[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.[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.[106–108] Various seizure types may occur, including generalized tonic or clonic, atypical absences, atonic, myoclonic, myoclonic astatic, or focal.[108–110] GLUT1 deficiency syndrome has rarely been reported in IS patients who responded to the ketogenic diet fully or partially,[110–112] including a patient with a missense mutation in *SLC2A1*[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).[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.[113] The authors conclude that lactate deprivation is the main reason for pathology in the presence of GLUT1 deficiency,[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.[114] In Xenopus 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.[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.[116] To our knowledge, there is one WS case with SCAD resistant to treatment in the literature[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).[118,119] Histopathologically, cerebral edema, astrocytic swelling, and neuronal mitochondrial injury,[120] and clinically, impaired thermoregulation in cold conditions are reported[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^+/K^+ATPase) activity, both of which may lead to neuronal impairment in neurotransmission.[122]

Deficiencies in metal metabolism

Menkes disease

IS have been commonly reported in patients presenting with Menkes disease[123–130] (Table 2). Bahi-Buisson et al.[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.[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.[127,134] Nevertheless, Cu supplementation is inefficient as a therapy in Menkes disease.[125,129] Even when the disease was first described in 1962, severe neurological symptoms and seizures were observed in 5 related patients.[131] However, the main mechanism leading to IS is still unknown (for review[135]).

Variations in the murine mottled (blotchy and dappled, *Mo*^{blo} and *Mo*^{dp}) locus are suggested to be the homolog of the human Menkes disease–causing *ATP7A* gene.[136,137] Neurological aspects of Menkes disease, including seizures, are reflected at most by the brindled mottled mouse (Mo^{br}), although no spasms were reported (Table 3).[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 Y.[137,138] Some of these changes in the brindled Mo^{br} can be rescued by the human Menkes transgene, although the Cu concentrations are not fully reversed to normal.[139] In addition, recently, non-mammalian models of Menkes disease have also been established. The normal brain expression of *atp7a* in a zebrafish model is very low,[140] whereas amidation impairments in a *Drosophila* model are similar to the murine model.[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_6-, pyridoxine dependency, and pyridoxal-5′-phosphate deficiency

Reports of nervous system symptoms, epileptiform activities, or seizures induced by pyridoxine (vitamin B_6) deficiency and of the seizure-suppressing effect of pyridoxine have been described for rats and humans.[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.[147] Similarly, Ohtahara et al.[148] and Pietz et al.[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.[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.[153]

The exact mechanisms of pyridoxine or PLP deficiency and vitamin B_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,[146] pyridoxine or PLP treatment can be effective. Vitamin B_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 γ-aminobutyric acid (GABA).[154] Low GABA levels are seen in some patients with neonatal seizures that were responsive to vitamin B6 and pyridoxine.[155,156] GABA is the main inhibitory neurotransmitter in the central nervous system (CNS), but also plays a role in oxidative energy metabolism.[157] Due to this relation, seizures are attributed to functional deficiencies in GAD1 and GAD2 genes and GABA synthesis,[158–160] but no significant linkage has been found in affected families.[161–163]

Autosomal recessive mutations in the pyridoxine-5′-phosphate oxidase (*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.[164] A patient with IS of unknown etiology who had normal CSF pyridoxal-5′-phosphate, carried a *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). [165] DNA sequencing from 13 individuals between 17 months and 15 years of age who had pyridoxine-dependent seizures revealed mutations in the α-aminoadipic semialdehyde dehydrogenase (ALDH7A1) gene that encodes antiquitin which is involved in lysine catabolism.[166] The location of the mutations in the *ALDH7A1* gene contributes to the phenotype of the patients.[167] In addition, unlike patients carrying *PNPO* mutations or having PNPO deficiency, in patients with ALDH deficiency, no increases in threonine or glycine in serum or CSF are found.

There are patients with *ALDH7A1* mutations and IS although there is a patient with antiquitin dysfunction but without a mutation suggesting an unknown mechanism in this deficiency[168,169] (Table 2). Of interest, patients with folinic acid deficiency, also a known but rare cause of seizures, may carry *ALDH7A1* mutations.[170] Although this condition is seen mostly with neonatal seizures, urine antiquitin measurement is advised when no underlying cause is present for IS.[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).[172] Interestingly, pyridoxal treatment is influenced by the genetic background of the mice, being effective fully

only in C57BL/6 mice, not effective in inbred 129/Sv and partially effective in hybrid B6129.[172] Litters born to both TNAP+/+ mice and heterozygous mice who are fed by pyridoxine-deficient diet also show epileptic seizures.[173] PLP and primidone suppress zebrafish seizures induced by Ginkgo biloba, leading to PLP and GABA reductions despite the fact that this model is not a specific model for PLP deficiency.[174]

Acidurias

D-Glyceric aciduria

D-Glyceric Aciduria (DGA) was first described in a 2-year old boy having symptoms similar to NKH such as high urinary glycine, myoclonic jerks, and motor and developmental retardation, but also with hyperglyceric acidemia and hyperglycericaciduria.[175] Autosomal recessive mutations in the D-glycerate kinase (*GLYCTK*) gene were identified in 3 patients including the DGA patient first described.[176] Regardless of the high urinary D-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[179] (Table 2). A fructose-free diet provided partial amelioration, with decreases in autistic 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).[180] *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.[181–183] 5′-Deoxyadenosylcobalamin is a cofactor of MUT; therefore its absence or deficient synthesis may also result in methylmalonic aciduria.[183–185] The disease progression, and treatment options and their success may differ depending on the location of autosomal recessive mutations affecting either the synthesis pathway of the apoenzyme or the cofactor.[183,186–188] IS due to MMA accumulation or B12 deficiency is reported in several patients with various responses to vitamin supplements[19,23,189–191] (Table 2). In bigger cohorts, the frequency of methylmalonic aciduria among the reported underlying etiologies in infants with IS varies between 0 and10%.[9,19,192]

Rats show clonic and tonic–clonic seizures after intrastriatal 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.[195] 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/TCbIR*) 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.[198] However, seizures have not been observed.

Homocysteinemias

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.[200–202] 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[203]).[204] 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.[205–207] In addition, homocysteine accumulation is associated with vascular and neurodegenerative diseases, and also with epilepsy (for review[208]). 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, hypsarrhythmia, 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[204] (Table 2).

Intraperitoneal homocysteine injection of rats of different age groups ranging between 7 and 90 days show age-specific seizures (Table 3).[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.[211] Likewise, subcutaneous chronic injection of homocysteine in rats from PN6 to PN28 decreases Na^+/K^+ATPase activity in the synaptic membrane preparations from the hippocampus ex vivo.[212] Few animal models present with homocysteinemia but the *Mthfr* KO mouse is the closest phenotype to the one seen in humans.[197] Heterozygote mice show a moderate increase in homocysteine, whereas homozygotes have a 10-fold increase and they have developmental retardation.[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.[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.[215–218] Due to the resulting accumulation of propionyl-CoA, secondary hypoglycemia, hyperammonemia, and hyperglycinemia, it is considered as a form of ketotic hyperglycinemia[216] but can also manifest without metabolic symptoms.[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.[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[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).[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.[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-α), interferon gamma (IFN-γ), 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.[226] Despite the fact that IS, especially due to symptomatic origin, is also a known risk factor for ASD,[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.[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.[228,229] Lactic acidosis was found to be due to the mutations in the pyrophosphate-dependent pyruvate decarboxylase (E1) α subunit of the PDHC,[230] and these mutations were shown to be the most prominent ones in patients with mild to severe neurological symptoms.[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 α subunit deficiency may have variable effects on tissues with sexually dimorphic features.[229,231,232]

There are several reports of patients presenting both PDHC deficiency and WS with variable responses to treatment[231,233–236] (Table 2). A preference for female patients with PDHC to develop WS has been reported.[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.[237]

Mice with a null mutation of PDHC E1 α 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

Pdha1 (Deltaex8) allele predominantly (Table 3).[238] 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.[239] 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,[240] indicating degenerative changes in the nigrostriatal system.[241] 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.[242] 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.[243]

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.[244] The lesions are now known to include basal ganglia, thalamus, cerebellum, and brainstem; the symptoms and signs include hypotonia, feeding problems, and psychomotor delay.[245] 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.[245–247]

Leigh and Leigh-like syndromes presenting with IS/WS were described in several patients due to PDHC mutations[20,246,248–251] (Table 2). Of interest, Tsuji et al.[246] 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,[252,253] *Ndufs4* KO mice were generated (Table 3).[254] 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.[254] 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.[255] Of interest, hypoxia (11% O_2) reversed neurodegenerative changes and increased the life span of *Ndufs4* KO mice.[256] 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 *Ndfus4* KO mice.[257] 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.[258] 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.[257,258]

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*) of *FARS2* gene (Phe-tRNA synthetase 2).[259–261] 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[260] (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.[262,263] 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).[264,265] Homozygous $PolgA^{mut/mut}$ mice manifest reduced body size and weight around the 20th week, prematurely age at around 48 weeks, and die by 61 weeks of life.[264,265] Heterozygous $PolgA^{mut/wt}$ mice do not show abnormalities in aging.[264] A zebrafish model was developed where *Polg−/−* larvae survived until juvenile age (4 weeks after fertilization).[266] 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.[267]

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

review[16,268]). These diseases may feature neuromuscular, respiratory, endocrine, cardiovascular, and morphological symptoms, although most patients may appear normal neonatally because the excess, harmful metabolites that are produced by the dysfunctional enzymes can be removed via the placenta during gestation.[268] Mutations in the lysosomal enzymes are mostly autosomal recessive, or in few exceptions such as Fabry disease, Hunter syndrome and Danon disease, are X-linked.[268]

There is a report of a 5-month-old boy with IS and a low α-L-iduronidase (IDUA) activity confirmed to have a severe type of mucopolysaccharidosis I, a lysosomal storage disease called Hurler syndrome[269] (Table 2). Another recent study reported a 5-month-old patient with IS having a form of Niemann-Pick disease (NPD) due to sphingomyelin phosphodiesterase enzyme deficiency caused by compound heterozygous mutations in sphingomyelin phosphodiesterase 1 (*SMPD1*), also known as the acid sphingomyelinase (*ASM*) gene[270] (Table 2).

There are different experimental models for various types of lysosomal storage diseases (for review[271]) (Table 3). For instance, *Idua* KO mice generated by targeted disruption of exon 5 of the gene in mice embryonic stem cells that are injected later into blastocysts have deficient IDUA activity.[272] These mice show some phenotypic features such as flat face and increase in glycosaminoglycan in urine, which are similar to those seen in human patients with Hurler syndrome. Abnormal lysosomal storage is detected only in glial cells at 4 weeks, but as the KO mice age, vacuolation in Purkinje cells and also neurons in the cortex are prominent without behavioral alterations.[272] When 6 to 7 week old *Idua* KO mice are injected with viruses containing human *IDUA* only into their putamen, the brain pathology is reversed.[273] Furthermore, ICV injection of a similar viral construct into 4- to 6-day-old mice brains also results in widespread expression that prevents the brain pathology and also spatial learning deficits in *Idua* KO mice.[274] *Asm* KO mice, on the other hand, show high levels of sphingomyelin accumulation and no detectable ASM activity, and die after 6 to 8 months with half of the body weight of controls and heterozygotes at the same age.[275] Also described is a transgenic model for NPD in mice with mutations in complete ASM KO background that may allow evaluation of the effects of different mutations.[276]

OTHER DISEASES

Leukodystrophies

Leukodystrophies present with white matter degeneration, spongy vacuolation, loss of myelin, and resulting motor dysfunction in the early stages of the diseases. Some of these diseases namely Alexander disease, Krabbe disease, X-linked adrenoleukodystrophy, hereditary diffuse leukoencephalopathy with spheroids, and metachromatic leukodystrophy also feature seizures and epilepsy.[16]

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 show 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).[298–300] 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[301]). A patient with drug-resistant WS having DBP deficiency has been reported[302] (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 (Table 3).[300,303] The surviving *MFP2* KO mice, however, have astrogliosis and microglial activation in the gray matter, which is not seen in humans.[304] 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.[305] 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.[306]

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.[307–309] 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.[307]

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[310,311] (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.[312] 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.[312,313] A recent study evaluating the candidate genes residing on chromosome 7 in a zebrafish knockdown model reported haploinsufficiency of *ywag* 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.[314] Because the WBS area encompasses a number of genes, the first experiments focused on both hetero- and homozygous single gene deletions in this region to elucidate the contribution of each gene to the phenotype (for review[192]). 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 pentylenetetrazole-induced seizure threshold and abnormalities in hippocampal structure, whereas the homozygous deletions also result in spatial learning impairments in mice (Table 2).[315] 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.[192,316] 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.[317] 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 (BNDF) levels in CA1-CA3 regions.[318]

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.[319,320] 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[319] (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[321]). 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 (Table 3).[322] 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.[323]

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 review[324]). *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 *Mocs*1 KO mice that are treated via hepatic injections of cyclic pyranopterin monophosphatase (cPMP), 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 as[330] Alzheimer's disease[331] and ischemia-hypoxia–induced brain injury[332] (for review[333]). 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 WS[335] (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 isovalerylglycine (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.[16,17] 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, hypotonia or hyperreflexia) or presence of movement disorders (Table 2).[17,20,339] Clinical examination may give hints such as dysmorphic features and neonatal diabetes (eg, DEND),[77,80] skin hypopigmentation (eg, Menkes disease),[123,130] facial elfin appearance (eg, Williams-Beuren syndrome),[310,311] abnormal facies (eg, PDHC deficiencies),[231,235,236] alopecia (eg, biotinidase deficiency),[293,294] abnormal visual responses (eg, NKH),[66] or alterations in auditory-evoked potentials (eg, NKH, methylmalonic aciduria, and biotinidase deficiency),[19,66,293,294] optic atrophy (eg, Leigh syndrome and biotinidase deficiency).[246,251,293]

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 (MCD), isovalerylglycine (isovaleric acidemia); and in CSF—increased pipecolic acid (pyridoxine dependency) give hints about 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).[20,339–341]

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 aciduria (abnormal signals from globus pallidi) or Leigh syndrome (basal ganglia and SN lesions) (Table 2).[20,339–341] Dysgenesis of corpus callosum and gyral abnormalities may also be present in certain patients with NKH.[342]

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

contents of this review. A.S.G. has no conflicts of interest with regard to this article. She is co-Editor in Chief of *Epilepsia Open* and has received royalties for publications from Elsevier. She has also received honorarium for participation in an advisory board meeting of Mallinckrodt, but there is no conflict of interest with regard to the contents of this review. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010;51:676–685.
2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58:512–521.
3. Lado FA, Rubboli G, Capovilla G, et al. Pathophysiology of epileptic encephalopathies. *Epilepsia* 2013;54(Suppl. 8):6–13.
4. West WJ. On a peculiar form of infantile convulsions. *Lancet* 1841;35:724–725.
5. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia* 2010;51:2175–2189.
6. Hrachovy RA, Frost JD Jr. Infantile spasms. *Handb Clin Neurol* 2013;111:611–618.
7. Frost JD Jr, Hrachovy RA. Pathogenesis of infantile spasms: a model based on developmental desynchronization. *J Clin Neurophysiol* 2005;22:25–36.
8. Galanopoulou AS, Moshe SL. Pathogenesis and new candidate treatments for infantile spasms and early life epileptic encephalopathies: a view from preclinical studies. *Neurobiol Dis* 2015;79:135–149.
9. Wirrell EC, Shellhaas RA, Joshi C, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. *Epilepsia* 2015;56:617–625.
10. Scheffer IE, French J, Hirsch E, et al. Classification of the epilepsies: new concepts for discussion and debate—special report of the ILAE Classification Task Force of the Commission for Classification and Terminology. *Epilepsia Open* 2016;1:37–44.
11. Euro E-RESC, Epilepsy Phenome/Genome P, Epi KC. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. *Am J Hum Genet* 2014;95:360–370.
12. Pardo CA, Nabbout R, Galanopoulou AS. Mechanisms of epileptogenesis in pediatric epileptic syndromes: Rasmussen encephalitis, infantile spasms, and febrile infection-related epilepsy syndrome (FIRES). *Neurotherapeutics* 2014;11:297–310.
13. Jellinger K. Neuropathological aspects of infantile spasms. *Brain Dev* 1987;9:349–357.
14. Wolf NI, Bast T, Surtees R. Epilepsy in inborn errors of metabolism. *Epileptic Disord* 2005;7:67–81.
15. Gkampeta A, Pavlou E. Infantile spasms (West syndrome) in children with inborn errors of metabolism: a review of the literature. *J Child Neurol* 2012;27:1295–1301.
16. Yu JY, Pearl PL. Metabolic causes of epileptic encephalopathy. *Epilepsy Res Treat* 2013;2013:124934.
17. Rahman S, Footitt EJ, Varadkar S, et al. Inborn errors of metabolism causing epilepsy. *Dev Med Child Neurol* 2013;55:23–36.
18. Van Hove JL, Lohr NJ. Metabolic and monogenic causes of seizures in neonates and young infants. *Mol Genet Metab* 2011;104:214–230.
19. Liu XM, Li R, Chen SZ, et al. Screening of inherited metabolic disorders in infants with infantile spasms. *Cell Biochem Biophys* 2015;72:61–65.
20. Alrifai MT, AlShaya MA, Abulaban A, et al. Hereditary neurometabolic causes of infantile spasms in 80 children presenting to a tertiary care center. *Pediatr Neurol* 2014;51:390–397.
21. Osborne JP, Lux AL, Edwards SW, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. *Epilepsia* 2010;51:2168–2174.
22. Zhongshu Z, Weiming Y, Yukio F, et al. Clinical analysis of West syndrome associated with phenylketonuria. *Brain Dev* 2001;23:552–557.
23. Malbora B, Yuksel D, Aksoy A, et al. Two infants with infantile spasms associated with vitamin B12 deficiency. *Pediatr Neurol* 2014;51:144–146.
24. Mercimek-Mahmutoglu S, Patel J, Cordeiro D, et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. *Epilepsia* 2015;56:707–716.
25. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology* 2017;89:893–899.
26. Folling I. The discovery of phenylketonuria. *Acta Paediatr Suppl* 1994;407:4–10.
27. Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet* 2010;376:1417–1427.
28. Blau N. Genetics of phenylketonuria: then and now. *Hum Mutat* 2016;37:508–515.
29. Crome L, Pare CMB. Phenylketonuria: a review and a report of the pathological findings in four cases. *Br J Psychiatry* 1960;106:862–883.
30. Crome L, Tymms V, Woolf LI. A chemical investigation of the defects of myelination in phenylketonuria. *J Neurol Neurosurg Psychiatry* 1962;25:143–148.
31. Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963;32:338–343.
32. Al Hafid N, Christodoulou J. Phenylketonuria: a review of current and future treatments. *Transl Pediatr* 2015;4:304–317.
33. Bilder DA, Kobori JA, Cohen-Pfeffer JL, et al. Neuropsychiatric comorbidities in adults with phenylketonuria: a retrospective cohort study. *Mol Genet Metab* 2017;121:1–8.
34. Fois A, Rosenberg C, Gibbs FA. The electroencephalogram in phenylpyruvic oligophrenia. *Electroencephalogr Clin Neurophysiol* 1955;7:569–572.
35. Low NL, Bosma JF, Armstrong MD. Studies on phenylketonuria. VI. EEG studies in phenylketonuria. *AMA Arch Neurol Psychiatry* 1957;77:359–365.
36. Bower BD, Jeavons PM. Phenylketonuria presenting as infantile spasms with sudden mental deterioration. *Dev Med Child Neurol* 1963;5:577–585.
37. Medici C, Varacchi C, Gonzalez G, et al. Unusual case of phenylketonuria with atypical brain magnetic resonance imaging findings. *J Child Neurol* 2013;28:1496–1499.
38. Ng J, Heales SJ, Kurian MA. Clinical features and pharmacotherapy of childhood monoamine neurotransmitter disorders. *Paediatr Drugs* 2014;16:275–291.
39. Kaufman S, Holtzman NA, Milstien S, et al. Phenylketonuria due to a deficiency of dihydropteridine reductase. *N Engl J Med* 1975;293:785–790.
40. Dianzani I, de Sanctis L, Smooker PM, et al. Dihydropteridine reductase deficiency: physical structure of the QDPR gene, identification of two new mutations and genotype-phenotype correlations. *Hum Mutat* 1998;12:267–273.
41. Mikaeloff Y, Plouin P, Dhondt JL, et al. Clinical and EEG videopolygraphic features of epileptic spasms in a child with dihydropteridine reductase deficiency. Efficiency of hydrocortisone. *Epileptic Disord* 2000;2:213–217.
42. Coughlin CR II, Hyland K, Randall R, et al. Dihydropteridine reductase deficiency and treatment with tetrahydrobiopterin: a case report. *JIMD Rep* 2013;10:53–56.
43. Tau GZ, Peterson BS. Normal development of brain circuits. *Neuropsychopharmacology* 2010;35:147–168.
44. Kwon C, Farrell PM. The magnitude and challenge of false-positive newborn screening test results. *Arch Pediatr Adolesc Med* 2000;154:714–718.
45. Cornejo V, Raimann E, Cabello JF, et al. Past, present and future of newborn screening in Chile. *J Inherit Metab Dis* 2010;33(Suppl. 3):S301–S306.
46. Shedlovsky A, McDonald JD, Symula D, et al. Mouse models of human phenylketonuria. *Genetics* 1993;134:1205–1210.
47. Glushakov AV, Dennis DM, Morey TE, et al. Specific inhibition of N-methyl-D-aspartate receptor function in rat hippocampal neurons by L-phenylalanine at concentrations observed during phenylketonuria. *Mol Psychiatry* 2002;7:359–367.

48. Glushakov AV, Glushakova O, Varshney M, et al. Long-term changes in glutamatergic synaptic transmission in phenylketonuria. *Brain* 2005;128:300–307.
49. Martynyuk AE, Ucar DA, Yang DD, et al. Epilepsy in phenylketonuria: a complex dependence on serum phenylalanine levels. *Epilepsia* 2007;48:1143–1150.
50. Martynyuk AE, van Spronsen FJ, Van der Zee EA. Animal models of brain dysfunction in phenylketonuria. *Mol Genet Metab* 2010;99 (Suppl. 1):S100–S105.
51. Dienel GA, Cruz NF. Biochemical, metabolic, and behavioral characteristics of immature chronic hyperphenylalanemic rats. *Neurochem Res* 2016;41:16–32.
52. Tada K, Kure S, Takayanagi M, et al. Non-ketotic hyperglycinemia: a life-threatening disorder in the neonate. *Early Hum Dev* 1992;29:75–81.
53. Tada K, Kure S. Non-ketotic hyperglycinaemia: molecular lesion, diagnosis and pathophysiology. *J Inherit Metab Dis* 1993;16:691–703.
54. Kure S, Kato K, Dinopoulos A, et al. Comprehensive mutation analysis of GLDC, AMT, and GCSH in nonketotic hyperglycinemia. *Hum Mutat* 2006;27:343–352.
55. Newell DW, Barth A, Ricciardi TN, et al. Glycine causes increased excitability and neurotoxicity by activation of NMDA receptors in the hippocampus. *Exp Neurol* 1997;145:235–244.
56. Turecek R, Trussell LO. Presynaptic glycine receptors enhance transmitter release at a mammalian central synapse. *Nature* 2001;411:587–590.
57. Schiffmann R, Kaye EM, Willis JK III, et al. Transient neonatal hyperglycinemia. *Ann Neurol* 1989;25:201–203.
58. Luder AS, Davidson A, Goodman SI, et al. Transient nonketotic hyperglycinemia in neonates. *J Pediatr* 1989;114:1013–1015.
59. Zammarchi E, Donati MA, Ciani F. Transient neonatal nonketotic hyperglycinemia: a 13-year follow-up. *Neuropediatrics* 1995;26:328–330.
60. Gerritsen T, Kaveggia E, Waisman HA. A new type of idiopathic hyperglycinemia with hypo-oxaluria. *Pediatrics* 1965;36:882–891.
61. Perry TL, Urquhart N, MacLean J, et al. Nonketotic hyperglycinemia. Glycine accumulation due to absence of glycerine cleavage in brain. *N Engl J Med* 1975;292:1269–1273.
62. Tada K, Narisawa K, Yoshida T, et al. Hyperglycinemia: a defect in glycine cleavage reaction. *Tohoku J Exp Med* 1969;98:289–296.
63. Hoover-Fong JE, Shah S, Van Hove JL, et al. Natural history of nonketotic hyperglycinemia in 65 patients. *Neurology* 2004;63:1847–1853.
64. Campistol J, Plecko B. Treatable newborn and infant seizures due to inborn errors of metabolism. *Epileptic Disord* 2015;17:229–242.
65. Seppalainen AM, Simila S. Electroencephalographic findings in three patients with nonketotic hyperglycinemia. *Epilepsia* 1971;12:101–107.
66. Markand ON, Garg BP, Brandt IK. Nonketotic hyperglycinemia: electroencephalographic and evoked potential abnormalities. *Neurology* 1982;32:151–156.
67. Mohamed S, El Melegy EM, Talaat I, et al. Neurometabolic disorders-related early childhood epilepsy: a single-center experience in Saudi Arabia. *Pediatr Neonatol* 2015;56:393–401.
68. Korman SH, Wexler ID, Gutman A, et al. Treatment from birth of nonketotic hyperglycinemia due to a novel GLDC mutation. *Ann Neurol* 2006;59:411–415.
69. Pai YJ, Leung KY, Savery D, et al. Glycine decarboxylase deficiency causes neural tube defects and features of non-ketotic hyperglycinemia in mice. *Nat Commun* 2015;6:6388.
70. Narisawa A, Komatsuzaki S, Kikuchi A, et al. Mutations in genes encoding the glycine cleavage system predispose to neural tube defects in mice and humans. *Hum Mol Genet* 2012;21:1496–1503.
71. Kojima-ishii K, Kure S, Ichinohe A, et al. Model mice for mild-form glycine encephalopathy: behavioral and biochemical characterizations and efficacy of antagonists for the glycine binding site of N-methyl D-aspartate receptor. *Pediatr Res* 2008;64:228–233.
72. Oda M, Kure S, Sugawara T, et al. Direct correlation between ischemic injury and extracellular glycine concentration in mice with genetically altered activities of the glycine cleavage multienzyme system. *Stroke* 2007;38:2157–2164.
73. Gomeza J, Hülsmann S, Ohno K, et al. Inactivation of the glycine transporter 1 gene discloses vital role of glial glycine uptake in glycinergic inhibition. *Neuron* 2003;40:785–796.
74. Cubelos B, Gimenez C, Zafra F. Localization of the GLYT1 glycine transporter at glutamatergic synapses in the rat brain. *Cereb Cortex* 2005;15:448–459.
75. Mayor F Jr, Martin A, Rodriguez-Pombo P, et al. Atypical nonketotic hyperglycinemia with a defective glycine transport system in nervous tissue. *Neurochem Pathol* 1984;2:233–249.
76. Alfadhel M, Nashabat M, Qahtani HA, et al. Mutation in SLC6A9 encoding a glycine transporter causes a novel form of non-ketotic hyperglycinemia in humans. *Hum Genet* 2016;135:1263–1268.
77. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004;350:1838–1849.
78. Proks P, Antcliff JF, Lippiat J, et al. Molecular basis of Kir6.2 mutations associated with neonatal diabetes or neonatal diabetes plus neurological features. *Proc Natl Acad Sci USA* 2004;101:17539–17544.
79. Gloyn AL, Diatloff-Zito C, Edghill EL, et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. *Eur J Hum Genet* 2006;14:824–830.
80. Bahi-Buisson N, Eisermann M, Nivot S, et al. Infantile spasms as an epileptic feature of DEND syndrome associated with an activating mutation in the potassium adenosine triphosphate (ATP) channel, Kir6.2. *J Child Neurol* 2007;22:1147–1150.
81. Shimomura K, Horster F, de Wet H, et al. A novel mutation causing DEND syndrome: a treatable channelopathy of pancreas and brain. *Neurology* 2007;69:1342–1349.
82. Singh P, Rao SC, Parikh R. Neonatal diabetes with intractable epilepsy: DEND syndrome. *Indian J Pediatr* 2014;81:1387–1388.
83. Ashcroft FM. Adenosine 5′-triphosphate-sensitive potassium channels. *Annu Rev Neurosci* 1988;11:97–118.
84. Yamada K, Ji JJ, Yuan H, et al. Protective role of ATP-sensitive potassium channels in hypoxia-induced generalized seizure. *Science* 2001;292:1543–1546.
85. Hernandez-Sanchez C, Basile AS, Fedorova I, et al. Mice transgenically overexpressing sulfonylurea receptor 1 in forebrain resist seizure induction and excitotoxic neuron death. *Proc Natl Acad Sci USA* 2001;98:3549–3554.
86. Ballanyi K. Protective role of neuronal KATP channels in brain hypoxia. *J Exp Biol* 2004;207:3201–3212.
87. Kumaran A, Kar S, Kapoor RR, et al. The clinical problem of hyperinsulinemic hypoglycemia and resultant infantile spasms. *Pediatrics* 2010;126:e1231–e1236.
88. Yang G, Zou LP, Wang J, et al. Neonatal hypoglycemic brain injury is a cause of infantile spasms. *Exp Ther Med* 2016;11:2066–2070.
89. Riikonen R, Donner M. Incidence and aetiology of infantile spasms from 1960 to 1976: a population study in Finland. *Dev Med Child Neurol* 1979;21:333–343.
90. Riikonen R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. *Neuropediatrics* 1982;13:14–23.
91. Udani JK, Singh BB, Barrett ML, et al. Lowering the glycemic index of white bread using a white bean extract. *Nutr J* 2009;8:52.
92. Udani V, Munot P, Ursekar M, et al. Neonatal hypoglycemic brain - injury a common cause of infantile onset remote symptomatic epilepsy. *Indian Pediatr* 2009;46:127–132.
93. Wong DS, Poskitt KJ, Chau V, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. *AJNR Am J Neuroradiol* 2013;34:1456–1461.
94. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. *Semin Neonatol* 2001;6:147–155.
95. Carlen PL, Zhang L. Metabolic disturbances: hypo- and hyperglycemic seizures in vivo and in vitro. In Pitkänen A, Buckmaster PS, Galanopoulou AS, Moshé SL (Eds) *Models of seizures and epilepsy*. 2nd Ed. London, UK: Elsevier Inc.; 2017:941–949; ISBN: 78-0-12-804066-9.
96. Auer RN, Olsson Y, Siesjo BK. Hypoglycemic brain injury in the rat. Correlation of density of brain damage with the EEG isoelectric time: a quantitative study. *Diabetes* 1984;33:1090–1098.
97. Zhou D, Qian J, Liu CX, et al. Repetitive and profound insulin-induced hypoglycemia results in brain damage in newborn rats: an

approach to establish an animal model of brain injury induced by neonatal hypoglycemia. *Eur J Pediatr* 2008;167:1169–1174.
98. Ennis K, Tran PV, Seaquist ER, et al. Postnatal age influences hypoglycemia-induced neuronal injury in the rat brain. *Brain Res* 2008;1224:119–126.
99. Yamada KA, Rensing N, Thio LL. Ketogenic diet reduces hypoglycemia-induced neuronal death in young rats. *Neurosci Lett* 2005;385:210–214.
100. Maheandiran M, Mylvaganam S, Wu C, et al. Severe hypoglycemia in a juvenile diabetic rat model: presence and severity of seizures are associated with mortality. *PLoS ONE* 2013;8:e83168.
101. Abdelmalik PA, Shannon P, Yiu A, et al. Hypoglycemic seizures during transient hypoglycemia exacerbate hippocampal dysfunction. *Neurobiol Dis* 2007;26:646–660.
102. Yamada KA, Rensing N, Izumi Y, et al. Repetitive hypoglycemia in young rats impairs hippocampal long-term potentiation. *Pediatr Res* 2004;55:372–379.
103. Velisek L, Veliskova J, Chudomel O, et al. Metabolic environment in substantia nigra reticulata is critical for the expression and control of hypoglycemia-induced seizures. *J Neurosci* 2008;28:9349–9362.
104. De Vivo DC, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med* 1991;325:703–709.
105. Dick AP, Harik SI, Klip A, et al. Identification and characterization of the glucose transporter of the blood-brain barrier by cytochalasin B binding and immunological reactivity. *Proc Natl Acad Sci USA* 1984;81:7233–7237.
106. Seidner G, Alvarez MG, Yeh JI, et al. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nat Genet* 1998;18:188–191.
107. Wang D, Kranz-Eble P, De Vivo DC. Mutational analysis of GLUT1 (SLC2A1) in Glut-1 deficiency syndrome. *Hum Mutat* 2000;16:224–231.
108. Wang D, Pascual JM, De Vivo D. Glucose transporter type 1 deficiency syndrome. In Adam MP, Ardinger HH, Pagon RA, et al. (Eds) *GeneReviews®*. [Internet]. Seattle, WA: University of Washington; 1993-2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1430/
109. Leary L, Wang D, Nordli D, et al. Seizure characterization and electroencephalographic features in glut-1 deficiencysyndrome. *Epilepsia* 2003;44:701–707.
110. Pong AW, Geary BR, Engelstad KM, et al. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. *Epilepsia* 2012;53:1503–1510.
111. Vykuntaraju KN, Bhat S, Sanjay KS, et al. Symptomatic west syndrome secondary to glucose transporter-1(GLUT1) deficiency with complete response to 4:1 ketogenic diet. *Indian J Pediatr* 2014;81:934–936.
112. Lee HH, Hur YJ. Glucose transport 1 deficiency presenting as infantile spasms with a mutation identified in exon 9 of SLC2A1. *Korean J Pediatr* 2016;59:S29–S31.
113. Wang D, Pascual JM, Yang H, et al. A mouse model for Glut-1 haploinsufficiency. *Hum Mol Genet* 2006;15:1169–1179.
114. Magistretti PJ, Pellerin L, Rothman DL, et al. Energy on demand. *Science* 1999;283:496–497.
115. Arsov T, Mullen SA, Rogers S, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. *Ann Neurol* 2012;72:807–815.
116. van Maldegem BT, Wanders RJ, Wijburg FA. Clinical aspects of short-chain acyl-CoA dehydrogenase deficiency. *J Inherit Metab Dis* 2010;33:507–511.
117. Mikati MA, Chaaban HR, Karam PE, et al. Brain malformation and infantile spasms in a SCAD deficiency patient. *Pediatr Neurol* 2007;36:48–50.
118. Wood PA, Amendt BA, Rhead WJ, et al. Short-chain acyl-coenzyme A dehydrogenase deficiency in mice. *Pediatr Res* 1989;25:38–43.
119. Amendt BA, Freneaux E, Reece C, et al. Short-chain acyl-coenzyme A dehydrogenase activity, antigen, and biosynthesis are absent in the BALB/cByJ mouse. *Pediatr Res* 1992;31:552–556.
120. Armstrong DL, Masiowski ML, Wood PA. Pathologic characterization of short-chain acyl-CoA dehydrogenase deficiency in BALB/cByJ mice. *Am J Med Genet* 1993;47:884–892.
121. Guerra C, Koza RA, Walsh K, et al. Abnormal nonshivering thermogenesis in mice with inherited defects of fatty acid oxidation. *J Clin Invest* 1998;102:1724–1731.
122. Ritter L, Kleemann D, Hickmann FH, et al. Disturbance of energy and redox homeostasis and reduction of Na+, K + -ATPase activity provoked by in vivo intracerebral administration of ethylmalonic acid to young rats. *Biochim Biophys Acta* 2015;1852:759–767.
123. Kreuder J, Otten A, Fuder H, et al. Clinical and biochemical consequences of copper-histidine therapy in Menkes disease. *Eur J Pediatr* 1993;152:828–832.
124. Chugani HT, Conti JR. Etiologic classification of infantile spasms in 140 cases: role of positron emission tomography. *J Child Neurol* 1996;11:44–48.
125. Sfaello I, Castelnau P, Blanc N, et al. Infantile spasms and Menkes disease. *Epileptic Disord* 2000;2:227–230.
126. Bahi-Buisson N, Kaminska A, Nabbout R, et al. Epilepsy in Menkes disease: analysis of clinical stages. *Epilepsia* 2006;47:380–386.
127. Prasad AN, Levin S, Rupar CA, et al. Menkes disease and infantile epilepsy. *Brain Dev* 2011;33:866–876.
128. Kim YH, Lee R, Yoo HW, et al. Identification of a novel mutation in the ATP7A gene in a Korean patient with Menkes disease. *J Korean Med Sci* 2011;26:951–953.
129. Verrotti A, Cusmai R, Darra F, et al. Epilepsy in Menkes disease: an electroclinical long-term study of 28 patients. *Epilepsy Res* 2014;108:1597–1603.
130. Jain P, Kannan L, Chakrabarty B, et al. Menkes disease - an important cause of early onset refractory seizures. *J Pediatr Neurosci* 2014;9:11–16.
131. Menkes JH, Alter M, Steigleder GK, et al. A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. *Pediatrics* 1962;29:764–779.
132. Danks DM, Campbell PE, Stevens BJ, et al. Menkes's kinky hair syndrome. An inherited defect in copper absorption with widespread effects. *Pediatrics* 1972;50:188–201.
133. Vulpe C, Levinson B, Whitney S, et al. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. *Nat Genet* 1993;3:7–13.
134. Harrison MD, Dameron CT. Molecular mechanisms of copper metabolism and the role of the Menkes disease protein. *J Biochem Mol Toxicol* 1999;13:93–106.
135. Verrotti A, Carelli A, Coppola G. Epilepsy in children with Menkes disease: a systematic review of literature. *J Child Neurol* 2014;29:1757–1764.
136. Levinson B, Vulpe C, Elder B, et al. The mottled gene is the mouse homolog of the menkes disease gene. *Nat Genet* 1994;6:369–373.
137. Lenartowicz M, Krzeptowski W, Lipinski P, et al. Mottled mice and non-mammalian models of menkes disease. *Front Mol Neurosci* 2015;8:72.
138. Niciu MJ, Ma XM, El Meskini R, et al. Altered ATP7A expression and other compensatory responses in a murine model of Menkes disease. *Neurobiol Dis* 2007;27:278–291.
139. Llanos RM, Ke BX, Wright M, et al. Correction of a mouse model of Menkes disease by the human Menkes gene. *Biochim Biophys Acta* 2006;1762:485–493.
140. Chen DS, Chan KM. PCR-cloning of tilapia ATP7A cDNA and its mRNA levels in tissues of tilapia following copper administrations. *Aquat Toxicol* 2011;105:717–727.
141. Sellami A, Wegener C, Veenstra JA. Functional significance of the copper transporter ATP7 in peptidergic neurons and endocrine cells in Drosophila melanogaster. *FEBS Lett* 2012;586:3633–3638.
142. Chick H, El Sadr MM, Worden AN. Occurrence of fits of an epileptiform nature in rats maintained for long periods on a diet deprived of vitamin B(6). *Biochem J* 1940;34:595–600.
143. Daniel EP, Kline OL, Tolle CD. A convulsive syndrome in young rats associated with pyridoxine deficiency. *J Nutr* 1942;23:205–2016.
144. Snyderman SE, Holt LE Jr, Carretero R, et al. Pyridoxine deficiency in the human infant. *J Clin Nutr* 1953;1:200–207.
145. Coursin DB. Convulsive seizures in infants with pyridoxine-deficient diet. *J Am Med Assoc* 1954;154:406.
146. Hunt AD Jr, Stokes J Jr, Mc CW, et al. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics* 1954;13:140–145.

147. Ohtsuka Y, Matsuda M, Ogino T, et al. Treatment of the west syndrome with high-dose pyridoxal phosphate. *Brain Dev* 1987;9:418–421.
148. Ohtahara S, Ohtsuka Y, Yamatogi Y, et al. Prenatal etiologies of west syndrome. *Epilepsia* 1993;34:716–722.
149. Pietz J, Benninger C, Schafer H, et al. Treatment of infantile spasms with high-dosage vitamin B6. *Epilepsia* 1993;34:757–763.
150. Watanabe K. Medical treatment of West syndrome in Japan. *J Child Neurol* 1995;10:143–147.
151. Ito M, Seki T, Takuma Y. Current therapy for West syndrome in Japan. *J Child Neurol* 2000;15:424–428.
152. Tsuji T, Okumura A, Ozawa H, et al. Current treatment of West syndrome in Japan. *J Child Neurol* 2007;22:560–564.
153. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004;62:1668–1681.
154. Tower DB. Neurochemical aspects of pyridoxine metabolism and function. *Am J Clin Nutr* 1956;4:329–345.
155. Kurlemann G, Loscher W, Dominick HC, et al. Disappearance of neonatal seizures and low CSF GABA levels after treatment with vitamin B6. *Epilepsy Res* 1987;1:152–154.
156. Kurlemann G, Ziegler R, Gruneberg M, et al. Disturbance of GABA metabolism in pyridoxine-dependent seizures. *Neuropediatrics* 1992;23:257–259.
157. Mc Khann G, Tower DB. gamma-Aminobutyric acid: a substrate for oxidative metabolism of cerebral cortex. *Am J Physiol* 1959;196:36–38.
158. Scriver CR, Whelan DT. Glutamic acid decarboxylase (Gad) in mammalian tissue outside the central nervous system, and its possible relevance to hereditary vitamin b6dependency with seizures. *Ann N Y Acad Sci* 1969;166:83–96.
159. Yoshida T, Tada K, Arakawa T. Vitamin B6-dependency of glutamic acid decarboxylase in the kidney from a patient with vitamin b6 dependent convulsion. *Tohoku J Exp Med* 1971;104:195–198.
160. Gospe SM, Olin KL, Keen CL. Reduced GABA synthesis in pyridoxine-dependent seizures. *Lancet* 1994;343:1133–1134.
161. Kure S, Sakata Y, Miyabayashi S, et al. Mutation and polymorphic marker analyses of 65K- and 67K-glutamate decarboxylase genes in two families with pyridoxine-dependent epilepsy. *J Hum Genet* 1998;43:128–131.
162. Battaglioli G, Rosen DR, Gospe SMJ, et al. Glutamate decarboxylase is not genetically linked to pyridoxine-dependent seizures. *Neurology* 2000;55:309–311.
163. Cormier-Daire V, Dagoneau N, Nabbout R, et al. A gene for pyridoxine-dependent epilepsy maps to chromosome 5q31. *Am J Hum Genet* 2000;67:991–993.
164. Mills PB, Surtees RA, Champion MP, et al. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5′-phosphate oxidase. *Hum Mol Genet* 2005;14:1077–1086.
165. Michaud JL, Lachance M, Hamdan FF, et al. The genetic landscape of infantile spasms. *Hum Mol Genet* 2014;23:4846–4858.
166. Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. *Nat Med* 2006;12:307–309.
167. Scharer G, Brocker C, Vasiliou V, et al. The genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy due to mutations in ALDH7A1. *J Inherit Metab Dis* 2010;33:571–581.
168. Kanno J, Kure S, Narisawa A, et al. Allelic and non-allelic heterogeneities in pyridoxine dependent seizures revealed by ALDH7A1 mutational analysis. *Mol Genet Metab* 2007;91:384–389.
169. Bennett CL, Chen Y, Hahn S, et al. Prevalence of ALDH7A1 mutations in 18 North American pyridoxine-dependent seizure (PDS) patients. *Epilepsia* 2009;50:1167–1175.
170. Gallagher RC, Van Hove JL, Scharer G, et al. Folinic acid-responsive seizures are identical to pyridoxine-dependent epilepsy. *Ann Neurol* 2009;65:550–556.
171. Lux AL. Latest American and European updates on infantile spasms. *Curr Neurol Neurosci Rep* 2013;13:334.
172. Waymire KG, Mahuren JD, Jaje JM, et al. Mice lacking tissue nonspecific alkaline phosphatase die from seizures due to defective metabolism of vitamin B-6. *Nat Genet* 1995;11:45–51.
173. Narisawa S, Wennberg C, Luis MJ. Abnormal vitamin B6 metabolism in alkaline phosphatase knock-out mice causes multiple abnormalities, but not the impaired bone mineralization. *J Pathol* 2001;193:125–133.
174. Lee GH, Sung SY, Chang WN, et al. Zebrafish larvae exposed to ginkgotoxin exhibit seizure-like behavior that is relieved by pyridoxal-5′-phosphate, GABA and anti-epileptic drugs. *Dis Model Mech* 2012;5:785–795.
175. Brandt NJ, Brandt S, Rasmussen K, et al. Letter: hyperglycericacidaemia with hyperglycinaemia: a new inborn error of metabolism. *Br Med J* 1974;4:344.
176. Sass JO, Fischer K, Wang R, et al. D-Glyceric aciduria is caused by genetic deficiency of D-glycerate kinase (GLYCTK). *Hum Mutat* 2010;31:1280–1285.
177. Duran M, Beemer FA, Bruinvis L, et al. D-glyceric acidemia: an inborn error associated with fructose metabolism. *Pediatr Res* 1987;21:502–506.
178. Bonham JR, Stephenson TJ, Carpenter KH, et al. D(+)-glyceric aciduria: etiology and clinical consequences. *Pediatr Res* 1990;28:38–41.
179. Topcu M, Saatci I, Haliloglu G, et al. D-glyceric aciduria in a six-month-old boy presenting with West syndrome and autistic behaviour. *Neuropediatrics* 2002;33:47–50.
180. Lozano I, Van der Werf R, Bietiger W, et al. High-fructose and high-fat diet-induced disorders in rats: impact on diabetes risk, hepatic and vascular complications. *Nutr Metab (Lond)* 2016;13:15.
181. Oberholzer VG, Levin B, Burgess EA, et al. Methylmalonic aciduria. An inborn error of metabolism leading to chronic metabolic acidosis. *Arch Dis Child* 1967;42:492–504.
182. Kolhouse JF, Utley C, Fenton WA, et al. Immunochemical studies on cultured fibroblasts from patients with inherited methylmalonic acidemia. *Proc Natl Acad Sci USA* 1981;78:7737–7741.
183. Matsui SM, Mahoney MJ, Rosenberg LE. The natural history of the inherited methylmalonic acidemias. *N Engl J Med* 1983;308:857–861.
184. Gurnani S, Mistry SP, Johnson BC. Function of vitamin B12 in methylmalonate metabolism. I. Effect of a cofactor form of B12 on the activity of methylmalonyl-CoA isomerase. *Biochim Biophys Acta* 1960;38:187–188.
185. Cox EV, White AM. Methylmalonic acid excretion: an index of vitamin-B12 deficiency. *Lancet* 1962;2:853–856.
186. Jansen R, Ledley FD. Heterozygous mutations at the mut locus in fibroblasts with Mut0 methylmalonic acidemia identified by polymerase-chain-reaction Cdna cloning. *Am J Hum Genet* 1990;47:808–814.
187. Ledley FD, Rosenblatt DS. Mutations in mut methylmalonic acidemia: clinical and enzymatic correlations. *Hum Mutat* 1997;9:1–6.
188. Gravel RA, Mahoney MJ, Ruddle FH, et al. Genetic complementation in heterokaryons of human fibroblasts defective in cobalamin metabolism. *Proc Natl Acad Sci USA* 1975;72:3181–3185.
189. Campeau PM, Valayannopoulos V, Touati G, et al. Management of West syndrome in a patient with methylmalonic aciduria. *J Child Neurol* 2010;25:94–97.
190. Erol I, Alehan F, Gumus A. West syndrome in an infant with vitamin B12 deficiency in the absence of macrocytic anaemia. *Dev Med Child Neurol* 2007;49:774–776.
191. Glaser K, Girschick HJ, Schropp C, et al. Psychomotor development following early treatment of severe infantile vitamin B12 deficiency and West syndrome–is everything fine? A case report and review of literature. *Brain Dev* 2015;37:347–351.
192. Osborne LR. Animal models of Williams syndrome. *Am J Med Genet C Semin Med Genet* 2010;154C:209–219.
193. Fighera MR, Queiroz CM, Stracke MP, et al. Ascorbic acid and alpha-tocopherol attenuate methylmalonic acid-induced convulsions. *NeuroReport* 1999;10:2039–2043.
194. de Mello CF, Begnini J, Jiménez-Bernal RE, et al. Intrastriatal methylmalonic acid administration induces rotational behavior and convulsions through glutamatergic mechanisms. *Brain Res* 1996;721:120–125.
195. Wyse AT, Streck EL, Barros SV, et al. Methylmalonate administration decreases Na+, K + -ATPase activity in cerebral cortex of rats. *NeuroReport* 2000;11:2331–2334.
196. Malfatti CR, Perry ML, Schweigert ID, et al. Convulsions induced by methylmalonic acid are associated with glutamic acid decarboxylase

inhibition in rats: a role for GABA in the seizures presented by methylmalonic acidemic patients? *Neuroscience* 2007;146:1879–1887.
197. Peng L, Dreumont N, Coelho D, et al. Genetic animal models to decipher the pathogenic effects of vitamin B12 and folate deficiency. *Biochimie* 2016;126:43–51.
198. Arora K, Sequeira JM, Hernandez AI, et al. Behavioral alterations are associated with vitamin B12 deficiency in the transcobalamin receptor/CD320 KO mouse. *PLoS ONE* 2017;12:e0177156.
199. Lai SC, Nakayama Y, Sequeira JM, et al. The transcobalamin receptor knockout mouse: a model for vitamin B12 deficiency in the central nervous system. *FASEB J* 2013;27:2468–2475.
200. Gerritsen T, Vaughn JG, Waisman HA. The identification of homocystine in the urine. *Biochem Biophys Res Commun* 1962;9:493–496.
201. Harvey Mudd S, William Uhlendorf B, Freeman JM, et al. Homocystinuria associated with decreased methylenetetrahydrofolate reductase activity. *Biochem Biophys Res Commun* 1972;46:905–912.
202. Goyette P, Sumner JS, Milos R, et al. Human methylenetetrahydrofolate reductase: isolation of cDNA, mapping and mutation identification. *Nat Genet* 1994;7:195–200.
203. Perla-Kajan J, Twardowski T, Jakubowski H. Mechanisms of homocysteine toxicity in humans. *Amino Acids* 2007;32:561–572.
204. Prasad AN, Rupar CA, Prasad C. Methylenetetrahydrofolate reductase (MTHFR) deficiency and infantile epilepsy. *Brain Dev* 2011;33:758–769.
205. Sprince H, Parker CM, Josephs JA Jr. Homocysteine-induced convulsions in the rat: protection by homoserine, serine, betaine, glycine and glucose. *Agents Actions* 1969;1:9–13.
206. Freed WJ, Taylor SP, Luchins DJ, et al. Production of convulsions in mice by the combination of methionine and homocysteine. *Psychopharmacology* 1980;69:275–280.
207. Flott-Rahmel B, Schurmann M, Schluff P, et al. Homocysteic and homocysteine sulphinic acid exhibit excitotoxicity in organotypic cultures from rat brain. *Eur J Pediatr* 1998;157(Suppl 2):S112–S117.
208. Diaz-Arrastia R. Homocysteine and neurologic disease. *Arch Neurol* 2000;57:1422–1427.
209. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998;316:894–898.
210. Kubova H, Folbergrova J, Mares P. Seizures induced by homocysteine in rats during ontogenesis. *Epilepsia* 1995;36:750–756.
211. Folbergrova J, Haugvicova R, Mares P. Behavioral and metabolic changes in immature rats during seizures induced by homocysteic acid: the protective effect of NMDA and non-NMDA receptor antagonists. *Exp Neurol* 2000;161:336–345.
212. Streck EL, Matte C, Vieira PS, et al. Reduction of Na(+), K(+)-ATPase activity in hippocampus of rats subjected to chemically induced hyperhomocysteinemia. *Neurochem Res* 2002;27:1593–1598.
213. Chen Z, Karaplis AC, Ackerman SL, et al. Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. *Hum Mol Genet* 2001;10:433–443.
214. Jadavji NM, Deng L, Malysheva O, et al. Mthfr deficiency or reduced intake of folate or choline in pregnant mice results in impaired short-term memory and increased apoptosis in the hippocampus of wild-type offspring. *Neuroscience* 2015;300:1–9.
215. Childs B, Nyhan WL, Borden M, et al. Idiopathic hyperglycinemia and hyperglycinuria: a new disorder of amino acid metabolism. I. *Pediatrics* 1961;27:522–538.
216. Hsia YE, Scully KJ, Rosenberg LE. Defective propionate carboxylation in ketotic hyperglycinÆmia. *Lancet* 1969;293:757–758.
217. Hsia YE, Scully KJ, Rosenberg LE. Inherited propionyl-Coa carboxylase deficiency in "ketotic hyperglycinemia". *J Clin Invest* 1971;50:127–130.
218. Lamhonwah AM, Barankiewicz TJ, Willard HF, et al. Isolation of cDNA clones coding for the alpha and beta chains of human propionyl-CoA carboxylase: chromosomal assignments and DNA polymorphisms associated with PCCA and PCCB genes. *Proc Natl Acad Sci USA* 1986;83:4864–4868.
219. Nyhan WL, Bay C, Beyer EW, et al. Neurologic nonmetabolic presentation of propionic acidemia. *Arch Neurol* 1999;56:1143–1147.
220. North KN, Korson MS, Gopal YR, et al. Neonatal-onset propionic acidemia: neurologic and developmental profiles, and implications for management. *J Pediatrics* 1995;126:916–922.
221. Schreiber J, Chapman KA, Summar ML, et al. Neurologic considerations in propionic acidemia. *Mol Genet Metab* 2011;105:10–15.
222. Harris DJ, Thompson RM, Wolf B, et al. Propionyl coenzyme A carboxylase deficiency presenting as non-ketotic hyperglycinaemia. *J Med Genet* 1981;18:156–157.
223. MacFabe DF, Cain DP, Rodriguez-Capote K, et al. Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders. *Behav Brain Res* 2007;176:149–169.
224. Shultz SR, MacFabe DF, Ossenkopp KP, et al. Intracerebroventricular injection of propionic acid, an enteric bacterial metabolic end-product, impairs social behavior in the rat: implications for an animal model of autism. *Neuropharmacology* 2008;54:901–911.
225. Shultz SR, Macfabe DF, Martin S, et al. Intracerebroventricular injections of the enteric bacterial metabolic product propionic acid impair cognition and sensorimotor ability in the Long-Evans rat: further development of a rodent model of autism. *Behav Brain Res* 2009;200:33–41.
226. El-Ansary AK, Ben Bacha A, Kotb M. Etiology of autistic features: the persisting neurotoxic effects of propionic acid. *J Neuroinflam* 2012;9:74.
227. Saemundsen E, Ludvigsson P, Rafnsson V. Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life. *Epilepsia* 2008;49:1865–1870.
228. Patel MS, Roche TE. Molecular biology and biochemistry of pyruvate dehydrogenase complexes. *FASEB J* 1990;4:3224–3233.
229. Dahl HHM. Pyruvate-dehydrogenase E1-alpha deficiency - males and females differ yet again. *Am J Hum Genet* 1995;56:553–557.
230. Endo H, Hasegawa K, Narisawa K, et al. Defective gene in lactic acidosis: abnormal pyruvate dehydrogenase E1 alpha-subunit caused by a frame shift. *Am J Hum Genet* 1989;44:358–364.
231. Robinson BH, MacMillan H, Petrova-Benedict R, et al. Variable clinical presentation in patients with defective E1 component of pyruvate dehydrogenase complex. *J Pediatr* 1987;111:525–533.
232. Brown RM, Dahl HH, Brown GK. X-chromosome localization of the functional gene for the E1 alpha subunit of the human pyruvate dehydrogenase complex. *Genomics* 1989;4:174–181.
233. Naito E, Ito M, Yokota I, et al. Concomitant administration of sodium dichloroacetate and thiamine in west syndrome caused by thiamine-responsive pyruvate dehydrogenase complex deficiency. *J Neurol Sci* 1999;171:56–59.
234. Naito E, Ito M, Yokota I, et al. Gender-specific occurrence of West syndrome in patients with pyruvate dehydrogenase complex deficiency. *Neuropediatrics* 2001;32:295–298.
235. Wada N, Matsuishi T, Nonaka M, et al. Pyruvate dehydrogenase E1alpha subunit deficiency in a female patient: evidence of antenatal origin of brain damage and possible etiology of infantile spasms. *Brain Dev* 2004;26:57–60.
236. Otero LJ, Brown GK, Silver K, et al. Association of cerebral dysgenesis and lactic acidemia with X-linked PDH E1 alpha subunit mutations in females. *Pediatr Neurol* 1995;13:327–332.
237. Takakubo F, Dahl HH. Analysis of pyruvate dehydrogenase expression in embryonic mouse brain: localization and developmental regulation. *Brain Res Dev Brain Res* 1994;77:63–76.
238. Johnson MT, Mahmood S, Hyatt SL, et al. Inactivation of the murine pyruvate dehydrogenase (Pdha1) gene and its effect on early embryonic development. *Mol Genet Metab* 2001;74:293–302.
239. Pliss L, Pentney RJ, Johnson MT, et al. Biochemical and structural brain alterations in female mice with cerebral pyruvate dehydrogenase deficiency. *J Neurochem* 2004;91:1082–1091.
240. Ojano-Dirain C, Glushakova LG, Zhong L, et al. An animal model of PDH deficiency using AAV8-siRNA vector-mediated knockdown of pyruvate dehydrogenase E1alpha. *Mol Genet Metab* 2010;101:183–191.
241. Ungerstedt U, Arbuthnott GW. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res* 1970;24:485–493.
242. Pliss L, Hausknecht KA, Stachowiak MK, et al. Cerebral developmental abnormalities in a mouse with systemic pyruvate dehydrogenase deficiency. *PLoS ONE* 2013;8:e67473.

243. Taylor MR, Hurley JB, Van Epps HA, et al. A zebrafish model for pyruvate dehydrogenase deficiency: rescue of neurological dysfunction and embryonic lethality using a ketogenic diet. *Proc Natl Acad Sci USA* 2004;101:4584–4589.
244. Leigh D. Subacute necrotizing encephalomyelopathy in an infant. *J Neurol Neurosurg Psychiatry* 1951;14:216–221.
245. Rahman S, Blok RB, Dahl HH, et al. Leigh syndrome: clinical features and biochemical and DNA abnormalities. *Ann Neurol* 1996;39:343–351.
246. Tsuji M, Kuroki S, Maeda H, et al. Leigh syndrome associated with West syndrome. *Brain Dev* 2003;25:245–250.
247. Richter RB. Infantile subacute necrotizing encephalopathy (Leigh's disease). It relationship to Wernick's encephalopathy. *Neurology* 1968;18:1125–1132.
248. Kamoshita S, Mizutani I, Fukuyama Y. Leigh's subacute necrotizing encephalomyelopathy in a child with infantile spasms and hypsarrhythmia. *Dev Med Child Neurol* 1970;12:430–435.
249. Muroi J, Okuno T, Kuno C, et al. An MRI study of the myelination pattern in West syndrome. *Brain Dev* 1996;18:179–184.
250. Tsao CY, Luquette M, Rusin JA, et al. Leigh syndrome, cytochrome C oxidase deficiency and hypsarrhythmia with infantile spasms. *Clin Electroencephalogr* 1997;28:214–217.
251. Desguerre I, Pinton F, Nabbout R, et al. Infantile spasms with basal ganglia MRI hypersignal may reveal mitochondrial disorder due to T8993G MT DNA mutation. *Neuropediatrics* 2003;34:265–269.
252. Petruzzella V, Vergari R, Puzziferri I, et al. A nonsense mutation in the NDUFS4 gene encoding the 18 kDa (AQDQ) subunit of complex I abolishes assembly and activity of the complex in a patient with Leigh-like syndrome. *Hum Mol Genet* 2001;10:529–535.
253. Loeffen J, Smeitink J, Triepels R, et al. The first nuclear-encoded complex I mutation in a patient with Leigh syndrome. *Am J Hum Genet* 1998;63:1598–1608.
254. Kruse SE, Watt WC, Marcinek DJ, et al. Mice with mitochondrial complex I deficiency develop a fatal encephalomyopathy. *Cell Metab* 2008;7:312–320.
255. Quintana A, Kruse SE, Kapur RP, et al. Complex I deficiency due to loss of Ndufs4 in the brain results in progressive encephalopathy resembling Leigh syndrome. *Proc Natl Acad Sci USA* 2010;107:10996–11001.
256. Ferrari M, Jain IH, Goldberger O, et al. Hypoxia treatment reverses neurodegenerative disease in a mouse model of Leigh syndrome. *Proc Natl Acad Sci USA* 2017;114:E4241–E4250.
257. Johnson SC, Yanos ME, Kayser EB, et al. mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. *Science* 2013;342:1524–1528.
258. Wang A, Mouser J, Pitt J, et al. Rapamycin enhances survival in a Drosophila model of mitochondrial disease. *Oncotarget* 2016;7:80131–80139.
259. Boyd SG, Harden A, Egger J, et al. Progressive neuronal degeneration of childhood with liver-disease (alpers disease) - characteristic neurophysiological features. *Neuropediatrics* 1986;17:75–80.
260. Tulinius MH, Holme E, Kristiansson B, et al. Mitochondrial encephalomyopathies in childhood. II. Clinical manifestations and syndromes. *J Pediatr* 1991;119:251–259.
261. Naviaux RK, Nyhan WL, Barshop BA, et al. Mitochondrial DNA polymerase gamma deficiency and mtDNA depletion in a child with Alpers' syndrome. *Ann Neurol* 1999;45:54–58.
262. Cho JS, Kim SH, Kim HY, et al. FARS2 mutation and epilepsy: possible link with early-onset epileptic encephalopathy. *Epilepsy Res* 2017;129:118–124.
263. Raviglione F, Conte G, Ghezzi D, et al. Clinical findings in a patient with FARS2 mutations and early-infantile-encephalopathy with epilepsy. *Am J Med Genet A* 2016;170:3004–3007.
264. Trifunovic A, Wredenberg A, Falkenberg M, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* 2004;429:417–423.
265. Kujoth GC, Hiona A, Pugh TD, et al. Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* 2005;309:481–484.
266. Rahn JJ, Bestman JE, Stackley KD, et al. Zebrafish lacking functional DNA polymerase gamma survive to juvenile stage, despite rapid and sustained mitochondrial DNA depletion, altered energetics and growth. *Nucleic Acids Res* 2015;43:10338–10352.
267. Hance N, Ekstrand MI, Trifunovic A. Mitochondrial DNA polymerase gamma is essential for mammalian embryogenesis. *Hum Mol Genet* 2005;14:1775–1783.
268. Staretz-Chacham O, Lang TC, LaMarca ME, et al. Lysosomal storage disorders in the newborn. *Pediatrics* 2009;123:1191–1207.
269. Gudino MA, Campistol J, Chavez B, et al. Hurler's syndrome, West's syndrome, and vitamin D-dependent rickets. *J Child Neurol* 2002;17:149–151.
270. Chetta M, Guacci A, Rizzo F, et al. Infantile spasms in early-onset Niemann–Pick disease with a novel compound heterozygous mutations in SMPD1 gene. *New Horizons Transl Med* 2015;2:155–158.
271. Xu M, Motabar O, Ferrer M, et al. Disease models for the development of therapies for lysosomal storage diseases. *Ann N Y Acad Sci* 2016;1371:15–29.
272. Clarke LA, Russell CS, Pownall S, et al. Murine mucopolysaccharidosis type I: targeted disruption of the murine alpha-L-iduronidase gene. *Hum Mol Genet* 1997;6:503–511.
273. Desmaris N, Verot L, Puech JP, et al. Prevention of neuropathology in the mouse model of Hurler syndrome. *Ann Neurol* 2004; 56:68–76.
274. Wolf DA, Lenander AW, Nan Z, et al. Direct gene transfer to the CNS prevents emergence of neurologic disease in a murine model of mucopolysaccharidosis type I. *Neurobiol Dis* 2011;43:123–133.
275. Horinouchi K, Erlich S, Perl DP, et al. Acid sphingomyelinase deficient mice: a model of types A and B Niemann-Pick disease. *Nat Genet* 1995;10:288–293.
276. Jones I, He X, Katouzian F, et al. Characterization of common SMPD1 mutations causing types A and B Niemann-Pick disease and generation of mutation-specific mouse models. *Mol Genet Metab* 2008;95:152–162.
277. Poser CM, Low NL. Autopsy findings in three cases of hypsarhythmia (Infantile Spasms with Mental Retardation)1. *Acta Paediatr* 1960;49:695–706.
278. Bignami A, Maccagnani F, Zappella N, et al. Familial infantile spasms and hypsarrhytmia associated with leukodystrophy. *J Neurol Neurosurg Psychiatry* 1966;29:129–134.
279. Meencke HJ, Gerhard C. Morphological aspects of aetiology and the course of infantile spasms (West-syndrome). *Neuropediatrics* 1985;16:59–66.
280. Gingold MK, Bodensteiner JB, Schochet SS, et al. Alexander's disease: unique presentation. *J Child Neurol* 1999;14:325–329.
281. Hagberg B. Krabbe's disease: clinical presentation of neurological variants. *Neuropediatrics* 1984;15(Suppl):11–15.
282. Lee JM, Kim AS, Lee SJ, et al. A case of infantile Alexander disease accompanied by infantile spasms diagnosed by DNA analysis. *J Korean Med Sci* 2006;21:954–957.
283. Brenner M, Johnson AB, Boespflug-Tanguy O, et al. Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease. *Nat Genet* 2001;27:117–120.
284. Suzuki K, Suzuki Y. Globoid cell leucodystrophy (Krabbe's disease): deficiency of galactocerebroside beta-galactosidase. *Proc Natl Acad Sci USA* 1970;66:302–309.
285. Sakai N, Inui K, Fujii N, et al. Krabbe disease: isolation and characterization of a full-length cDNA for human galactocerebrosidase. *Biochem Biophys Res Commun* 1994;198:485–491.
286. Tanaka KF, Takebayashi H, Yamazaki Y, et al. Murine model of Alexander disease: analysis of GFAP aggregate formation and its pathological significance. *Glia* 2007;55:617–631.
287. Messing A, Head MW, Galles K, et al. Fatal encephalopathy with astrocyte inclusions in GFAP transgenic mice. *Am J Pathol* 1998;152:391–398.
288. Hagemann TL, Gaeta SA, Smith MA, et al. Gene expression analysis in mice with elevated glial fibrillary acidic protein and Rosenthal fibers reveals a stress response followed by glial activation and neuronal dysfunction. *Hum Mol Genet* 2005;14:2443–2458.
289. Wolf B, Grier RE, Allen RJ, et al. Biotinidase deficiency: the enzymatic defect in late-onset multiple carboxylase deficiency. *Clin Chim Acta* 1983;131:273–281.
290. Wolf B, Feldman GL. The biotin-dependent carboxylase deficiencies. *Am J Hum Genet* 1982;34:699–716.
291. Pomponio RJ, Reynolds TR, Cole H, et al. Mutational hotspot in the human serum biotinidase gene as a cause of biotinidase deficiency. *Am J Hum Genet* 1995;57:28.

292. Wolf B, Heard GS, Weissbecker KA, et al. Biotinidase deficiency: initial clinical features and rapid diagnosis. *Ann Neurol* 1985;18:614–617.
293. Kalayci Ö, Coskun T, Tokatli A, et al. Infantile spasms as the initial symptom of biotinidase deficiency. *J Pediatr* 1994;124:103–104.
294. Mikati MA, Zalloua P, Karam P, et al. Novel mutation causing partial biotinidase deficiency in a Syrian boy with infantile spasms and retardation. *J Child Neurol* 2006;21:978–981.
295. Rybak LP, Whitworth C, Weberg AD, et al. Rat as a potential model for hearing-loss in biotinidase deficiency. *Ann Otol Rhinol Laryngol* 1991;100:294–300.
296. Pindolia K, Jordan M, Guo C, et al. Development and characterization of a mouse with profound biotinidase deficiency: a biotin-responsive neurocutaneous disorder. *Mol Genet Metab* 2011;102:161–169.
297. Pindolia K, Chen J, Cardwell C, et al. Neurological deficits in mice with profound biotinidase deficiency are associated with demylination and axonal degeneration. *Neurobiol Dis* 2012;47:428–435.
298. van Grunsven EG, van Berkel E, Ijlst L, et al. Peroxisomal D-hydroxyacyl-CoA dehydrogenase deficiency: resolution of the enzyme defect and its molecular basis in bifunctional protein deficiency. *Proc Natl Acad Sci USA* 1998;95:2128–2133.
299. Suzuki Y, Jiang LL, Souri M, et al. D-3-hydroxyacyl-CoA dehydratase/D-3-hydroxyacyl-CoA dehydrogenase bifunctional protein deficiency: a newly identified peroxisomal disorder. *Am J Hum Genet* 1997;61:1153–1162.
300. Huyghe S, Mannaerts GP, Baes M, et al. Peroxisomal multifunctional protein-2: the enzyme, the patients and the knockout mouse model. *Biochim Biophys Acta* 2006;1761:973–994.
301. Möller G, van Grunsven EG, Wanders RJA, et al. Molecular basis of d-bifunctional protein deficiency. *Mol Cell Endocrinol* 2001;171:61–70.
302. Buoni S, Zannolli R, Waterham H, et al. D-bifunctional protein deficiency associated with drug resistant infantile spasms. *Brain Dev* 2007;29:51–54.
303. Baes M, Huyghe S, Carmeliet P, et al. Inactivation of the peroxisomal multifunctional protein-2 in mice impedes the degradation of not only 2-methyl-branched fatty acids and bile acid intermediates but also of very long chain fatty acids. *J Biol Chem* 2000;275:16329–16336.
304. Huyghe S, Schmalbruch H, Hulshagen L, et al. Peroxisomal multifunctional protein-2 deficiency causes motor deficits and glial lesions in the adult central nervous system. *Am J Pathol* 2006;168:1321–1334.
305. Verheijden S, Bottelbergs A, Krysko O, et al. Peroxisomal multifunctional protein-2 deficiency causes neuroinflammation and degeneration of Purkinje cells independent of very long chain fatty acid accumulation. *Neurobiol Dis* 2013;58:258–269.
306. Kim YI, Bhandari S, Lee JN, et al. Developmental roles of D-bifunctional protein-A zebrafish model of peroxisome dysfunction. *Mol Cells* 2014;37:74–80.
307. Pober BR. Williams-Beuren syndrome. *N Engl J Med* 2010;362:239–252.
308. Palacios-Verdu MG, Segura-Puimedon M, Borralleras C, et al. Metabolic abnormalities in Williams-Beuren syndrome. *J Med Genet* 2015;52:248–255.
309. Williams JC, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation* 1961;24:1311–1318.
310. Tsao CY, Westman JA. Infantile spasms in two children with Williams syndrome. *Am J Med Genet* 1997;71:54–56.
311. Morimoto M, An B, Ogami A, et al. Infantile spasms in a patient with williams syndrome and craniosynostosis. *Epilepsia* 2003;44:1459–1462.
312. Marshall CR, Young EJ, Pani AM, et al. Infantile spasms is associated with deletion of the MAGI2 gene on chromosome 7q11.23-q21.11. *Am J Hum Genet* 2008;83:106–111.
313. Noebels JL, Qiao X, Bronson RT, et al. Stargazer: a new neurological mutant on chromosome 15 in the mouse with prolonged cortical seizures. *Epilepsy Res* 1990;7:129–135.
314. Komoike Y, Fujii K, Nishimura A, et al. Zebrafish gene knockdowns imply roles for human YWHAG in infantile spasms and cardiomegaly. *Genesis* 2010;48:233–243.
315. Zhao C, Aviles C, Abel RA, et al. Hippocampal and visuospatial learning defects in mice with a deletion of frizzled 9, a gene in the Williams syndrome deletion interval. *Development* 2005;132:2917–2927.
316. Li HH, Roy M, Kuscuoglu U, et al. Induced chromosome deletions cause hypersociability and other features of Williams-Beuren syndrome in mice. *EMBO Mol Med* 2009;1:50–65.
317. Segura-Puimedon M, Sahun I, Velot E, et al. Heterozygous deletion of the Williams-Beuren syndrome critical interval in mice recapitulates most features of the human disorder. *Hum Mol Genet* 2014;23:6481–6494.
318. Borralleras C, Mato S, Amedee T, et al. Synaptic plasticity and spatial working memory are impaired in the CD mouse model of Williams-Beuren syndrome. *Mol Brain* 2016;9:76.
319. Thiel C, Schwarz M, Peng J, et al. A new type of congenital disorders of glycosylation (CDG-Ii) provides new insights into the early steps of dolichol-linked oligosaccharide biosynthesis. *J Biol Chem* 2003;278:22498–22505.
320. Jaeken J. Congenital disorders of glycosylation. *Handb Clin Neurol* 2013;113:1737–1743.
321. Thiel C, Korner C. Mouse models for congenital disorders of glycosylation. *J Inherit Metab Dis* 2011;34:879–889.
322. Wang Y, Tan J, Sutton-Smith M, et al. Modeling human congenital disorder of glycosylation type IIa in the mouse: conservation of asparagine-linked glycan-dependent functions in mammalian physiology and insights into disease pathogenesis. *Glycobiology* 2001;11:1051–1070.
323. El-Hattab AW, Scaglia F. Disorders of carnitine biosynthesis and transport. *Mol Genet Metab* 2015;116:107–112.
324. Reiss J, Hahnewald R. Molybdenum cofactor deficiency: mutations in GPHN, MOCS1, and MOCS2. *Hum Mutat* 2011;32:10–18.
325. Lee HJ, Adham IM, Schwarz G, et al. Molybdenum cofactor-deficient mice resemble the phenotype of human patients. *Hum Mol Genet* 2002;11:3309–3317.
326. Hahnewald R, Wegner W, Reiss J. AAV-mediated gene therapy for metabolic diseases: dosage and reapplication studies in the molybdenum cofactor deficiency model. *Genet Vaccines Ther* 2009;7:9.
327. Jakubiczka-Smorag J, Santamaria-Araujo JA, Metz I, et al. Mouse model for molybdenum cofactor deficiency type B recapitulates the phenotype observed in molybdenum cofactor deficient patients. *Hum Genet* 2016;135:813–826.
328. Heinonen OJ, Takala J. Moderate carnitine depletion and long-chain fatty acid oxidation, exercise capacity, and nitrogen balance in the rat. *Pediatr Res* 1994;36:288–292.
329. Spaniol M, Brooks H, Auer L, et al. Development and characterization of an animal model of carnitine deficiency. *Eur J Biochem* 2001;268:1876–1887.
330. Nasca C, Xenos D, Barone Y, et al. L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. *Proc Natl Acad Sci USA* 2013;110:4804–4809.
331. Pettegrew JW, Levine J, McClure RJ. Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. *Mol Psychiatry* 2000;5:616–632.
332. Wainwright MS, Mannix MK, Brown J, et al. L-carnitine reduces brain injury after hypoxia-ischemia in newborn rats. *Pediatr Res* 2003;54:688–695.
333. Jones LL, McDonald DA, Borum PR. Acylcarnitines: role in brain. *Prog Lipid Res* 2010;49:61–75.
334. Beaudet AL. Brain carnitine deficiency causes nonsyndromic autism with an extreme male bias: a hypothesis. *BioEssays* 2017;39:1700012-n/a.
335. Sezer T, Balci O. Infantile spasms during acute metabolic decompensation in an infant with isovaleric acidemia. *J Clin Neurol* 2016;12:376–377.
336. Vockley J, Ensenauer R. Isovaleric acidemia: new aspects of genetic and phenotypic heterogeneity. *Am J Med Genet C Semin Med Genet* 2006;142C:95–103.
337. Ribeiro CA, Balestro F, Grando V, et al. Isovaleric acid reduces Na+, K + -ATPase activity in synaptic membranes from cerebral cortex of young rats. *Cell Mol Neurobiol* 2007;27:529–540.
338. Solano AF, Leipnitz G, De Bortoli GM, et al. Induction of oxidative stress by the metabolites accumulating in isovaleric acidemia in brain cortex of young rats. *Free Radic Res* 2008;42:707–715.
339. Dulac O, Plecko B, Gataullina S, et al. Occasional seizures, epilepsy, and inborn errors of metabolism. *Lancet Neurol* 2014;13:727–739.

340. Vernon HJ. Inborn errors of metabolism: advances in diagnosis and therapy. *JAMA Pediatr* 2015;169:778–782.
341. Sharma S, Prasad AN. Inborn errors of metabolism and epilepsy: current understanding, diagnosis, and treatment approaches. *Int J Mol Sci* 2017;18:E1384.
342. Mohammad SA, Abdelkhalek HS. Nonketotic hyperglycinemia: spectrum of imaging findings with emphasis on diffusion-weighted imaging. *Neuroradiology* 2017;59:1155–1163.
343. Tekgul H, Serdaroglu G, Karapinar B, et al. Vigabatrin caused rapidly progressive deterioration in two cases with early myoclonic encephalopathy associated with nonketotic hyperglycinemia. *J Child Neurol* 2006;21:82–84.
344. Camurdan MO, Cinaz P, Serdaroglu A, et al. Persistent hyperinsulinemic hypoglycemia presenting with a rare complication: West syndrome. *J Pediatr Endocrinol Metab* 2004;17:1465–1468.
345. Basura GJ, Hagland SP, Wiltse AM, et al. Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. *Eur J Pediatr*. 2009;168:697–704.