Minireview

Metabolic and monogenic causes of seizures in neonates and young infants

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Abstract

Seizures in neonates or young infants present a frequent diagnostic challenge. After exclusion of acquired causes, disturbances of the internal homeostasis and brain malformations, the physician must evaluate for inborn errors of metabolism and for other non-malformative genetic disorders as the cause of seizures. The metabolic causes can be categorized into disorders of neurotransmitter metabolism, disorders of energy production, and synthetic or catabolic disorders associated with brain malformation, dysfunction and degeneration. Other genetic conditions involve channelopathies, and disorders resulting in abnormal growth, differentiation and formation of neuronal populations. These conditions are important given their potential for treatment and the risk for recurrence in the family. In this paper, we will succinctly review the metabolic and genetic non-malformative causes of seizures in neonates and infants less than 6 months of age. We will then provide differential diagnostic clues and a practical paradigm for their evaluation.

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1. Introduction

Seizures are a common neurologic symptom in neonates and young infants. They can portend a poor prognosis, particularly when they are associated with an epileptic encephalopathy. The electroencephalogram patterns of burst suppression and hypsarrhythmia tend to be associated with a particularly poor prognosis. There are many causes for seizures in neonates and young infants. These can include environmental factors such as hypoxic-ischemic injury, traumatic brain injury, or congenital infections, malformations such as holoprosencephaly or cortical migration abnormalities, and genetic factors such as trisomies or chromosomal deletion syndromes. Up to 10% of infants with severe seizure disorders have microdeletions. Other genetic causes of early seizures include channelopathies, neurotransmitter receptor mutations and developmental problems such as mutations in the ARX gene. Metabolic disorders make up a special category of causes of neonatal and early infantile seizures. They are particularly important because many conditions are treatable, and all of them have a risk for recurrence in the same family. In this article, we will review inherited metabolic diseases that present predominately with seizures in neonates and young infants. We will review the conditions and present a paradigm for their evaluation.

General disturbances of internal homeostasis that affect the functioning of the cell will cause seizures. This includes a lack of oxygen as in hypoxic-ischemic injury, electrolyte abnormalities such as hypocalcemia, hypoglycemia, hyperammonemia, and severe metabolic disturbances such as organic acidurias and maple syrup urine disease. In such cases, the decreased consciousness and the abnormal neurological and clinical picture dominate the clinical presentation rather than the seizures. Broad screening of electrolytes, glucose, ammonia, plasma or serum amino acids and urine organic acids should be obtained immediately, particularly if accompanied by decreased consciousness.

Specific metabolic causes of epilepsy in neonates and early infancy can be categorized in three groups:

1. disturbances in neurotransmission associated with an epileptic encephalopathy,
2. disorders of energy production such as the use of glucose, pyruvate, the Krebs cycle, and the respiratory chain,
3. disorders associated with brain malformation, dysfunction, and degeneration on a metabolic basis.

Monogenic causes of epilepsy can include syndromic forms of brain malformation or can involve genes that have a specific predisposition for seizures without major brain malformations. Genes responsible for brain cortical malformation as causes of seizures have been reviewed elsewhere [1–3]. Here we will review the latter. These genes are involved in channelopathies or the abnormal growth, differentiation, and formation of neuronal populations.

2. Disorders of neurotransmitter metabolism

2.1. Nonketotic hyperglycinemia

Nonketotic hyperglycinemia is caused by deficient glycine cleavage enzyme activity and characterized by elevated glycine in body fluids. Patients with classic nonketotic hyperglycinemia present as neonates in the first days of life with hypotonia, feeding difficulties, lethargy progressing to coma, seizures, and apnea requiring ventilation in 70% of cases [4–7]. They often have a burst suppression pattern on electroencephalogram (EEG), which over time evolves into hypsarrhythmia, and later multifocal epilepsy. On magnetic resonance imaging (MRI), most neonatally presenting patients have increased signal on diffusion-weighted images in the areas that are myelinated at birth, most often in the posterior limb of the internal capsule and sometimes in the long tracts in the brain stem. Some patients have hypoplasia or agenesis of the corpus callosum, hydrocephalus with posterior fossa abnormalities, or simplification of gyri. One third of patients present in early to mid infancy with seizures, hypotonia, and developmental delay. Long term, the majority of patients have a very poor outcome. These patients make no developmental progress, and have signs of spasticity at less than 6 months of age. They develop progressive brain atrophy and multifocal seizures. However, a subset of patients (1/6 of patients presenting neonatally and 1/2 of patients presenting in infancy) have a better outcome [4–7]. These patients make developmental progress, but remain moderately to severely mentally retarded (IQ 20–60); they can learn to sit and grasp, and develop choreatic movements. Their seizure disorder is milder and is often easily treated with a single anticonvulsant.

The glycine cleavage enzyme system consists of 4 subunits named P, T, H, and L. Diagnosis of nonketotic hyperglycinemia is made by finding elevated glycine in serum and cerebrospinal fluid (CSF) with an increased ratio of CSF:plasma glycine (>0.06 with normal ≤0.02) [8]. The diagnosis can be confirmed by enzyme activity assay in a liver biopsy or by mutation analysis. Mutations have been found in the AMT gene encoding the T-protein in 25% of patients and in the GLDC gene encoding the P-protein in 75% of patients [7,9]. Up to 20% of mutations in the GLDC gene are exon deletions [10]. The condition is usually treated with benzoate to reduce the glycine levels, and with NMDA receptor blockers such as dextromethorphan. Early myoclonic seizures respond to benzodiazepines, but seizure control becomes more difficult in severely affected patients during the first year of life, often requiring multiple anticonvulsants by 1 year of age.

2.2. Pyridoxal-5′-phosphate responsive encephalopathy

Pyridoxal-5′-phosphate is the active cofactor form of vitamin B6 and is used in many enzymatic reactions including such brain processes as the synthesis of GABA as well as in the glycine cleavage enzyme. Pyridoxine and pyridoxamine are phosphorylated to pyridox(am)ine-phosphate and are then oxidized to pyridoxal-phosphate by pyridox
identical to pyridoxine-dependent epilepsy [26]. These patients should have been born prematurely often with low Apgar scores [12,13]. They develop neonatal seizures and an epileptic encephalopathy with myoclonic and severe tonic–clonic seizures. The EEG shows a burst suppression pattern. Diagnosis is suggested by finding in CSF elevated levels of threonine and glycine and low levels of monoamine metabolites. The decline in normal values in CSF threonine from 45–120 μM in the first week to 20–45 μM by 6 months of age should be taken into account. A more direct and reliable indicator is a low level of pyridoxal-5′-phosphate in CSF [14]. The diagnosis is confirmed by sequencing the PNPO gene [15]. Treatment with pyridoxal-5′-phosphate (30 mg/kg/day) can result in a good outcome if treatment is initiated early [13]. These patients do not respond to pyridoxine, and this condition is different from pyridoxine-dependent epilepsy, which is described below.

2.3. Pyridoxine-dependent epilepsy

The vast majority of patients with pyridoxine-dependent epilepsy have a deficiency in α-amino adipic semialdehyde dehydrogenase [16]. Alpha-amino adipic semialdehyde is derived from the catabolism of lysine through piperocic acid and is in equilibrium with Δ1-piperidine-6-carboxylic acid (6-PC), which reacts with pyridoxal-5′-phosphate. These patients have elevated α-amino adipic semialdehyde and 6-PC in urine and serum and a secondary elevation of piperocic acid in serum. They present with seizures in the neonatal period or early infancy [17–20]. They are often encephalopathic with irritability and temperature instability. As neonates, they usually have a burst suppression pattern on EEG. Later they have hypsarrhythmia and often develop multifocal seizures. Most patients have developmental delay and some have white matter abnormalities. Diagnosis is made by treatment with intravenous pyridoxine 100 mg under EEG monitoring, followed with oral pyridoxine 30 mg/kg/day for at least 3 days. The response to intravenous pyridoxine alone lacks sensitivity and specificity [21]. A more direct diagnosis is by demonstration of α-amino adipic semialdehyde or 6-PC in urine or serum and confirmation by sequencing analysis of the ALDH7A1 gene [16,22]. Treatment is with oral pyridoxine 15 to 30 mg/kg/day, and monitoring for neuropathy in those patients treated at high doses. Most patients have seizure control, but still have some developmental delay.

A few rare patients have been reported who present with West syndrome with hypsarrhythmia whose seizures respond to pyridoxine. These patients do not have α-amino adipic semialdehyde dehydrogenase deficiency and represent a separate disorder, the cause of which is currently not yet known [19,23]. The outcome in these patients seems to be favorable with treatment. This treatable condition warrants a three day trial with pyridoxine in all patients with West syndrome regardless of biochemical findings.

2.4. Folinic acid responsive seizures

Patients were described who presented with an abnormal peak on HPLC analysis of CSF for monoamine metabolites [24]. The patients presented with myoclonic seizures evolving into multifocal seizures since birth or early infancy. On EEG they had burst suppression or hypsarrhythmia evolving into multifocal epilepsy. They have been described as responding to folic acid 3 to 5 mg/kg/day, although the outcome of these patients has been poor. Some of these patients have responded to pyridoxine [24,25]. Recent studies have shown that all patients diagnosed based on the abnormal peak detectable during monoamine metabolite analysis had elevated α-amino adipic semialdehyde and mutations in the ALDH7A1 gene, thus making the condition identical to pyridoxine-dependent epilepsy [26]. These patients should be treated with pyridoxine.

2.5. Mitochondrial glutamate transporter

Patients with this condition have a deficiency in the mitochondrial H+/glutamate transporter encoded by the SLC25A22 gene [27,28]. Patients present with neonatal intractable myoclonic seizures and develop brain atrophy. They have a burst suppression pattern on EEG. The visual evoked potentials are of low amplitude although the electroretinogram (ERG) is normal in some, abnormal in others. Diagnosis is made by decreased mitochondrial oxidation of glutamate and by mutation analysis. There is no specific treatment. This condition was identified in 2 of 30 patients screened with early seizures [28]. Absence of clinically available testing and of a specific biomarker makes this condition hard to diagnose.

2.6. Aromatic amino acid decarboxylase deficiency (AADC)

Aromatic amino acid decarboxylase catalyzes the conversion of dopa to dopamine and of 5-hydroxytryptophan to serotonin. Its deficiency results in severely reduced dopamine and serotonin, and low concentrations of their CSF metabolites homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) [29]. CSF dopa levels are increased and vannillactic acid is present in urine. These patients present in the first months with motor symptoms of axial hypotonia, hypokinesia, atethosis, dystonia, and limb rigidity [29,30]. They have ocular symptoms of oculogyric crises and convergence spasms, which can resemble seizures. They have autonomic symptoms of ptosis, nasal congestion, hypothermia, sweating, temperature instability, and blood pressure lability. They often have abnormal sleep, feeding difficulties, and gastroesophageal reflux. Patients with AADC deficiency do not have seizures but the oculogyric crises with autonomic instability are often misdiagnosed as seizures. Patients who were reported with a biochemical picture of AADC and who had neonatal seizures were later shown to have a deficiency in pyridox(am)ine phosphate oxidase, since pyridoxal-5′-phosphate is a cofactor of this enzyme [31]. The outcome of AADC deficiency tends to be poor with marked impairment in motor and speech. Diagnosis is made by monoamine metabolite analysis in CSF and by measurement of the enzyme activity in serum, with confirmation by mutation analysis of the AADC gene. These children are treated with dopamine agonists, monoamine oxidase inhibitors, and with trihexyphenidyl.

2.7. D-2-hydroxyglutaric aciduria

D-2-hydroxyglutaric acid is made from bacterial gut metabolism, from catabolism of hydroxylysine, from 5-aminolevulinc acid in the porphyrin synthesis via 2-ketogluturate semialdehyde and S-2-hydroxyglutarylglutathione, and from GABA via its conversion to succinic semialdehyde through the hydroxy acid:oxoacid transhydrogenase (Hot) enzyme [32]. D-2-hydroxyglutaryl acid is removed by the enzyme D-2-hydroxyglutarate dehydrogenase to 2-ketoglutarate [33]. Deficiency of this enzyme causes an autosomal recessive condition where severely affected patients present with neonatal or early infantile, severe epilepsy [34]. They have hypotonia, visual failure, and severe developmental delay. Some patients have cardiomyopathy, facial dysmorphisms, and episodic vomiting. On MRI they have delayed brain maturation of the white matter, of gyration, and particularly of operculum. They often had subependymal cysts and dilated ventricles [35,36]. Three patients have been described with spondyloenchondrodysplasia [37,38]. Patients with a milder form of the disorder who present with hypotonia, developmental delay, and even asymptomatic patients have been described. There does not seem to be a genotype–phenotype correlation, since twins with the same genetic make-up can have divergent phenotypes [39]. Diagnosis is made by finding 2-hydroxyglutarate on urine organic acids and separation of this into the D- and L-form. GABA is sometimes elevated in CSF. The diagnosis can be
confirmed by molecular analysis of the D2HGD gene [33]. There is no specific treatment.

2.8. GABA disorders: 4-hydroxybutyric aciduria or succinic semialdehyde dehydrogenase deficiency and GABA transaminase deficiency

Patients with succinic semialdehyde dehydrogenase deficiency accumulate succinic semialdehyde derived from GABA transamination, which is converted into 4-hydroxybutyric acid and excreted in urine. These patients present with motor delay, ataxia, language delay, hypotonia, and mental delay, each present in more than 70% of patients [40,41]. Seizures are present in 48% of patients and EEG abnormalities were noted in 26% of patients. Seizures often start in infancy. Less frequent symptoms include absent reflexes or hyperkinesis or excessive sleepiness. Whereas 26% of patients have problems in the neonatal period, an equal number have normal early development. The diagnosis is suspected on finding 4-hydroxybutyric acid on urine organic acids analysis, and confirmation can be done by enzyme assay or molecular analysis of the ALDH5A1 gene. Treatment is symptomatic [42].

GABA transaminase deficiency is a rare disorder described in two families [43,44]. The phenotype involves psychomotor retardation, infantile seizures, hypotonia, hyperreflexia, and accelerated growth. MRI showed diffusion restriction in the internal and external capsule and subcortical white matter areas. There is elevation of GABA, beta-alanine, and homocarnosine, most notable in the CSF [43]. Elevated GABA can be recognized on magnetic resonance spectroscopy [44]. The diagnosis can be confirmed by enzyme assay or mutation analysis of the ABAT gene [43].

3. Disorders of energy metabolism

3.1. Glucose transporter deficiency

Glucose is the main fuel of the brain. It is transported across the blood–brain-barrier and into astrocytes by the glucose transporter (GLUT1, also called SLC2A1). Patients are haploinsufficient due to a mutation in the GLUT1 gene and have a partial deficiency of the transporter function [45]. Most (76%) patients present in the first 6 months of life [46–50]. They have a variety of seizures including complex seizures, generalized seizures, and myoclonic seizures. Early absence seizures have also been reported. The seizures, which are often therapy resistant, sometimes improve with feeding and worsen with barbiturates, such as phenobarbital, which partially inhibits this transporter. The EEG often shows a 2.5 to 4 Hz spike wave pattern. Other symptoms include ataxia which is sometimes intermittent, language delay, developmental delay, spasticity, choreoathetosis, and dystonia. They can develop microcephaly. Hypometabolism in the thalami and temporal lobes has been demonstrated on PET scanning. Untreated patients have substantial developmental delay. The diagnosis is suspected by the finding of hypoglycorachia (<45 mg/dl in CSF, and a CSF:plasma glucose ratio <0.4 (normal 0.6), in the absence of other causes of hypoglycorachia. The diagnosis can be confirmed by mutation analysis of the GLUT1 gene or by an uptake assay of labeled 3-O-methylglucose into red blood cells. Treatment consists of feeding the brain with an alternative fuel, specifically ketones, using a ketogenic diet. The aim is to keep the serum ketones above 3 mM. Inhibitors of the GLUT1 transporter such as barbiturates and caffeine should be avoided. Seizure control is improved with treatment, but residual developmental delays often persist.

3.2. Pyruvate dehydrogenase deficiency (PDH) and pyruvate carboxylase deficiency (PCD)

The pyruvate dehydrogenase complex catalyzes the conversion of pyruvate to acetyl-coenzyme A. It is composed of multiple subunits, and defects in each of them have been described. The most frequent genetic defects reside in the E1α-subunit which is located on the X-chromosome [51]. Boys with this defect tend to have a mild mutation with residual enzyme activity. They present with Leigh disease, lactic acidosis, ataxia, and often agenesis of the corpus callosum [52,53]. Girls tend to have severe mutations, but have a mixed clinical picture due to the effects of lyonization. They present with dysmorphisms, microcephaly, moderate to severe mental retardation, and spastic quadriplegia. They often have periventricular multicystic leukoencephalopathy and agenesis of the corpus callosum. In these girls, seizures are common. They present in the first 6 months of life, often as West syndrome with infantile spasms or with severe myoclonic seizures [52,53]. Pyruvate dehydrogenase will show an elevated lactate and an elevated pyruvate with a normal ratio if the lactate is greater than 2.5 mmol/L [54]. In contrast, pyruvate carboxylase deficiency will show an increased lactate with elevated lactate:pyruvate ratio. Diagnosis can be made by enzyme assay either in lymphocytes or in fibroblasts (more accurate), and confirmed by molecular sequencing [52]. Pyruvate dehydrogenase deficiency is treated by providing the brain an alternative fuel, specifically ketones through a ketogenic diet, which can sometimes result in surprising improvements in functionality [55], including improvements of seizures [53]. A few patients respond to pharmacologic treatment with thiamine [56]. Pyruvate carboxylase deficiency presents with marked lactic acidosis. Patients develop a leukoencephalopathy with seizures. Pyruvate carboxylase deficiency can be treated with anaplerotic support such as trileptanoin oil or aspartate and citrate [57,58].

3.3. Biotinidase deficiency

In biotinidase deficiency, biotin is not recycled from biocytin to biotin. This leads to a deficiency of the biotin cofactor with subsequent deficient enzyme activities of the carboxylases: pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and the acetyl-CoA carboxylases. The clinical presentation is in infancy on average starting around 7 weeks of age. Patients present with seizures, often grand mal or myoclonic. They have hypotonia, lethargy, and ataxia. They develop a skin rash which is often eczematoïd, alopecia, and keratoconjunctivitis [59]. Untreated, they develop psychomotor retardation, hearing loss, and can develop irreversible optic atrophy. Some patients have initially presented with severe infantile seizures such as Ohhtahara syndrome [60]. The biochemical presentation mimics holocarboxylase synthase deficiency. Clinical diagnosis is suspected from elevated lactate and from metabolites of the carboxylases on urine organic acids such as elevated 3-hydroxyisovaleric acid, 3-methylcrotonylglycine, lactic acid, methylcitric acid, 3-hydroxypropiionate, or from an abnormal plasma acylcarnitine profile (elevated C3- and hydroxy-C5-acylcarnitines). It is confirmed by assaying the biotinidase enzyme activity in serum in which patients with severe deficiency have less than 10% residual activity [61], and by mutation analysis [62]. Most patients are currently detected presymptomatically by newborn screening, preventing a clinical presentation with seizures. Treatment with biotin 10 mg/day results in good outcome. This utterly treatable condition should not be missed as an etiology of infantile seizures and physicians should not rely solely on the results of newborn screening, which does not replace diagnostic testing.

3.4. Respiratory chain disorders

Respiratory chain disorders have many phenotypes. The lethal infantile phenotype presents with a severe neurological picture. This often includes severe and progressive brain damage which includes seizures. These patients nearly always have elevated lactate in serum or CSF. Enzymatic defects in each of the complexes have been described with this presentation. Mutations can exist in mitochondrial DNA or in nuclear DNA in genes encoding for components of the
respiratory chain, for the assembly of these components, or for the maintenance and expression of mitochondrial DNA.

Leigh disease is a condition in which damage occurs in the basal ganglia, brain stem, and dentate nuclei of the cerebellum. Patients often present with progressive motor dysfunction including dystonia, ataxia, bulbar symptoms, and Parkinsonism. There are many genetic causes of Leigh disease in infancy and include the mitochondrial tRNALeu(UUR) gene with the mt.A3243G mutation, the assembly proteins of complex IV such as the SURF1 protein, nuclear coding genes of complex I, but also the mt.T8993G mutation in complex V. In most cases of Leigh disease, seizures are a late symptom, except in the mt.T8993G mutation, where seizures can be an early and presenting symptom [63].

Alpers disease is a combination of a progressive poliodystrophy and a hepatopathy [64,65]. Seizures are usually the first symptom and worsen progressively [66]. They may have been preceded by developmental delay, failure to thrive, and vomiting. There is neurological regression, and often lesions in the occipital and temporal lobes. Liver disease is often initially insidious and biochemically subtle, until sudden hepatic failure develops, often following treatment with valproate. There is fibrosis and steatosis on liver biopsy. The brain exhibits neuronal loss, spongiosis, and astrocytosis, particularly in the striate cortex with a predilection for the calcarine cortex. There is occasionally hypoglycemia [66] or elevated 3-methylglutaconic acid in blood or urine [67]. On brain imaging there is cortical atrophy mostly in the posterior and occipital lobes. The EEG shows polyspikes, high amplitude slow activity predominantly posterior, or epilepsia partialis continua [68]. Lactate levels in serum and CSF are often normal, but CSF protein is usually elevated. The respiratory chain enzymes are often normal in muscle, but deficient in liver, and always normal in fibroblasts. A depletion of mtDNA is often present in liver. Common genetic causes are mutations in mitochondrial DNA polymerase-γ encoded by the POLG1 gene, resulting in deficient polymerase γ activity with depletion of mtDNA [64,69].

3.5. Menkes disease

In Menkes disease, copper is not effectively exported from cells, resulting in poor incorporation into copper containing enzymes such as cytochrome c oxidase, dopamine β-hydroxylase, and lysyl-oxidase. This X-linked condition presents in baby boys with seizures, hypotonia, failure to thrive, and progressive spasticity with loss of milestones. On brain imaging there is brain atrophy and delayed myelination, with a lactate peak on MRS, and tortuous vessels on MR angiography. Connective tissue symptoms include skin laxity, cephhalohematoma, wormian bones, hernias, pectus excavatum, hair loss with pili torti, and bladder diverticula. Lactic acid can be present. Most patients die in early childhood. Therapy resistant seizures often start at age 2 to 3 months and involve focal clonic status epilepticus or intractable infantile spasms [70–72]. Diagnosis is often suspected with the finding of low serum copper (<11 μM) and low ceruloplasmin (<210 mg/L). An improved biochemical marker is the analysis of serum catecholamines with an increased ratio of dihydroxyphenylalanine:dihydroxyphenylglycol reflecting the poor activity of dopamine β-hydroxylase [72,73], and confirmation of diagnosis is performed by sequencing the APTA7 gene [71]. Treatment with parenteral copper histidine has been successful following very early treatment, particularly in mildly affected patients including improved control of seizures [72–74].

3.6. Fumarase deficiency

The fumarase enzyme converts fumarate to malate. Both the cytosolic enzyme and the mitochondrial Krebs cycle enzyme are encoded by the same FH gene. The clinical presentation is in infancy with a static neurological picture including severe hypotonia, profound mental retardation (IQ~25), and seizures of various types with a generalized convulsive status being present in 44% of patients [75,76]. On EEG, 10/11 patients had epileptiform features. There is visual impairment, optic atrophy, dysmorphic features including frontal bossing, hypertelorism, and a depressed nasal bridge. On brain MRI imaging, there is an open sylvian operculum, enlarged ventricles, and in several patients, polymicrogyria, decreased white matter volume, small brain stem, and agenesis of the corpus callosum. The outcome is severe mental retardation and children often die in the first years of life. The diagnosis is suspected by findings on urine organic acids analysis of high fumarate, and to a lesser extent, elevation of succinate and α-ketoglutarate. The diagnosis is confirmed by enzyme assay in fibroblasts or leukocytes and by mutation analysis. Treatment is symptomatic.

3.7. Sulfite oxidase deficiency

Sulfite oxidase with its cofactor molybdopterin performs the last step in the metabolism of sulfur-containing amino acids by oxidizing sulfite derived from cysteine to sulfate. When sulfite oxidase is deficient, sulfite builds up along with the other toxic metabolites, such as S-sulfocysteine and thiosulfate. The clinical presentation of sulfite oxidase or molybdo- terin cofactor deficiency includes neonatal or early infantile presentation of refractory convulsions, severe psychomotor retardation, failure to thrive, hypo- or hypertonnia, lens dislocation, and early death [77]. Lactate is elevated in 50% of cases, and homocysteine reduced to below normal [78]. Brain MRI imaging often shows initial edema followed by cystic degeneration. Early seizures with burst suppression pattern, sometimes mimicking hypoxic ischemic injury with restricted diffusion in the cortex and subcortical white matter, is common [79,81,82]. More mildly affected patients have involvement of the globus pallidus [83]. Sulfite oxidase can occur as isolated sulfite oxidase deficiency or can be due to a deficiency in the cofactor molybdopterin with an associated deficiency in xanthine oxidase [84]. Diagnosis of sulfite oxidase deficiency is made by finding increased S-sulfocysteine in urine or plasma. Isolated sulfite oxidase deficiency is diagnosed by molecular analysis of the SUOX gene. Defects in the synthesis of molybdopterin are diagnosed additionally by elevated xanthine and severely reduced uric acid (usually <1 mg/dL); verification is made by molecular analysis of MOC1 (type A), MOCS2 and MOCS3 (type B), and Gephyrin CPHN (type C) genes [85]. Treatment includes dietary limitation of sulfur-containing amino acids cysteine and methionine for mildly affected cases, but is ineffective for severely affected patients. For patients with type A and a defect in the MOCS1 gene, treatment with intravenous cyclic pyranopterin monophosphate (cPMP) improves metabolic control and symptoms [86].

3.8. Purine disorders: adenylosuccinate lyase deficiency and AICA-ribosiduria

The de novo synthesis of purines from ribose-5-phosphate begins with the formation of phosphoribosyl pyrophosphate (PRPP). PRPP is then converted in ten steps to inosine monophosphate (IMP). The eighth step in the biosynthesis converts 5-phosphoribosyl-5-aminoimidazole-4-(N-succinyl)carboxamide (SAICAR) to 5′-phosphoribosyl-5-aminoimidazole-4-carboxamide (AICAR) by the enzyme adenylosuccinate lyase. In its absence, SAICAR accumulates. The next step converts AICAR to 5′-phosphoribosyl-5-formamidimidazole-4-carboxamide by the enzyme phosphoribosylaminomimidazole-carboxylase formyl transferase (AICAR transformylase), and in its absence AICAR accumulates. Inosine is converted to adenosine by the formation of adenylosuccinate, followed by the release of succinate by adenylosuccinate lyase. Thus, adenylosuccinate lyase deficiency has an increase in both SAICAR and adenylosuccinate, whereas AICAR transformylase deficiency accumulates AICAR and to a lesser extent SAICAR.

Deficiency of adenylosuccinate lyase results in three types of clinical presentations depending on the severity. Patients with Group I (classic) present with severe psychomotor retardation, seizures, autistic features, and muscle wasting. Patients with Group II (mild) have severe hypotonia and mild developmental delays. Patients with
3.9. Creatine synthesis and transporter defects

Creatine is important in brain and skeletal muscles as it provides a source for conversion into phosphocreatine, which is involved in energy transmission. Creatine synthesis and transporter defects result in decreased creatine in the brain. Two enzymes, arginine glycine amidinotransferase (AGAT) and guanidoacetate methyltransferase (GAMT) are involved in synthesis of creatine, and a transporter (CRT1) is involved in creatine transport from the blood into the brain.

Patients with severe deficiency of GAMT activity present in infancy with severe to intractable seizures, severe mental retardation, expressive speech delay, hypotonia, and symptoms of autism. They can also develop extrapyramidal symptoms and brain imaging may show global pallidus lesions [95,96]. Patients with a mild deficiency in GAMT activity present with mild seizures, mental retardation, and particularly expressive speech delay. Patients with AGAT deficiency present with mild febrile seizures, developmental delay, and language delay [97]. Patients with a defect in CRT1 present with moderate seizures, mental retardation, severe language delay, autistic symptoms, and behavioral problems [98].

The diagnosis is made by assaying creatine and guanidoacetate in urine and plasma [99,100]. Creatine in the brain will be low on magnetic resonance spectroscopy in all cases. Urine and plasma creatine levels will be low in GAMT deficiency and high in CRT1 deficiency with an elevated creatine:creatinine ratio. Urine and plasma guanidoacetate will be elevated in GAMT deficiency, decreased in AGAT deficiency and low or normal in CRT1 deficiency. The diagnosis can be confirmed with enzymatic assays or by molecular analysis of the GAMT and AGAT genes, and in CRT1 deficiency by creatine uptake assay in fibroblasts or more commonly by molecular analysis of the gene SLC6A8. Treatment of AGAT and GAMT deficiency includes creatine supplementation, and in GAMT deficiency dietary arginine restriction with ornithine supplementation [101,102]. There is currently no effective treatment for CRT1 defects.

4. Biosynthetic defects: brain malformation and dysfunction

4.1. Peroxisomal disorders

Peroxisomes are important cellular organelles for the beta-oxidation of very long chain fatty acids, branched chain fatty acids, and bile acids, for alpha-oxidation of 2-methylbranched chain fatty acids, and for the synthesis of ether lipids. Disorders of peroxisomes occur when the peroxisomes are not formed correctly (biogenesis disorder) or when an enzyme used in the peroxisomes is deficient. Patients with peroxisomal biogenesis disorders or single enzyme deficiencies can present neonatally with multi-system involvement including seizures, hypotonia, and polymicrogyria in the perisylvian fissure, dysmorphic features including a broad forehead with a broad anterior fontanel, cholestasis, liver fibrosis, chondrodysplasia punctata, and adrenal dysfunction [103]. The severity ranges from the most severe form of Zellweger syndrome, to the least severe form of infantile Refsum disease. Seizures are present in 92% of Zellweger patients [104]. Diagnosis is made by finding elevated very long chain fatty acids with an elevated C26:0/C22 ratio being the most sensitive indicator [105]. If elevated, one should measure other metabolites which include abnormal bile acids, decreased plasmalogens, and increased phytic acid in older patients. Abnormalities in all these metabolites indicate the diagnosis of a peroxisomal biogenesis disorder. Confirmation is made with molecular analysis of the PEX genes. The most common causes of peroxisomal biogenesis disorders are mutations in the PEX1 gene. Testing for other PEX genes is also available. In rare patients with D-bifunctional protein deficiency, which typically presents with seizures in the first month of life, very long chain fatty acids are normal, but MRI findings such as polymicrogyria or white matter disease can guide one to the need for more biochemical testing such as C26:0 β-oxidation in fibroblasts [106].

4.2. Congenital disorders of glycosylation (CDG)

After translation, many proteins are modified by the addition of sugar moieties to an asparagine in N-linked glycosylation or to a serine or threonine in O-linked glycosylation [107,108]. N-linked glycosylation is a multistep process and involves first the synthesis of a polyglycan chain on dolichol, followed by transfer of the glycan onto the nascent protein in the endoplasmic reticulum, and subsequent modification of this glycan on its protein in the Golgi apparatus. CDG syndromes are classified as CDG Type I which includes all enzymatic defects in the synthesis in the cytosol and endoplasmic reticulum, or as CDG Type II which includes enzymatic or processing defects of glycan modification in the Golgi apparatus. Combined defects also involve a deficiency of O-linked glycosylation in addition to N-linked glycosylation. So far, more than 25 different enzymes have been identified whose disruption results in a clinical phenotype. This is, not surprisingly, a diverse group of disorders that can present clinically in many different ways. Common clinical phenotypes include some or all of the following symptoms: mild to severe seizures, developmental delay, hypotonia, ataxia, and dysmorphic features (including microcephaly, inverted nipples and persistent fat pads or lipodystrophy). Other organ systems that can be involved include gastrointestinal with hepatic fibrosis, protein-losing enteropathy, hypoglycemia, failure to thrive as well as hematologic with coagulopathy, thrombocytopenia, and anemia. Diagnosis is made by analyzing the glycosylation of a prototypic N-glycosylated protein transferrin such as by isoelectric focusing or by mass spectrometry, which will identify most CDG syndromes but not all. Urine oligosaccharides may identify an additional disorder. Diagnosis is confirmed by genetic sequencing of the enzyme directly involved in that particular step. Only symptomatic treatment is available.

Some disorders have severe seizures dominating the clinical picture. They also have severe mental retardation and hypotonia. These include the disorders ALG3-CDG (CDG-Ia), DPM1-CDG (CDG-Ie), ALG2-CDG (CDG-IIa), DPAGT1-CDG (CDG-Ij), ALG1-CDG (CDG-Ik), RFT1-CDG (CDG-1m), ALG11-CDG (CDG-1p), and GCS1-CDG (CDG-Ib). Additional symptoms for these are coloboma for ALG3-CDG (CDG-Ia), DPAGT1-CDG (CDG-Ij), ALG1-CDG (CDG-Ik) and GCS1-CDG (CDG-Ib), corpus callosum hypoplasia for ALG3-CDG (CDG-Ia), liver dysfunction for ALG1-CDG (CDG-Ik) and GCS1-CDG (CDG-Ib), nephrotic syndrome in ALG1-CDG (CDG-Ik), infantile spasms in DPAGT1-CDG (CDG-Ij), sensorineural hearing loss in ALG11-CDG (CDG-1p), and dry, ichthyosiform and parchment-like skin in DPM1-CDG (CDG-Ie). Each of these disorders can be identified by analysis of the transferrin glycan forms, except for GCS1-CDG (CDG-Ib) which is identified by the excretion of a
tetrasaccharide in urine identified on urine oligosaccharide analysis [109–124]. Some disorders have mild seizures with a static neurological picture. These include the disorders PMM2-CDG (CDG-Ia), MPDUD1-CDG (CDG-II), ALG9-CDG (CDG-II), and MGAT2-CDG (CDG-IIa). Additional symptoms include dysmorphism in the severe form of PMM2-CDG (CDG-Ia) and MGAT2-CDG (CDG-IIa), ichthyosiform skin in MPDUD1-CDG (CDG-II), decreased immunoglobulins in ALG12-CDG (CDG-Ig), pericardial effusions in PMM2-CDG (CDG-Ia) and ALG9-CDG (CDG-II), cerebellar hypoplasia in PMM2-CDG (CDG-Ia), very low cholesterol in ALG6-CDG (CDG-Ic), and nephrotic syndrome in PMM2-CDG (CDG-Ia) [125–130].

The combined defects of N-linked and O-linked glycosylation are due to trafficking defects in the Golgi apparatus. The propensity for seizures varies. COG7-CDG (Ile) and ATP6V0A2-CDG disorders have encephalopathy with some seizures, failure to thrive, hyperthermia, and cutis laxa. COG8-CDG patients have episodes of encephalopathy often with seizures, and a cerebellar syndrome, whereas COG1-CDG patients did not have seizures [131,132].

4.3. Glycolipid synthesis: GM3 synthase deficiency

GM3 synthase catalyzes the initial step in the formation of GM3 ganglioside from lactosylceramide. Gangliosides are important in the cell membrane, the myelin, and are involved in cell-signaling in the central nervous system. Absence of GM3 synthase activity was described in infants presenting from 3 weeks to 2 months with poor tone, feeding difficulties, and failure to thrive [133]. In the first year of life, an affected child will develop difficult to control tonic-clonic seizures, myoclonus, and an EEG showing multifocal epileptiform discharges. With the onset of seizures, there can be profound developmental stagnation or regression, choreoathetoid movements, reduced deep tendon reflexes, and visual deterioration. Brain MRI can be normal or show diffuse atrophy. Patients can be screened for this disorder by analysis of ganglioside composition showing increased lactosylceramide and absent gangliosides of the series GM1-GM2-GM3, with increased neutral glycosphingolipids Gb3 and G4. The disorder is autosomal recessive and molecular analysis of the gene SIAT9 confirms the diagnosis. No specific treatment is available. A clinical screening assay of gangliosides should be developed for easy recognition of this group of conditions.

4.4. Cholesterol synthesis: Smith–Lemli–Opitz syndrome

Smith–Lemli–Opitz Syndrome is caused by a deficiency in 7-dehydrocholesterol reductase which catalyzes the final step in the biosynthesis of cholesterol, and is biochemically characterized by increased 7,8-dehydrocholesterol [134]. The clinical presentation is variable and can involve multiple organ systems. Neurologically, these patients can present with seizures, developmental delay, autistic symptoms and behavioral problems [135]. The most severely affected patients have brain malformations, present in 37% of biochemically confirmed patients [135], and these patients can have neonatal onset seizures [136] or infantile spasms [135]. They usually have dysmorphic features including antverted nares, ptosis, cleft palate, microcephaly, and low-set ears. Other organ systems involved can include cardiac, renal, genital, pulmonary, and gastrointestinal. Aclrim abnormalities are common. Up to 99% of patients have 2–3 toe syndactyly, which provides an easy recognizable clinical diagnostic sign. Rare patients without 2–3 toe syndactyly have been reported, but their neurological involvement is mild and would not include early onset seizures [137]. Diagnosis is made by assaying for elevated 7,8-dehydrocholesterol and mutation analysis of the DHCR7 gene. The inheritance is autosomal recessive. Severity correlates with the ratio of 7,8-dehydrocholesterol to cholesterol [138] and with mutations [139]. Treatment has included dietary supplementation of cholesterol and treatment with the HMG-CoA reductase inhibitor simvastatin. Both have improved the biochemical profile, but clinical effect on developmental progress was not demonstrated [140,141], and not enough data is available on the impact of either treatment on seizures.

4.5. Deficiency syndromes of the amino acids serine and glutamine

Serine is an amino acid involved in the synthesis of important brain components such as glycine, cysteine, sphingomyelins, and cerebrosides. Serine is synthesized from glucose by conversion of the glycolytic intermediate 3-phosphoglycerate to 3-phosphopyruvate by 3-phosphoglycerate dehydrogenase, followed by formation of 3-phosphoserine by 3-phosphoserine aminotransferase, and finally serine is formed by 3-phosphoserine phosphatase [142]. Deficiency in either 3-phosphoglycerate dehydrogenase or 3-phosphoserine aminotransferase presents with severe psychomotor retardation, congenital microcephaly, and with white matter hypointensity in 3-phosphoglycerate dehydrogenase. Seizures may begin anywhere from 2 months to 14 months. Initially patients can be diagnosed with West syndrome with hypersarrhythmia on EEG [143], but the seizures develop into multiple different types as patients grow older. Other clinical features include spastic tetraparesis, adducted thumbs, and hyperexcitability. Occasionally, cataracts, nystagmus, hypogonadism, and megaloblastic anemia have been reported. Brain MRI shows absent myelination with cortical and subcortical atrophy. CSF amino acids show decreased CSF serine (<15 μM, normal 42–86) and glycine (1–4 μM, normal 6–21 μM in neonates). Sometimes, decreased CSF 5-methylfolate may also be seen. Fasting plasma amino acids will also show a decreased plasma serine, but postprandial plasma amino acids may be normal. The diagnosis is confirmed by finding decreased enzyme activity in fibroblasts, and mutations in the respective genes [144]. Treatment with serine (400–500 mg/kg/day) in 4 to 6 doses per day and glycine (200–300 mg/kg/day) results in clinical improvement after 1 to 2 weeks, including major improvement of seizures in all patients [145]. If identified prenatally, treatment of the mother during pregnancy is indicated [146].

Glutamine synthetase is a key enzyme in the glutamine–glutamate cycle between astrocytes and neurons. Deficiency of glutamine synthetase was described in two neonates with immature brain with hyperintense white matter, microcephaly and attenuated gyri, and neonatal mortality [147]. There were multifocal generalized seizures. Other symptoms in one patient were erythema of the skin and enteropathy, ascites, and renal failure. Glutamine levels were very low in serum and CSF, but glutamate was normal. A more mildly affected patient presented in early infancy with encephalopathy, seizures, and white matter atrophy, and is still alive at age 3 years [148].

4.6. Methylation disorders: homocysteine and folate disorders

Homocysteine is a component of the metabolic pathway of the sulfur-containing amino acid methionine. There are several disorders in this pathway that can cause seizures including cystathionine β-synthase deficient homocystinuria, methylene-tetrahydrofolate reductase deficiency, and cobalamin deficiency (specifically Cobalamin C and sometimes Cobalamin D, E, or G). Half of the patients with these conditions present in the neonatal period, frequently with seizures [149].

Classic homocystinuria is caused by the absent cystathionine β synthase enzyme activity. This defect results in multi organ system involvement including developmental delay and seizures. Seizures occur in 50% of affected individuals, although rarely in infancy (1/55) [80]. Diagnosis is made by finding elevated homocysteine, elevated methionine, decreased cystathionine, and low levels of cysteine. Treatment includes oral pyridoxine, folic acid, betaine supplementation, and a low methionine diet with cysteine supplementation.

Methylene-tetrahydrofolate reductase catalyzes the reduction of 5,10-methylene-tetrahydrofolate to 5-methyltetrahydrofolate which then donates a carbon group in the methylation of homocysteine to methionine. Deficiency of methylene-tetrahydrofolate reductase can result in seizures in infancy as well as a progressive encephalopathy, developmental delay, microcephaly, and apnea [149,150]. Brain imaging can show hydrocephalus, progressive atrophy, and microgyria. The diagnosis is made with elevated homocysteine and low methionine and confirmed by enzyme assay performed on skin fibroblasts. Treatment may include betaine and folic acid supplementation, vitamin B12, and sometimes supplementation with methionine. Early recognition and treatment with betaine may prevent severe brain disease [151,152].

Dihydrofolate reductase deficiency due to mutations in the DHFR gene was described in patients with megaloblastic anemia and cerebral folate deficiency. These patients developed therapy resistant seizures in the first weeks of life. Some patients had cerebral and cerebellar atrophy, some patients had calcifications in basal ganglia and subcortical white matter, and one patient had abnormal white matter mostly subcortical [153]. Development was normal until 3 months of age, but became severely delayed thereafter. The seizures and the anemia responded to treatment with folinic acid. Levels of plasma homocysteine, methylymalonic acid, folate, and vitamin B12 are normal, but 5-methyltetrahydrofolate and tetrahydrobiopterin in CSF are reduced.

Cobalamin (vitamin B12) is a cofactor for multiple enzymes in the body. Cobalamin C defect refers to an early step in cobalamin processing. This affects formation of methylcobalamin which is a necessary cofactor for methionine synthase to convert homocysteine to methionine. It also affects the formation of adenosylcobalamin which is a cofactor in the conversion of methylmalonyl-CoA to succinyl-CoA. The cobalamin C defect is the most frequent inborn error of cobalamin metabolism. Patients present in infancy with developmental delay and some infants have seizures. They can also have nystagmus, microcephaly, lethargy, and feeding difficulties. Imaging may show hydrocephalus or brain atrophy. Laboratory studies will show elevated plasma homocysteine and cystathionine, low or normal plasma methionine and elevated methylmalonic acid levels. Confirmation of the diagnosis is made by molecular testing of the MMACHC gene or by complementation studies of functional defects in cellular metabolism. Cobalamin D and Cobalamin G defects can mimic these clinical symptoms as well. Treatment includes parenteral hydroxocobalamin (0.1 to 0.3 mg/kg/day parenterally depending on patient response) and oral betaine (250 mg/kg/day), and diet. Clinical response with improvement in biochemistry and functionality is common, but certain symptoms, particularly retinopathy, persist in cobalamin C disorder.

4.7. Neuronal ceroid lipofuscinosis

The congenital form of neuronal ceroid lipofuscinosis (CLN10) is caused by a deficiency of cathepsin D, which is a lysosomal aspartic protease involved in the regulation of apoptosis [154]. This is the most severe form of neuronal ceroid lipofuscinosis and patients may present with prenatal and neonatal status epilepticus, severe congenital microcephaly, spasticity, respiratory distress, and apnea [154,155]. These patients may die in the first few days or weeks of life. Examination of the brains at autopsy shows a small brain with severe neuronal and white matter loss. Histopathology of neurons shows granular osmiophilic deposits (GROD) in a whirling, laminated pattern. Diagnosis can be made by skin biopsy and identifying GROD bodies in nonmyelinated Schwann cells [156]. This is an autosomal recessive disorder and molecular analysis shows mutations in the CTSD gene. There is no treatment for this disorder. Other neuronal ceroid lipofuscinosis disorders, including the infantile variant, exhibit symptoms after 6 months of age.

4.8. Lysosomal disorders

Many lysosomal enzymes are involved in the degradation of brain molecules such as sphingolipids. Missing or malfunctioning lysosomal enzymes result in the accumulation of specific sphingolipids which results in interference with other cell functions. Many classic neuronal lysosomal disorders with an infantile presentation exhibit excessive startle and some developmental slow down in the first 6 months of life, but seizures develop only after 6 months of age. This includes disorders such as Tay-Sachs disease, GM1 gangliosidosis, Niemann-Pick disease type A, early onset metachromatic leukodystrophy, multiple sulfatidase deficiency, Gaucher disease type II, mannosidosis, and fucosidosis. Krabbe disease results from deficiency of galactosylceramidase which breaks down galactosylceramide, which is a major component of myelin [157]. A toxic metabolite called galactosylsphingosine induces apoptosis of cells. Infantile Krabbe disease presents in the first 6 months of life with clinical symptoms of irritability, stiffness, arrest in motor and intellectual development, and episodes of temperature elevation. Some patients present with seizures in the first 6 months. Peripheral neuropathy with hypotonia and hyporeflexia develops. CSF studies reveal increased protein. A brain MRI will show increased signal intensity of the white matter on T2 and FLAIR sequences with decreased signal intensity in the thalami. There can be high signal on diffusion weighted images and loss of diffusional anisotropy. Diagnosis is made by assaying galactocerebrosidase enzyme activity in leukocytes or fibroblasts, and genetic testing of the GALS1 gene. Treatment is primarily symptomatic. Hematopoietic stem cell transplantation has a poor outcome in symptomatic individuals. However if performed presymptomatically in newborns following diagnosis prenatally or neonatally, it has shown some stabilization of the cerebral disease, but continued progression of the peripheral neuropathy [158].

5. Monogenic causes of neonatal and early infantile seizures

Other monogenic genetic causes of seizures in the first 6 months of life without apparent brain malformations are:

- **ARX**: in boys with West syndrome
- **CDKL5**: in girls with West syndrome, also less frequently in boys
- **STXB1**: in males and females with West syndrome
- **MECP2** in males and PNKP with congenital brain disease
- Rare causes: **MAG2**, alpha-II spectrin, phospholipase C beta-1 deficiency
- Microdeletions/duplications in 10% of resistant seizures
- Channelopathies: potassium and sodium channelopathies and related genes
- elf2B-related disorders

5.1. ARX gene

**ARX** mutations are seen in boys with West syndrome. They are also observed in boys with neonatal or very early infantile epileptic encephalopathy with burst suppression pattern. Seizures are often therapy resistant and progressive brain atrophy follows. Abnormal genitalia such as a small penis can sometimes be an indicator. A common mutation is the expansion of the polyalanine tract from 16 to 27 alanines due to a duplication [159]. A variety of other mutations including truncating mutations have also been reported with this phenotype. **ARX** mutations also cause X-linked mental retardation, Proust syndrome, Partington syndrome, X-linked myoclonic epilepsy with spasticity and intellectual disability, and X-linked lissencephaly with abnormal genitalia.

5.2. CDKL5 gene

CDKL5 is another gene located on the X-chromosome which was first identified in two girls with X-linked West syndrome [160] and later in girls and boys with atypical early Rett syndrome [161]. Girls with mutations in the CDKL5 gene present with hypotonia and early seizures with onset between 1 and 15 weeks, often therapy resistant [162,163]. Some develop infantile spasms. They develop microcephaly with deceleration of head growth, stereotypes and hand apraxia at later age, and some have hyperventilation episodes. CDKL5 mutations or deletions account for approximately 10% of girls with early seizures, and 28% of girls with early onset seizures and infantile spasms [163]. Early epilepsy with normal interictal EEG and severe hypotonia, often later developing into infantile spasms are key clinical features [162]. MRI can show mild cortical and cerebellar atrophy and abnormal high signal in the posterior white matter and dentate nuclei. Rare boys with early infantile seizures, severe mental retardation and spasticity, and mutations in CDKL5 have also been reported [164].

5.3. STXBP1 gene

Patients with heterozygous missense mutations or deletion in the syntaxin binding protein 1 (STXBP1) gene exhibited early onset epileptic syndromes (seizures between 3 days and 4.5 months) such as early infantile epileptic encephalopathy with burst suppression pattern as Ohtahara syndrome, West syndrome, and less specific epileptic syndromes [165,166]. Males and females are both affected accounting for 5.6% of patients with early onset epileptic encephalopathies. Epileptic spasms were preceded by other seizure types often partial epilepsy [167]. Some also had myoclonic seizures compatible with early myoclonic encephalopathy. All patients develop severe mental retardation, and most have ataxia and often are wheelchair bound. Vigabatrin is the most effective antiepileptic medication. The STXBP1 protein regulates synaptic vesicle release by binding syntaxin 1A and the SNARE complex.

5.4. MECP2 gene

Males with MECP2 gene mutations or deletions present with congenital encephalopathy often with respiratory insufficiency and apnea as well as seizures [168,169]. If the infant survives, he shows hypotonia, deceleration of head growth, movement disorders and lack of cognitive development. The family history can have female relatives with a diagnosis of Rett syndrome with typical clinical features. Diagnosis is made through sequencing of MECP2 or analysis for deletions using multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridization (aCGH). Treatment is symptomatic with antiepileptic medications and supportive care. Diagnosis of this in a male infant may also have important reproductive implications for females in the family. Epilepsy is common in girls with Rett syndrome due to mutations in MECP2, but occurs after 7 months of age and on average at age 3 years [170].

5.5. PNKP gene

PNKP gene mutations have been documented in six families with individuals who presented with infantile-onset intractable seizures, severe microcephaly, developmental delay, and variable behavioral problems [171]. Brain magnetic resonance imaging shows preserved brain structure, and no other neurologic problems are reported. This gene has been implicated in the repair of single and double-stranded DNA breaks. The inheritance is autosomal recessive affecting both boys and girls. Treatment is symptomatic with antiepileptic medications and supportive care.

5.6. Rare seizure genes

Rarely described causes of West syndrome include MAGI2, alpha-II spectrin, and phospholipase C beta-1 deficiency. Some patients with Williams–Beuren syndrome and larger deletions exhibit infantile spasms and hypsarrhythmia. Fine mapping of the deletions identified hemizygosity of the MAGI2 gene as responsible for the epileptic phenotype. Additional symptoms include delayed development and hypotonia. The MAGI2 gene is involved in the synaptic scaffold of synapses.

In-frame deletions in the alpha-II spectrin gene were identified in 2 patients with West syndrome and severe hypomyelination including thin, shortened corpus callosum and atrophy of the cerebellum, resulting in severe spastic quadriplegia, no developmental progress, and visual inattention [172]. This gene is involved in maintaining voltage-gated channels in position.

A boy is described with focal seizures at 10 weeks developing into West syndrome at age 6 months, who was found to have a deletion in the phospholipase C beta 1 gene, which is associated with hippocampal acetylcholine receptor signaling [173]. Mutations in this gene were excluded in 12 other patients with infantile spasms.

Microdeletions or duplications in a variety of locations were identified by array CGH in up to 10% of patients with syndromic epilepsy including infantile spasms [174].

5.7. Channelopathies

Benign familial neonatal seizures are an autosomal dominant syndrome caused by mutations in the voltage-gated potassium channel genes, KCNQ2 or, more rarely, KCNQ3 [175,176]. Seizures start in the first week of life as brief, generalized or focal, tonic–clonic seizures sometimes with apnea, with a normal physical exam and normal EEG, but a few patients may have focal discharges. The seizures respond to phenobarbital. The neurodevelopmental outcome is normal, and seizures disappear after 2 to 15 weeks with normalization of the EEG in 24 months. Up to 16% of patients later develop epilepsy. Rare patients have therapy resistant seizures with cognitive delays and myokymia. Both point mutations and deletions have been noted. Voltage-gated channels regularize neuronal membranes after activation of excitatory neurotransmitter ion channels, and neurons with reduced function of KCNQ2 would remain longer depolarized and activated. Benign neonatal-infantile seizures with onset around 3 months are related to mutations in the sodium channel SCN2A [177].

Mutations in the sodium channel SCN1A cause a number of clinical phenotypes including severe myoclonic epilepsy of infancy. Patients with severe myoclonic epilepsy of infancy develop generalized seizures, often associated with fever, around 6 months of age. They often present with hemiconic or febrile status epilepticus. The subsequent seizures develop into generalized tonic–clonic, myoclonic, absence, and simple and complex partial seizures. They later have developmental stagnation, moderate developmental delay, and ataxia. They are caused by de novo mutations in the sodium channel gene SCN1A. Missense mutations account for 70% of patients and copy number variations for about 3% of patients, with truncating mutations and more dissimilar missense mutations more likely associated with this phenotype [178,179]. Rare patients have mutations in SCN1B, SCN2A, or the voltage-gated GABA receptor gene, GABRG2 [177,180]. Vaccine-related epileptic encephalopathies have been later attributed to SCN1A mutations [181].

5.8. eIF2B genes

Mutations in the eIF2B-subunits cause vanishing white matter syndrome. The protein complex eIF2B is composed of five subunits encoded by five genes (eIF2B1–eIF2B5) and interacts with initiation factors of mRNA translation. This condition is characterized with
defective myelination and development of multicystic leukodystrophy. Most patients present in childhood or adulthood with progressive neurological decline with cerebellar ataxia, spasticity and relatively mild mental decline, often in an episodic nature following stressors such as fever or minor head trauma. Ovarian dysfunction is prevalent. However, a subset of these patients presents in early infancy with prenatal growth retardation, oligohydramnios, progressive hypotonia, irritability, feeding difficulties, and the development of intractable seizures as young infants [182]. Hepatosplenomegaly and cataract may also be present. On brain MRI imaging, the cerebral white matter has higher T2 signal intensity than normal unmyelinated white matter, becoming more abnormal on follow-up. On fluid-attenuated inversion recovery (FLAIR) sequences, the cerebral white matter had lower signal intensity in parts, but not as low as CSF, indicative of white matter rarefaction. Patients with this early presentation have died in the first 2 years of life.

Mutations in the ARX or CDKL5 gene are not found in severe myoclonic epilepsy of infancy [183]. Mutations in SCN1A were not found in patients with West syndrome or early myoclonic encephalopathy [184]. Mutations in the PCDH19 gene are a frequent cause of epilepsy and mental retardation and autism in females, but seizures appear only in the second half of the first year (age 6 months to 5 years) [185–187]. Mutations in the TBC1D24 gene are found in patients with generalized afebrile seizures starting between 4 and 7 months followed by the development of myoclonic seizures [188,189].

6. Clinical conclusions

The initial work-up of neonatal and early infantile seizures should include both electrophysiological description of the event using a video-coupled EEG and brain imaging using MRI, preferably with spectroscopy. The following features identified on brain MRI can provide differential diagnostic guidance: polymicrogyria, signal changes on diffusion weighted images in the white matter of the internal capsule, subcortical T2 changes, microcephaly with severe brain atrophy, changes in the basal ganglia or thalami, hypoplastic to absent corpus callosum, cystic lesions, leukodystrophy, hypomyelination, hydrocephalus. Fig. 1 provides
differential diagnostic guidance and Fig. 2 shows some examples of representative images.

Typical EEG patterns include a burst-suppression pattern in neonates and hypsarhythmia in older infants.

Neonatal epileptic encephalopathy with burst-suppression is seen in: nonketotic hyperglycinemia, pyridox(am)ine phosphate oxidase deficiency, pyridoxine-dependent epilepsy, mitochondrial glutamate transporter defect, sulfite oxidase deficiency, adenylsuccinase deficiency, congenital ceroid lipofuscinosis CLN10, Smith–Lemli–Opitz syndrome, ARX in boys, CDKL5 (some patients), STXBPI, MECPI2 in boys.

West syndrome (infantile spasms, developmental delay, and hypsarhythmia) is seen in: ARX in boys, CDKL5 in girls, STXBPI, pyruvate dehydrogenase deficiency in girls, Menkes disease, biotinidase deficiency, mtDNA:8993G->A, pyridoxine-dependent epilepsy, glucose transporter defect, CDG syndrome (DPAGT1-CDG), serine deficiency syndrome, and rarely: MAGI2, alpha-II-spectrin, phospholipase C beta-1.

A completely normal EEG and clinical neurological exam is unusual, and should suggest benign neonatal epilepsy or aromatic amino acid decarboxylase deficiency.

Certain clinical features can be a very useful guide to the etiology.

Apnea requiring intubation and ventilation is seen in some severe epileptic encephalopathic syndromes such as: nonketotic hyperglycinemia, pyridox(am)ine-phosphate oxidase deficiency, pyridoxine-dependent epilepsy, methylene-tetrahydrofolate reductase deficiency, Leigh disease, congenital neuronal ceroid Lipofuscinosis (CLN10), and MECPI2 in boys.

We would advocate wide biochemical testing which can identify quickly treatable conditions [63,190]. The following biochemical tests are advised for the work-up of neonatal and early infantile epilepsy (with bolded tests in first line):

**Blood tests include:**

- **Plasma or Serum amino acids**, particularly for alanine (elevation), glycine (elevation), serine (decrease), threonine (elevation) and glutamine (decrease)
- **Lactate and pyruvate** with the lactate:pyruvate ratio calculated
- **Copper and ceruloplasmin**

**Syndactyly of toes 2–3:** Smith–Lemli–Opitz syndrome

**Skin rash:** biotinidase, CDG-If or Im, glutamine synthetase

**Hair loss:** biotinidase, Menkes

**Coloboma:** CDG-Id

**Hypothermia:** Menkes disease, pyridoxine-dependent epilepsy, aromatic amino acid decarboxylase deficiency, pyridox(am)ine phosphate oxidase (PNPO) deficiency, male MECPI2

**Cardiomyopathy:** D-2-hydroxyglutaric aciduria, respiratory chain disorders, CDG syndrome, cobalamin C deficiency

**Anemia:** serine synthesis defects, cobalamin C, dihydrofolate reductase deficiency, CDG syndrome

**Hypogenitalism:** ARX, Smith–Lemli–Opitz syndrome

**Wormian bones:** Menkes Disease

**Fig. 2.** Select brain MRI images of young infants with seizures. Legend: Restricted diffusion of the long tract in the brain stem (A) and posterior crux of the internal capsule (B) in a newborn patient with nonketotic hyperglycinemia. Multiple periventricular cysts and brain atrophy are noted in a girl with pyruvate dehydrogenase deficiency (C). Increased signal is noted on T2 weighted images in the striatum of a patient with a mitochondrial DNA mutation mt.8993G->A (D). In a young infant with Menkes disease, diffusion restriction is noted in the striatum on both diffusion weighted images (E) and ADC mapping (F). Perisylvian polymicrogyri are noted on the coronal section of this neonate with Zellweger syndrome (G). Hydrocephalus due to aqueduct stenosis developed in this infant with methylene-tetrahydrofolate reductase deficiency (H).

Biotinidase enzyme activity
Uric acid
Total homocysteine
Very long chain fatty acids
7-dehydrocholesterol
Pipeolic acid and alpha-amino adipic semialdehyde
Creatine and guanidinoacetate
CDG testing such as glycosylation analysis of transferrin

Urine analysis should include:
Succinylpurines
Creatine and guanidinoacetate
Urine organic acids looking for fumarate, 4-hydroxybutyrate and 2-hydroxyglutarate
Alpha-aminoadipic semialdehyde or 6-PC
Sulfocysteine and xanthine

Cerebrospinal fluid should be analyzed in all neonates and infants with a severe seizure disorder for:
Always cell count and protein (at least to ensure adequate quality, since any admixture of blood or serum causes false interpretation of many metabolic tests; protein is elevated in POLG1 and in Krabbe disease)
Glucose in CSF and in blood (obtained immediately before the spinal tap)
Amino acids: glycine, serine, threonine and glutamine (with plasma amino acids at a similar time)
Lactate and pyruvate

Pyridoxal-5'-phosphate
Monoamine metabolites (Homovanillic acid, 5-hydroxyindoleacetic acid and 3-O-methylidopa)
Methyltetrahydrofolate

A skin biopsy must be considered, particularly if there is microcephaly and brain atrophy, looking for storage products specifically for congenital ceroid neuronal lipofuscinosis (CLN10).
The following treatment trials should be initiated, particularly in neonatal epileptic encephalopathy, but also for infantile seizures:

Pyridoxine 100 mg intravenous, then 30 mg/kg/day enterally divided in 3 doses for 3 days
Pyridoxal-5'phosphate 30 mg/kg/day divided in 3 doses for 3 days
A therapeutic trial with folinic acid is no longer indicated.

Finally, genetic testing should be considered since several genes have a substantial diagnostic yield. The clinical utility of testing for genes such as ARX, CDKL5, and STXBP1 is considered high due to the ability to provide a firm diagnosis to avoid complex further etiologic testing, and for its genetic counseling implications [191]. All children should have testing for STXBP1 and an array CGH, and in addition for boys: ARX, MECP2, and for girls: CDKL5. The place of SLC25A22 is yet unclear as the high yield in one study still requires confirmation.
The presentations of these disorders are often dramatic, and despite extensive investigations causes are only found in a small portion of cases. The new genetic causes have increased the diagnostic yield, yet only about 20% of cases are etiologically solved in those children where perinatal injury, malformations, and infections have been excluded. The therapeutic yield of these investigations is limited.
However, several conditions have specific therapies such as vitamin-responsive conditions (pyridoxine-responsive epilepsy, pyridoxal phosphate-responsive encephalopathy, biotinidase deficiency), a ketogenic diet in glucose transporter defect and in pyruvate phosphate responsive encephalopathy, biotinidase deficiency, Menkes disease and Molybdenum cofactor deficiency (MOCIS).

Table 1

<table>
<thead>
<tr>
<th>Disorders with clinically significant treatment.</th>
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<tr>
<td>Nonketotic hyperglycinemia</td>
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<tr>
<td>Pyridoxine-dependent epilepsy</td>
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<td>Pyridox(am)ine phosphate oxidase deficiency</td>
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<td>Aromatic amino acid decarboxylase deficiency</td>
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<td>Glucose transporter defect</td>
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<td>Pyruvate dehydrogenase deficiency</td>
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<td>Pyruvate carboxylase deficiency</td>
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<tr>
<td>Biotinidase deficiency</td>
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<tr>
<td>Menkes disease</td>
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<tr>
<td>Molybdenum cofactor deficiency (MOCIS)</td>
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<tr>
<td>Guanidinoacetate methyltransferase deficiency</td>
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<td>Smith–Lemli–Opitz syndrome</td>
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<td>Serine deficiency syndromes</td>
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<tr>
<td>Glutamine deficiency</td>
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<td>Methylenetetrahydrofolate reductase deficiency</td>
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<tr>
<td>Cystathionine beta synthase deficiency</td>
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<td>Cbl A, B</td>
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<td>Krabbe disease (presymptomatic)</td>
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<td>STXBP1</td>
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<td>KCNQ2, KCNQ3</td>
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</table>

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