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Clinical review of genetic epileptic encephalopathies

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Abstract

Seizures are a frequently encountered finding in patients seen for clinical genetics evaluations. The differential diagnosis for the cause of seizures is quite diverse and complex, and more than half of all epilepsies have been attributed to a genetic cause. Given the complexity of such evaluations, we highlight the more common causes of genetic epileptic encephalopathies and emphasize the usefulness of recent technological advances. The purpose of this review is to serve as a practical guide for clinical geneticists in the evaluation and counseling of patients with genetic epileptic encephalopathies. Common syndromes will be discussed, in addition to specific seizure phenotypes, many of which are refractory to anti-epileptic agents. Divided by etiology, we overview the more common causes of infantile epileptic encephalopathies, channelopathies, syndromic, metabolic, and chromosomal entities. For each condition, we will outline the diagnostic evaluation and discuss effective treatment strategies that should be considered.

Keywords

Epilepsy; Dravet syndrome; Rett syndrome; Infantile spasms; West syndrome; Ohtahara syndrome

1. Introduction

Seizures are a common presenting symptom in patients seen by clinical genetics consultants. The Centers for Disease Control and Prevention estimates a prevalence of 2 million Americans affected by epilepsy [1]. More than half of all epilepsies have been attributed to a genetic cause [2]. The Online Mendelian Inheritance in Man (OMIM) database lists more than 280 entities when the search term “seizure” is used. We will highlight the more common causes of genetic epileptic encephalopathies.

The purpose of this review is to serve as a practical guide for clinical geneticists in the genetic evaluation and counseling for patients with common genetic epileptic encephalopathies. Focus will be placed on different seizure phenotypes, particularly those that are refractory to anti-epileptic agents, and discussion will be divided into different etiologies including: infantile epileptic encephalopathies, channelopathies, syndromic, metabolic, and chromosomal causes. We will discuss the work-up that should be considered for each of these entities, in addition to appropriate management options.

2. Infantile epileptic encephalopathies

Generally, infantile epileptic encephalopathies are defined by very frequent or severe seizures, or subcontinuous paroxysmal interictal activity contributing to a progressive

disturbance of cerebral function. These serious syndromes presenting during the first 12 months of life can be divided into several categories: Dravet syndrome, Ohtahara syndrome, and West syndrome.

2.1. Dravet syndrome

Individuals with Dravet syndrome, or severe myoclonic epilepsy of infancy, present with prolonged and recurrent febrile seizures, or with generalized or hemiclonic activity in the first year of life. Development is initially normal, but marked delay with behavioral changes (e.g. autistic or psychotic traits, hyperactivity) is often apparent by 1–4 years of age [3]. Myoclonic and atypical absence or partial seizures also become more prevalent with time. Electroencephalography (EEG) findings are usually characterized by normal to generalized epileptiform discharges [4].

Significant clinical factors associated with Dravet syndrome include: hemiconvulsions, a total of five or more seizures, and prolonged seizures lasting more than 10 min. Hattori et al. designated each of these risk factors 3 points in a screening test developed to predict Dravet syndrome in the first year of life. Onset of seizures > 7 months and hot water-induced seizures were assigned 2 points; focal and myoclonic seizures were designated 1 point. Using this risk factor screening test, a clinical score > 6 resulted in 98% sensitivity and 94% specificity for Dravet syndrome [4].

Mutations detected by sequencing of the *SCN1A* gene, which encodes the sodium channel, neuronal type 1 α subunit, can be found in 70–80% of patients with Dravet syndrome. Mutations in *SCN1A* also confer a risk of other seizure phenotypes which will be mentioned in the channelopathies section. *SCN1A* deletion or duplication can be found in an additional 2–3% of individuals with Dravet syndrome [5]. Most cases are de novo, but parental genetic testing should be considered to assess recurrence risk. Treatment shown to be effective includes stiripentol, valproic acid, clobazam and other benzodiazepines [6], topiramate, levetiracetam [7], and a ketogenic diet (a high-fat, low-carbohydrate diet that mimics the metabolic state of fasting) [8]. Elevation of body temperature (i.e. hot baths, fever), lamotrigine, phenytoin, vigabatrin, oxcarbazepine, and carbamazepine may exacerbate seizures [9–11].

2.2. Ohtahara syndrome

Ohtahara syndrome is characterized by early onset intractable tonic spasms within the first 3 months of life. Affected infants have a burst suppression pattern on interictal EEG, described as high-voltage activity alternating with nearly flat suppression phases. Clinical findings evolve into West syndrome (characterized by clusters of tonic spasms with arrest of psychomotor development, and hypsarrhythmia, a highly disorganized high amplitude EEG pattern) between 3 and 6 months of life, with continuation of epileptic encephalopathy between the ages of 1 and 3. Structural brain abnormalities are a major cause for this condition [12].

Ohtahara associated genes include syntaxin binding protein 1 (*STXBPI*) [13] and Aristaless-related homeobox (*ARX*) [14]. Milh et al. found five novel *STXBPI* mutations in a cohort of 38 patients (13%) diagnosed with Ohtahara syndrome; none of these patients had any cortical malformation on brain magnetic resonance imaging (MRI) [15,16]. In another series by Mignot et al., 2 of 29 (7%) patients with early-onset infantile epileptic encephalopathy without brain MRI anomalies, were found to carry a de novo heterozygous mutation in *STXBPI* [17]. In a study of early infantile epileptic encephalopathy with burst suppression pattern, 71% of individuals with *STXBPI* mutations had onset of spasms after 1 month of life, suggesting relatively later onset of epilepsy [18]. A recent study noted that testing of the

STXBPI gene is particularly warranted when there is evolution of the phenotype with disappearance of epileptic seizures and EEG paroxysmal activity followed by appearance of fast rhythms after the end of the first postnatal year [15]. *STXBPI* mutations have also been identified in a few cases of West syndrome [19], two cases of severe non-specific epilepsy and one case of isolated developmental delay without seizures [20]. Information in regards to the sensitivity and specificity of mutations in *STXBPI* has not been well established.

Apart from Ohtahara syndrome, mutations in the *ARX* gene are responsible for a range of phenotypes including brain malformation, genital anomalies, X-linked cognitive impairment, Partington and Proud syndrome. Partington syndrome is characterized by intellectual disability and variable movement disturbances [21]. Typical findings of Proud syndrome include agenesis of the corpus callosum, abnormal genitalia, severe cognitive impairment, seizures and spasticity [22]. At least 44 different mutations have been reported, with 10 well-defined clinical entities ascertained from individuals with *ARX* mutations [23]. Specific statements about the sensitivity and specificity of *ARX* mutations have not been reported.

2.3. West syndrome

Infantile spasms such as those which occur in West syndrome can usually be seen in the first 4–6 months of life. West syndrome refers to the triad of infantile spasms with psychomotor retardation and characteristic EEG pattern known as hypsarrhythmia, which consists of random, high-voltage, nonsynchronous spikes and slow waves. West syndrome is seen in 20% of cases deemed cryptogenic, or due to an unknown cause with developmental delay; many cases are attributed to brain abnormalities secondary to a neonatal asphyxia. The differential for idiopathic, or genetic causes, can be narrowed with the help of clinical examinations and neuroimaging. Brain malformations such as those seen in tuberous sclerosis and lissencephaly can further delineate the genetic cause, while metabolic conditions should be considered in the absence of brain malformations.

Early infantile epileptic encephalopathy is genetically heterogeneous; in addition to *STXBPI* and *ARX*, we will highlight other genes with their associated clinical presentation (e.g. cyclin-dependent kinase-like 5 (*CDKL5*) and solute carrier family 25 member 22 (*SLC25A22*)) in other sections of this guide. Due to the pleiotropic nature of these genetic mutations and genetic heterogeneity observed, clear data is not available for most genes regarding sensitivity and specificity of testing.

3. Channelopathies

Ion channels are ubiquitous in human tissues, and mutations in these channels can result in disorders affecting important organs (e.g. heart, brain, pancreas). In the central nervous system, these channels are located in brain cell membranes. A change in the normal ionic balance of a cell due to malfunctioning of the gate keepers of charged molecules, confers a transfer of “current,” which is the source of the seizure.

In some patients there may be more than one variant in channelopathy genes causing the seizure phenotype [24]. Ion channels are multimeric protein complexes that are expressed in specific cell types, where they exert unique but overlapping control over excitability and signaling. Using exome sequencing, a recent study compared variants in 237 ion channel genes in individuals with sporadic idiopathic epilepsy with an unaffected group. Rare missense mutations were found in both groups, suggesting that risk of epilepsy may be difficult to predict from individual deleterious ion channel mutations, and that the occurrence of disease may depend on the specific combination of variants [25].

3.1. Excitatory ion channel genes

Excitatory ion channel genes include sodium, nicotinic acetylcholine, and calcium channel genes. Sodium channel genes associated with idiopathic epilepsy include *SCN1A*, *SCN1B*, and *SCN2A*. Mutations in *SCN1A* are associated with a broad spectrum of phenotypes, ranging from Dravet syndrome to benign febrile seizures as well as generalized epilepsy with febrile seizures plus; the latter is also seen with mutations in *SCN1B*. Genetic epilepsy with febrile seizures plus is an epileptic condition characterized by childhood febrile seizures and later development of epilepsy. The majority of mutations in *SCN1A* are de novo events. Mutations in *SCN2A* result in clinical variability ranging from benign familial neonatal-infantile seizures [26], genetic epilepsy with febrile seizures plus, Dravet syndrome, to intractable childhood epilepsies [27]. It is clear that mutations in *SCN1A* are the most common cause of epilepsy resulting from channelopathy. There is a much smaller contribution of mutations in other channelopathy genes resulting in increased susceptibility to epilepsy. Studies, if available, involving the other genes are summarized below.

Mutations in the acetylcholine receptor genes (i.e. *CHRNA4*, *CHRNA2*, *CHRNA2*) confer a risk of developing autosomal dominant nocturnal frontal lobe epilepsy, characterized by nocturnal seizures occurring mostly during non-REM sleep. There have been some reports of patients also affected with intellectual deficiency, and schizophrenia-like symptoms in a few families [26]. In a study of 150 affected individuals from 19 families in 13 countries, a majority (67%) were found to have mutations in *CHRNA4*, 27% were found to have mutations in *CHRNA2*, and 6% with mutations in *CHRNA2* [26].

Genetic mutations affecting the calcium channel (i.e. *CACNA1A*, *CACNB4*, *CACNA1H*) have been associated with several phenotypes including idiopathic generalized epilepsy [28], juvenile myoclonic epilepsy [29], and childhood absence epilepsy [30].

3.2. Inhibitory ion channel genes

Seizures are also observed in individuals with mutations in genes encoding inhibitory ion channels (i.e. potassium channels, chloride channels, γ -aminobutyric acid (GABA) receptor). Benign familial neonatal seizures (BFNS) are an autosomal dominant condition caused by mutations in *KCNQ2* and *KCNQ3*, which encode voltage-gated potassium channel subunits. Individuals with BFNS often present with generalized or focal tonic-clonic seizures around postnatal day 3, which spontaneously remit in the first month of life. Most infants have a normal interictal EEG, about 25% demonstrate a “theta pointu alternant” pattern. Monitoring through EEGs should be done periodically as EEGs usually normalize after age 24 months. Psychomotor development is usually normal. About 10–15% of individuals with BFNS develop epileptic seizures later in life. Sequence analysis of *KCNQ2* or *KCNQ3* detects 60–70% of BFNS families. Most affected individuals respond readily to treatment with anti-epileptic medications [31].

Mutations affecting the chloride channel gene, *CLCN2*, have been shown to result in childhood absence seizures, epilepsy with grand mal seizures upon awakening [32], and other idiopathic generalized epilepsies [33].

Mutations in genes encoding the GABA receptor, *GABRD* and *GABRG2*, confer susceptibility to various seizure phenotypes including idiopathic generalized epilepsy, juvenile myoclonic epilepsy, generalized epilepsy with febrile seizures plus, Dravet syndrome, familial febrile seizures, and childhood absence epilepsy [34,35].

4. Syndromic causes

4.1. Tuberous sclerosis complex

Tuberous sclerosis complex [36] is an autosomal dominant condition with an incidence of 1 per 6000 live births [37]. Characteristic findings include abnormalities of the skin (i.e. hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), central nervous system (i.e. cortical tubers, subependymal nodules, subependymal giant-cell astrocytoma), kidney (i.e. angiomyolipomas, cysts), and heart (i.e. rhabdomyomas, arrhythmias). Diagnosis is based on clinical findings [38] and/or molecular testing of two causative genes, *TSC1* and *TSC2*. Mutations in *TSC1* and *TSC2* are found in 85% of individuals who meet diagnostic criteria [39].

The major neurologic manifestations include seizures, developmental delays and cognitive disability. Epilepsy is the most common manifesting symptom in TSC and occurs in 80–90% of individuals during their lifetime [40]. Seizure severity in TSC has been linked to the number of cortical tubers [41], and tuber burden (i.e. tuber/brain proportion) [42], with an increase in tuber counts found with mutations in *TSC2* and infantile spasms [43]. Up to one third of children affected with TSC develop infantile spasms; vigabatrin is the preferred treatment in these patients [44]. Several studies have shown excellent results once epileptogenic tubers were removed from individuals with TSC complicated by drug-resistant seizures [45,46].

4.2. Angelman syndrome

Angelman syndrome (AS) is a distinct neurogenetic syndrome previously characterized by severe cognitive disability, absent speech, periods of inappropriate laughter, postnatal microcephaly, ataxic gait, jerky movements, and epilepsy. Depending on the inherited genetic mechanism, the phenotype can be variable; although, consistent features include characteristic EEG findings, scoliosis, and specific behavioral traits (i.e. happy sociable behavior, love of water, sleep disorder). The incidence of AS is estimated to be between 1/10,000 and 1/20,000 [47] with all genetic causes interfering with expression of the maternal copy of ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15q11-q13. Deletion of the 15q11-q13 critical region accounts for 60–75% of cases where affected individuals present with microcephaly, marked delay or inability to walk, hypopigmentation (i.e. light hair and eye color compared to family), typical facial features (i.e. deep set eyes, pointed chin, macrostomia, wide-spaced teeth and brachycephaly), and seizures (95% of deletion cases) [48]. Paternal uniparental disomy (UPD) [49] and imprinting defects [50] are each implicated in 2–5% of cases and tend to have a milder phenotype with less ataxia, better communication skills, less obvious facial features, absent hypopigmentation, and fewer seizures (20% in UPD). Mutations in the *UBE3A* gene are responsible for about 10% of patients who generally have a small head, less ataxia, absent hypopigmentation, some facial features, better communication skills, and begin walking around age 3 years. Seizures occur in around half of patients with mutations in *UBE3A*. Among the remaining 5–26% of individuals with a clinical diagnosis of AS but unproven genetic defect, the recurrence risk is unknown but could be as high as 50% [51].

Seizures are present in 85% of patients with AS within the first three years of life [52]. All seizure types have been observed, with multiple seizure types in half of the patients deleted for the critical region. Boyd et al. described three typical EEG patterns, which are commonly observed in AS patients as early as the fourth month of life, and present in the awake and sleeping stage: 1. Persistent rhythmic 4–6/sec activities reaching more than 200 microV not associated with drowsiness. 2. Prolonged runs of rhythmic 2–3/sec activity (200–500 microV) often more prominent anteriorly, sometimes associated with discharges (ill-defined

spike/wave complexes). 3. Spikes mixed with 3–4/sec activity, usually more than 200 microV, mainly posteriorly, and facilitated by, or only seen with, eye closure [53]. High amplitude rhythmic 4–6 Hz activity, prominent in the occipital regions with spikes (which can be facilitated by eye closure), is often seen in children under the age of 12 years. Laan et al. also reported that the pattern most frequently observed in both children and adults is prolonged runs of high amplitude rhythmic 2–3 Hz activity predominantly over the frontal regions with superimposed interictal epileptiform discharges [54]. In addition to seizures, Fiumara et al. suggested that another neurological clue to the diagnosis of AS in young children may be the observation of fine finger tremors [55].

Since these seizures are generalized in onset, they respond to anti-epileptic drugs that treat generalized seizures. Topiramate [52], ethosuximide [53], and lamotrigine [54] have been shown to decrease seizure frequency, while valproate and ethosuximide were helpful in controlling recurrent myoclonic status epilepticus. Antiepileptic agents that treat partial seizures, such as carbamazepine, oxacarbazepine, and vigabatrin [51] can worsen seizures in this population.

4.3. Rett syndrome

Rett syndrome (RS) can present with similar findings as AS including: ataxia, postnatal microcephaly, brachycephaly, frequent laughter, absent speech, scoliosis, and seizures with abnormal EEG. Both conditions typically have severe neurodevelopmental problems, especially with movement and absent or deficient speech, but regression and breathing abnormalities suggest a diagnosis of RS. Classic RS is defined by several stages of disease with specific diagnostic criteria including postnatal-onset microcephaly, normal psychomotor development during the first 6 months of life, followed by loss of purposeful hand skills between age 6–30 months, hand stereotypies, impairment of locomotion, evolving social withdrawal, communication dysfunction, loss of acquired speech, and cognitive impairment [46]. Classic RS is usually a sporadic X-linked disorder, affecting females since males usually die early in life from neonatal encephalopathy. Sequence variants in the methyl-CpG-binding protein 2 (*MECP2*) gene are identified in 80% of classic RS, while 8% of cases are found to have a deletion of *MECP2*. Several studies have found that the majority of mutations in *MECP2* arise on the paternally derived chromosome, and it is unclear whether there are associations with advancing paternal age [56,57]. Duplications of *MECP2* primarily affect males who present with developmental delay, hypotonia, absent speech, and a family history of neonatal death in maternal male relatives. Females can be overall asymptomatic carriers, but may have a specific neuropsychiatric profile despite favorable skewing of X-inactivation in peripheral blood [58].

A large study of more than 600 participants with *MECP2* mutations revealed that 60% of individuals with either the classic or atypical form of RS were affected with epilepsy. Seizures were not observed under the age of 2. Between the ages of 5 and 10 years, 62% of individuals were observed to have seizures which increased to 86% by 15–20 years of age [59]. Generalized tonic-clonic and partial complex seizures appear to predominate [55]; although, other seizure types (e.g. focal tonic activity) have been observed [56]. EEG findings that can be seen early in the disease course of RS patients include slowing of the occipital dominant rhythm and background activity with spike or sharp wave discharges during sleep. During the regression stage, EEG shows loss of occipital dominant rhythm, further slowing of background activity, and loss of non-rapid eye movement sleep characteristics. Theta and delta activity is markedly slowed, with multifocal spike and wave discharges [47]. The T158M mutation in *MECP2* has a statistically significant association with epilepsy (78%).

The occurrence of seizures is associated with greater clinical severity in the ability to ambulate and purposefully use hands. Most individuals were treated with one anti-epileptic agent, with the most common agents being lamotrigine, carbamazepine, and levetiracetam. Alternative therapies include vagus nerve stimulator and a ketogenic diet [59]. Atypical forms of RS can be milder or more severe than classic RS, accounting for 40% of *MECP2* mutations found with sequencing and an additional 3% with deletion analysis [47].

Mutations in other genes such as *CDKL5* and forkhead box G1 (*FOXG1*) can also give rise to the atypical or variant form of RS with early-onset seizures. Mutations or copy number variations in *CDKL5* have been identified in males and females who present with seizure onset before age six months, severe early-onset encephalopathy and Rett-like clinical features [48–51,60,61]. Bahi-Buisson et al. screened a cohort of 183 females with encephalopathy and early-onset seizures, and found *CDKL5* mutations in 20 unrelated patients. Key clinical features included early epilepsy with normal interictal EEG and severe hypotonia, with some features of RS (i.e. deceleration of head growth, stereotypies and hand apraxia) more apparent in older, ambulatory patients [62]. Another French cohort of 177 patients found a *CDKL5* mutation in 8.6% of women with early-onset seizures, with an even higher mutation rate (28%) in women with early-onset seizures and infantile spasms [60]. Overall, there does not appear to be a particular identifiable EEG pattern associated with *CDKL5* mutations, and there is variation in the clinical severity of seizures, although most appear to be drug-resistant [63]. In one reported case, seizures were better controlled with addition of a ketogenic diet to pharmacotherapy [63].

The congenital variant of Rett syndrome, in which there is no initial period of normal development and regression is never clearly identified, is associated with mutations or deletions of the autosomal gene *FOXG1*. *FOXG1* is a transcription factor known to regulate telencephalon development. The phenotype linked to *FOXG1* is characterized by postnatal microcephaly and growth deficiency, severe mental retardation, absent language, deficient social interaction (e.g. poor eye contact), dyskinesias, seizures, poor sleep patterns and corpus callosum hypogenesis [23,52,53]. Recent studies indicate mutations or deletions of *FOXG1* may be considered a distinct syndrome, since the presence of specific findings (e.g. true dyskinesias, neuroimaging abnormalities) and absence of other signs (e.g. regression, breathing irregularities) help differentiate this entity from other causes of congenital Rett syndrome. One patient with a *FOXG1* genomic deletion, at the age of 3 displayed stereotypic movements of his hands, as well as dystonic movement of his left arm, with decreased visual attention. He was intermittently able to move his hands in the general direction of an object but not able to grab it (Video 1, personal encounter). His dysmorphic features (Fig. 1) include microcephaly, wide and round face, sloping forehead, bitemporal narrowing, full cheeks, flat midface, large ears, and micrognathia; these findings are also described in other individuals with *FOXG1* deletion [36].

Supplementary video related to this article can be found at [doi:10.1016/j.ejmg.2011.12.010](https://doi.org/10.1016/j.ejmg.2011.12.010).

Seizure onset is typically observed between 3 months and 6 years, and tends to be variable (e.g. tonic, generalized tonic clonic, and partial complex seizures) without specific EEG findings [36]. Individuals with duplication of *FOXG1* present with cognitive impairment, severe epilepsy (i.e. infantile spasms in at least half the reported patients), and severely impaired speech, suggesting a dosage sensitive role for *FOXG1* in the developing brain [64,65].

4.4. Pitt-Hopkins syndrome

In addition to AS and RS, Pitt-Hopkins syndrome (PHS) should also be considered in the differential diagnosis for intellectual disability with severe speech impairment, motor

incoordination, postnatal microcephaly, breathing anomalies, and seizures. The distinct facial appearance in PHS may help distinguish this diagnosis from others with similar clinical findings. These specific findings include bitemporal narrowing, deep-set eyes, arched eyebrows, full cheeks, broad nasal bridge, wide mouth with tented upper lip, full lower lip, widely spaced teeth, and cup shaped ears with thick helices [66]. Individuals with PHS may have behavioral similarities to AS including sleep disturbances and a happy demeanor. PHS is inherited in an autosomal dominant manner, typically resulting from a de novo mutation of transcription factor 4 (*TCF4*). In a study of 112 patients with PHS 40% were found to have point mutations, 30% small insertions/deletions, and 30% deletions [67].

In a study of 14 individuals found to have a *TCF4* mutation, the majority were found to have subtle brain magnetic resonance imaging (MRI) findings (i.e. hypoplastic corpus callosum, enlarged ventricles, thin hindbrain), breathing anomalies (i.e. apnea, hyperventilation), and a distinctive facial gestalt [66]. There is conflicting evidence as to whether missense mutations within *TCF4* correlate with increased seizure activity [68]; loss of function mutations have been observed to correlate with seizure activity in PHS patients [66]. EEG findings may include occipital or central delta waves unusual for age, and in older patients, pseudoperiodic complexes during wakefulness, mixed with spikes and slow spikes/waves [55].

4.5. Mowat Wilson syndrome

Mowat Wilson syndrome (MWS) is another important syndrome to consider when presented with microcephaly, agenesis of the corpus callosum, cognitive disability with severe speech impairment, and seizures. MWS is frequently the result of a de novo dominant mutation resulting in an increased incidence of specific structural anomalies including Hirschsprung disease, genitourinary anomalies (particularly hypospadias), congenital heart defects, and agenesis or hypogenesis of the corpus callosum.

Characteristic facial features include bitemporal narrowing, hypertelorism with downslanting palpebral fissures, square jaw with micrognathia, pointed chin, malar hypoplasia, open mouth, rounded nasal tip, broad nasal bridge, columella extended below nasal tip, unusual ears with thick cupped helices and upturned fleshy lobes (Fig. 2). MWS is caused by heterozygous deletions, translocations, and intragenic mutations of the zinc finger E-box binding homeobox 2 (*ZEB2*) gene (also known as *ZFHX1B* or *SIP-1*), which encodes Smad Interacting Protein 1, a zinc finger transcription factor involved in the *TGF-β/BMP/Smad* signaling cascade. *ZEB2* mRNA is expressed during early embryogenesis in nearly all human tissues. Loss of function mutations in *ZEB2* are found in 70% of cases, while deletions account for 20% [69].

Seizures are present in 70% of individuals, with multiple seizure types observed consisting of focal, myoclonic, generalized, and absence seizures. Seizure onset, generally in the second year of life, ranges from the neonatal period to over 10 years of age [70]. EEG findings include right frontal fast activity in patients with myoclonic seizures and asynchronous delta slowing with superimposed spindle forms in a patient with generalized seizures [71]. The manageability of seizures appears to improve with age in some cases [72]. In at least one patient, anti-seizure medications were discontinued at the age of 17 without recurrence of seizures [71].

4.6. Progressive encephalopathy with edema, hypersarrhythmia, and optic atrophy (PEHO) syndrome

PEHO is characterized by infantile hypotonia, seizure onset in the first year of life, severe developmental delay, atrophy of the optic disks by age 2 years, and progressive brain

atrophy (i.e. cerebellum and brain stem) as evidenced on neuroimaging studies [73]. Associated features may include subcutaneous peripheral and facial edema, postnatal microcephaly, dysmorphic features (i.e. narrow forehead, epicanthal folds, short nose, open mouth, small chin, midface hypoplasia, and tapering fingers) [74], and more recently, precocious puberty [75]. Individuals with PEHO-like syndrome may have many of the findings delineated above, but without the neuroradiologic or ophthalmologic signs. Seizures initially manifest as infantile spasms, as defined by hypsarrhythmia on EEG, which are resistant to anti-epileptic agents. Infantile spasms are replaced by generalized epilepsy and associated with severe neurologic sequela. EEG findings may evolve to slow spike-wave activity or background EEG abnormality with generalized or diffuse paroxysmal activity [76]. Recurrence in affected siblings suggests autosomal recessive inheritance [73,77]. Biochemical abnormalities in the cerebrospinal fluid (CSF) of individuals with PEHO or PEHO-like syndrome include increased nitric oxide metabolites [78], and reduced levels of insulin-like growth factor 1 (IGF-1) [74,79]. It has been suggested that the decrease in IGF-1 levels may not be sufficient to prevent nitric oxide mediated neuronal damage, leading to increased nitric oxide production, neurodegeneration and seizures [74].

4.7. Microcephaly-capillary malformation syndrome

A new syndrome with multiple macular capillary malformations, severe congenital microcephaly and cognitive disability, intractable seizures including infantile spasms, hypoplastic distal phalanges, and spastic quadriplegia has recently been described in 4 unrelated patients and one pair of siblings [80–82]. Most infants were small for gestational age at birth with multiple round 1–2 cm capillary malformations (port wine stains) on the skin at birth (Fig. 3), intractable seizures in the first few weeks of life, striking progressive microcephaly, severe developmental delay, hypoplasia of the distal phalanges and dysmorphic facial features. Facial features (Fig. 3) include unusual hair pattern with hair standing straight up, ptosis, hypertelorism, short nose, and downturned mouth [80]. One patient had moderate developmental delay, a low frontal hairline, flat nasal bridge, bilateral epicanthus, hypertelorism, thin upper lip and interrupted eyebrows [81]. A report by Mirzaa et al. documented recurrence in siblings, suggesting autosomal recessive inheritance [82].

Brain findings showed a low frontal hairline with sloping forehead, severe congenital microcephaly with birth occipitofrontal circumference -2 to -6 SD below mean for age. MRI (Fig. 3) showed a very simplified gyral pattern with widened extra-axial spaces suggesting atrophy, relative sparing of the cerebellum, severe hypomyelination, thin corpus callosum, and thin optic tracts. EEG studies showed diffuse, active epileptiform disturbance with abnormally slow background activity in the first patient, and diffusely slow background with multifocal frequent spikes in the second described patient. The first patient was treated with a combination of phenobarbital and clonazepam, but still had brief tonic seizures several times a week, and almost constant myoclonus of the limbs and eyelids [80]. The third patient had a normal MRI at 1 year of age and did not have intractable seizures [81]. The cases reported by Mirzaa et al. all had refractory epilepsy requiring multiple anti-epileptic medications.

4.8. Megalencephaly-capillary malformation syndrome

Megalencephaly-capillary malformation (MCAP) syndrome was first described by Moore et al. [83] and Clayton-Smith et al. [84]. Since then, more than 130 patients have been reported. This disorder features a spectrum of anomalies including primary (congenital or early postnatal) megalencephaly ($+4$ or more SD above the mean), prenatal overgrowth, brain and body asymmetry, cutaneous vascular malformations, digital anomalies (primarily syndactyly and/or postaxial polydactyly), and connective tissue dysplasia involving the skin, subcutaneous tissue, and joints (Fig. 4C). Neuroimaging features (Fig. 4A, B) are

distinctive, and include ventriculomegaly that may progress to hydrocephalus, asymmetry of the brain (especially the lateral ventricles), cerebellar tonsillar ectopia (which may be progressive), large cerebellum, posterior fossa crowding, thickened corpus callosum and polymicrogyria (PMG), which is most often bilateral perisylvian PMG [85,86]. PMG is quite distinctive when it occurs, but in some patients may be subtle or overlooked. Patients with PMG (specifically of the frontal region) often have spasticity and pseudobulbar problems as older children; while younger children have hypotonia, are not spastic, but may also have pseudobulbar problems. Seizures were observed in over one third of patients, which is less than that seen in typical PMG, where the epilepsy risk is approximately 80%. The severity of epilepsy, however, seems to correlate with the degree of PMG, with refractory epilepsy seen in children with more severe PMG. This is usually a sporadic disorder in an otherwise normal family, with growth asymmetry suggesting the presence of a somatic mosaic mutation, such as that recently demonstrated in Proteus syndrome [87].

5. Inborn errors of metabolism

Seizures may be the presenting symptom in many of the inborn errors of metabolism (IEM). An IEM should be suspected with (1) epilepsy that does not match a classical epileptic syndrome, (2) progressive myoclonic epilepsy, (3) association with other neurological or systemic signs, (4) family history, (5) seizures related to eating times, (6) seizures that worsen with certain anti-epileptic drugs, (7) unexplained status epilepticus especially when refractory to standard medications, (8) unexplained slowing of the background activity on EEG, or (9) paroxysmal responses during the photic intermittent stimulation at low frequencies on EEG [88].

We will give a broad overview of IEM which can present as intractable seizures in the neonatal period with a focus primarily on treatable causes (Table 1). Recognition of these disorders is crucial, as it may alter the course of disease and management.

5.1. Vitamin responsive inborn errors of metabolism

5.1.1. Pyridoxine dependent seizures—Pyridoxine dependent seizures (PDS) are an autosomal recessive inborn error of metabolism defined by antiquitin (ATQ) deficiency, which results from mutations in the aldehyde dehydrogenase 7 family, member A1 (*ALDH7A1*) gene. In addition to seizures unresponsive to conventional therapy, patients may present on the first day after birth with flaccidity, abnormal eye movements, and irritability; most seizure types have been observed. There are a number of atypical forms of PDS that have been reported as well, ranging from late onset cases, seizures that initially respond to anticonvulsants then subsequently do not respond to conventional therapy, and infants whose seizures which do not respond to the initial large doses of pyridoxine but become quiescent when a second trial of pyridoxine, or pyridoxal phosphate is given days later [89–92]. We recently followed a neonate, who presented with myoclonic jerks which improved with pyridoxine supplementation, but showed no EEG changes until the 6th week of life, when EEG findings indicated seizure activity. Molecular testing revealed heterozygous mutations in *ALDH7A1*. Rare diagnostic possibilities for seizures that respond to pyridoxine (i.e. hyperprolinemia type 2 or hypophosphatasia) were considered and excluded based on normal plasma amino acids, urine organic acids and alkaline phosphatase levels (personal encounter). EEG findings in patients with pyridoxine dependent seizures may show intermittent or continuous generalized slowwaves with focal or multifocal spike or spike and wave activity. Structural brain abnormalities can include cerebellar hypoplasia, generalized brain atrophy, and a thin corpus callosum.

ATQ functions as an aldehyde dehydrogenase in the lysine degradation pathway. ATQ, or α -amino adipic semialdehyde dehydrogenase, deficiency results in accumulation of α -

aminoadipic semialdehyde (AASA), piperidine-6-carboxylate (P6C) and pipercolic acid, which serve as diagnostic markers in urine, plasma, and CSF. While on continuous EEG monitoring, a dose of 100 mg of pyridoxine-HCl can be given intravenously, every 5–10 min up to 500 mg maximum dose with a clinical response usually evident within minutes. First administration may result in respiratory arrest in responders, and thus treatment should be performed with supportive respiratory management. Alternatively, an oral dose of 30 mg/kg/day can be given for those experiencing short frequent anticonvulsant resistant seizures, with clinical response observed within 3–7 days. To make sure that late and masked response is not missed, treatment with oral/enteral pyridoxine should be continued until ATQ deficiency is excluded by negative biochemical or genetic testing [93]. A recent study has shown that pyridoxine administration may not identify or exclude all individuals with pyridoxine dependent seizures [94], suggesting that metabolic or molecular confirmation of the *ALDH7A1* gene should be pursued in all cases where the diagnosis of PDS is entertained. Mutations in *ALDH7A1* were found in 36/36 patients presenting with typical neonatal-onset seizures, while a mutation was found in 3/6 individuals presenting with late onset seizures [95].

Long-term treatment dosages of pyridoxine vary between 15 and 30 mg/kg/day in infants or up to 200 mg/day in neonates, and 500 mg/day in adults [93]. Reversible sensory neuropathy caused by pyridoxine neurotoxicity can develop if dosages exceed 500 mg/day. Seizures increase during febrile illnesses, and pyridoxine doses can be doubled for the few days the patient is sick. Patients with PDS do not need to be treated with other anticonvulsants unless there is another cause for seizures to be present. For subsequent at-risk pregnancies, mothers have been recommended to take a daily dose (50–100 mg) of pyridoxine during the last half of gestation [96]. Early diagnosis and effective treatment of PDS results in better neurodevelopmental outcomes; in general, the late onset form of disease portends a better prognosis.

5.1.2. Folinic acid responsive seizures—Folinic acid responsive seizures (FARS) have recently been discovered to be allelic to ATQ deficiency [97]. Similar to PDS, patients previously diagnosed with FARS have been found to have increased CSF α -AASA and mutations in *ALDH7A1*, which has important clinical implications. Patients should be treated with pyridoxine since it has been shown to be efficacious, although some cases have been reported to require a pyridoxine trial over 3 consecutive days in order to achieve a clinical response. Also, some affected individuals have had continued seizures while on treatment with pyridoxine, achieving remission after folinic acid was given, and subsequently diagnosed with FARS. The biochemical basis for the added benefit of folinic acid is still unclear; yet, it has been suggested that perhaps all patients with α -AASA dehydrogenase deficiency should be treated with both pyridoxine and folinic acid [97]. Measurement of urinary α -AASA can be a helpful tool in cases of epileptic encephalopathy, while treating with combined pyridoxine 100 mg intravenous dose followed by 30 mg/kg/day for 3–7 days and folinic acid 3–5 mg/kg/day to assess for clinical response. Clinical molecular testing of the *ALDH7A1* gene is currently available and can also be used to confirm a suspected diagnosis.

5.1.3. Pyridoxal 5'-phosphate (PLP)-dependent epilepsy—Pyridoxal 5'-phosphate (PLP)-dependent epilepsy is caused by pyridox(am)ine 5'-phosphate oxidase (*PNPO*) gene mutations which encode pyridox(am)ine 5'-phosphate oxidase, an enzyme that interconverts the phosphorylated forms of pyridoxine and pyridoxamine to PLP. Diagnosis can be confirmed in several ways: low CSF PLP, complete resolution of previously intractable seizures with PLP supplementation, or molecular confirmation. In a study of 5 patients whose seizures ceased after PLP supplementation, all were found to have homozygous mutations in the *PNPO* gene [98]. Associated clinical findings usually include prematurity,

immediate signs of encephalopathy and seizures with biochemical changes including the presence of hypoglycemia, lactic acidosis, urine vanillic acid, and in the CSF, increased L-DOPA and 3-methoxytyrosine with decreased homovanillic acid and 5-hydroxyindoleacetic acid [99]. EEG findings may include interictal burst suppression, multifocal independent sharp waves, and electrical status epilepticus in sleep. Runs of unilateral spike/slow waves can be seen both ictally and interictally [100]. A therapeutic trial of PLP can be given at 30 mg/kg/day divided into 3 or 4 doses enterally for 3–5 days.

5.1.4. Multiple carboxylase deficiency—Multiple carboxylase deficiency is an autosomal recessive condition generally characterized by metabolic acidosis, neurological abnormalities and skin disease (i.e. erythematous, scaly eruptions, often perioral, with or without moniliasis). Due to variable expressivity, this diagnosis should be considered in all children with neurological problems even in the absence of organic aciduria and/or cutaneous manifestations. Deficiency of either holocarboxylase synthetase or biotinidase can lead to deficiency of all biotin-dependent carboxylases (i.e. multiple carboxylase deficiency). Holocarboxylase synthetase deficiency can present in the first few days of life with lethargy, hypotonia, vomiting, seizures, hypothermia, and respiratory difficulties. Similarly, biotinidase deficiency can present in the neonatal period with the most frequent initial symptoms being neurological (e.g. lethargy, hypotonia, seizures) [101–103].

Urine organic acids may reveal a typical profile of multiple carboxylase deficiency, especially if taken during a period of illness. To differentiate between deficiency of holocarboxylase synthetase or biotinidase deficiency, biotinidase enzyme activity levels can be assayed; testing of the latter has been integrated into most newborn screening programs in the United States. Molecular testing of the *BTD* gene for biotinidase deficiency and *HLCS* gene for holocarboxylase synthetase deficiency is available. Mutations are identified in 99% of individuals with biotinidase deficiency; no large deletions have been reported [104]. The amount of biotin given for supplementation is dependent on the severity of the enzyme defect; appropriate doses prevent all clinical and biochemical abnormalities. Individuals found to have holocarboxylase synthetase deficiency usually respond to 10–20 mg/day, while those with complete biotinidase deficiency should be treated with 5–10 mg biotin per day, and in patients with partial biotinidase deficiency, small doses (2.5–5 mg/week) may be sufficient [105].

5.2. Other treatable causes of inborn errors of metabolism

5.2.1. GLUT1 deficiency—Glucose transporter defect (GLUT1) deficiency syndrome typically presents as an early-onset epileptic encephalopathy with later onset complex movement disorder. There is no discrimination as to the type of seizures at presentation, which are often refractory to anticonvulsant therapy, and aggravated by fasting. Individuals with GLUT1 deficiency may also present with absence seizures or paroxysmal exertion-induced dyskinesias. Interictal EEGs and neuroimaging assessing for structural abnormalities are usually unrevealing. Positron emission tomography (PET) scans may show diminished cortical uptake with a more severe metabolic reduction in the mesial temporal regions and thalami [106]. Associated clinical features include global developmental delay, hypotonia, and complex movement disorder (e.g. ataxia, dystonia and spasticity). Most patients carry a de novo heterozygous mutation in the solute carrier family 2, member 1 (*SLC2A1*) gene, which can be tested clinically.

CSF glucose concentrations are usually reduced in relation to plasma glucose (hypoglycorrhachia), with a low ratio of CSF to plasma glucose levels following a 4 h fast. Under these conditions, the ratio is consistently about 0.33 ± 0.01 (normal ratio: 0.65 ± 0.01) [107]. Confirmation of GLUT1 deficiency can be done through erythrocyte glucose

transporter activity, which is typically reduced by half, and/or sequencing of the *SLC2A1* gene. Sequence analysis detects 91% of mutations in affected individuals; 4 individuals with whole gene deletions have been reported [107]. Treatment is unique in that a high-fat, low-carbohydrate ketogenic diet can effectively control seizure activity due to GLUT1 deficiency [108]. Under normal physiologic conditions, ketones are generated in response to fasting, thereby providing energy to the brain. The ketogenic diet simulates these conditions to restore brain energy metabolism. Inhibitors of GLUT1 should be avoided, including anticonvulsants (i.e. phenobarbital, choral hydrate, diazepam, valproate), methylxanthines (e.g. theophylline, caffeine), alcohol, green tea, tyrosine kinase inhibitors, genistein, guanosine triphosphate analogs, dioxine, androgens, tricyclic antidepressants, and general anesthetics [109–111].

5.2.2. 3-Phosphoglycerate dehydrogenase deficiency—Deficiency of the first enzyme in the serine biosynthesis pathway, 3-phosphoglycerate dehydrogenase (3-PGD), can present with congenital microcephaly, intractable seizures including hypsarrhythmia, nystagmus, severe spastic tetraplegia, and psychomotor retardation. Fasting plasma amino acids may reveal decreased levels of serine, and CSF analysis always demonstrates decreased serine levels. 3-PGD is inherited in an autosomal recessive manner, and diagnosis can be confirmed by evaluation of enzymatic activity or analysis of the *PHGDH* gene. A small number of patients have been reported with varying mutations along the *PHGDH* gene [112,113]. Oral L-serine treatment (up to 600 mg/kg/ day in six divided doses) has shown beneficial biochemical and clinical effects [105].

5.2.3. Primary hyperinsulinemic hypoglycemia—Primary hyperinsulinemic hypoglycemia, or congenital hyperinsulinemia presents with inappropriate insulin secretion by the pancreatic β cells with symptoms resulting from hypoglycemia (e.g. seizures, coma) [114]. There are two main types of histopathological lesions: diffuse and focal, which can be differentiated with ^{18}F -fluoro-L-DOPA PET imaging. Focal lesions may be definitely cured when partial pancreatectomy removes the whole lesion. Surgery may also be required when medical and dietary therapies (i.e. intravenous dextrose infusion, frequent feedings, glucagon, diazoxide and octreotide) are not sufficient to maintain normoglycemia [115]. Primary hyperinsulinemic hypoglycemia is a heterogeneous condition; with a genetic diagnosis recognized in about half of patients [116]. Mutations in the ATP-binding cassette, subfamily C, member 8 (*ABCC8*) and/or potassium channel, inwardly rectifying, subfamily J, member 11 (*KCNJ11*) genes result in a dysfunctional KATP channel; when inherited in a recessive manner, patients are unresponsive to diazoxide, a KATP channel agonist. Dominant or sporadic mutations can also occur, and are usually responsive to treatment with diazoxide. In a cohort of 109 patients with primary hyperinsulinemic hypoglycemia unresponsive to diazoxide, mutations in *ABCC8* and *KCNJ11* were found to be causative in 82% of cases, with a predominance of paternally inherited mutations in patients with the diffuse form and a single heterozygous mutation [117]. Primary hyperinsulinemic hypoglycemia should be distinguished from other genetic syndromes which can present with hypoglycemia (e.g. congenital disorders of glycosylation, Usher syndrome 1c, and overgrowth syndromes including Sotos, Beckwith-Wiedemann and Simpson Gohlabi Behmel syndrome) [115].

5.2.4. Congenital magnesium malabsorption—Primary hypomagnesemia with secondary hypocalcemia is a rare autosomal recessive disorder caused by impaired magnesium uptake from the gut [118]. Mutations in *TRPM6* cause a defective protein, a member of the long transient receptor potential (TRPM) channel family, which prevents formation of an ion channel for magnesium at the cell surface [119]. Severe hypomagnesemia can cause low parathyroid hormone levels resulting in associated

hypocalcemia. Patients commonly present in the first few months of life with generalized seizures and symptoms of neuromuscular excitability (e.g. irritability, muscle spasms). Diagnosis is suspected with hypomagnesemia, hypocalcemia, reduced urinary excretion of magnesium and inappropriately low parathyroid levels in the absence of renal disease. Treatment with magnesium normalizes calcium serum levels, while serum magnesium is increased to subnormal levels with resolution of symptoms. A study of 28 individuals from 21 families found 23 different mutations in the *TRPM6* gene [120].

5.2.5. Cerebral creatine disorders—Cerebral creatine disorders include autosomal recessive guanidinoacetate methyltransferase (GAMT) and arginine:glycine amidinotransferase (AGAT) deficiencies, and the X-linked creatine transporter (SLC6A8) deficiency. All three disorders present with cognitive impairment, expressive speech delay, epilepsy, and cerebral creatine deficiency as detected on proton magnetic resonance spectroscopy (MRS). GAMT deficiency is the most severe clinical phenotype with intractable seizures, progressive extrapyramidal signs, low plasma creatine, and increased guanidinoacetate concentrations in plasma, urine, and CSF [105]. In one review, mutations in the *GAMT* gene were found in all 27 individuals with intellectual deficiency, seizures, deficiency of brain creatine and elevated guanidinoacetate levels [121]. Oral creatine and ornithine supplementation combined with arginine restriction have been reported to improve clinical and biochemical findings [122,123].

5.3. Other inborn errors of metabolism presenting with intractable seizures in the neonatal period

5.3.1. Glycine encephalopathy—Glycine encephalopathy, also known as nonketotic hyperglycinemia, typically presents within the first few hours of birth with lethargy, hypotonia, and a depressed Moro response. Irregular respiration with apneic periods, hiccups (which may have been felt in utero), myoclonus, and tonic or clonic seizures may also develop with progressive encephalopathy. EEG may show a burst suppression pattern, which transforms into hypsarrhythmia by the first month of life. A defective cleavage system produces the increased glycine concentrations in plasma, urine and cerebrospinal fluid; a CSF to plasma glycine ratio >0.08 is diagnostic in classic neonatal cases. Glycine encephalopathy is a recessive disorder with mutations in the glycine decarboxylase (*GLDC*) gene found in 75% of cases and mutations in the aminomethyltransferase (*AMT*) gene accounting for an additional 20% of cases [124]. There is no available treatment, and the few affected individuals that survive have severe cognitive impairment [105].

5.3.2. D-2-hydroxyglutaric aciduria—D-2-hydroxyglutaric aciduria, due to deficiency of D-2-hydroxyglutaric acid dehydrogenase, gives rise to a variable phenotype, ranging from severe neonatal-onset seizures, absent psychomotor development and early death [125] to mild cognitive impairment in otherwise asymptomatic individuals [126]. Severely affected individuals may also have severe hypotonia, cortical visual failure, and one third have cardiomyopathy. They usually have neuroimaging abnormalities including disturbed and delayed gyration, abnormal myelination and incomplete opercularization, ventriculomegaly, pronounced occipital horns, and cysts above the head of the caudate nucleus [105]. D-2-hydroxyglutaric acid is elevated in all body fluids. In a series of 50 patients with confirmed D-2-hydroxyglutaric acid dehydrogenase deficiency, 24 were found to have recessive mutations in *D2HGDH* [127], which suggests genetic heterogeneity for this condition. In a separate study, 15 of 17 patients with idiopathic D-2-hydroxyglutaric aciduria (i.e. elevated D-2-hydroxyglutaric acid with normal levels of D-2-hydroxyglutaric acid dehydrogenase and no mutations in *D2HGDH*) were found to have a heterozygous mutation in *IDH2* which encodes isocitrate dehydrogenase 2 [128]. Prognosis is poor for severely affected

individuals, while the clinical course does not appear progressive in affected children without an early-onset epileptic encephalopathy [105].

5.3.3. Pyruvate carboxylase deficiency—Pyruvate carboxylase deficiency is an autosomal recessive disorder which can present with a wide ranging phenotype, from death in the neonatal period to variable degrees of developmental delay, seizures, failure to thrive, neurological signs (e.g. pyramidal tract signs, ataxia, nystagmus) and metabolic acidosis. Neuroradiological findings include subdural effusions, severe antenatal ischemia-like brain lesions and cystic periventricular leukomalacia [129]. Deficient lipogenesis can lead to widespread demyelination of white matter. These white matter changes may be confused with other causes of hypoxic ischemic encephalopathy or non-accidental trauma. Brain MRS may reveal high levels of lactate and choline, and low levels of N-acetylaspartate [130]. Diagnosis can be attained from analysis of amino and organic acids, deficiency of pyruvate carboxylase in fibroblasts, or sequencing of the pyruvate carboxylase (*PC*) gene [131]. Sequence analysis of *PC* promoters and coding region detects mutations in 95% of affected individuals; no deletions or duplications of *PC* have been reported to cause disease [130]. Acute metabolic crises should be treated with intravenous dextrose and fasting should be avoided. There are reports of improved biochemical abnormalities with orthotopic hepatic transplantation [132] and use of triheptanoin to restore anaplerosis, through the generation of Krebs cycle intermediates [133].

5.3.4. Sulfite oxidase deficiency and/or molybdenum cofactor deficiency—Sulfite oxidase deficiency, which can be due to molybdenum cofactor deficiency typically presents with early refractory seizures, severe psychomotor retardation, failure to thrive, microcephaly, hypotonia, lens dislocation and early death. Deficiency of sulfite oxidase results in accumulation of the suspected toxic compound sulfite, and a byproduct, S-sulfocysteine, which can be detected in urine and plasma. Low plasma uric acid levels, and high urine purine (i.e. xanthine, hypoxanthine) levels can be seen with molybdenum cofactor deficiency. EEG may show a burst suppression pattern. MRI findings are similar to abnormalities observed with hypoxic ischemic encephalopathy, and include encephalomalacia with cystic changes [131]. Homozygous mutations in sulfite oxidase (*SUOX*), gephyrin (*GPHN*), and molybdenum cofactor synthesis genes 1 (*MOCST1*) and 2 (*MOCST2*) have been associated with sulfite oxidase deficiency. In a small series of 10 patients with elevated S-sulfocysteine levels, undetectable sulfite oxidase activity, and normal urine purine levels, all but one patient had a mutation in the *SUOX* gene felt to be causative for sulfite oxidase deficiency [134]. One patient has been treated successfully with purified cyclic pyranopterin monophosphate (cPMP) with biochemical and clinical improvement [135].

5.3.5. 4-Aminobutyrate aminotransferase (GABA transaminase) deficiency—GABA transaminase converts GABA, an inhibitory neurotransmitter, to succinic semialdehyde. Three individuals have been reported with GABA transaminase deficiency; the first two were a sibship of a Flemish family who presented with intractable seizures, hypotonia, hyperreflexia, lethargy and a high pitched cry [136]. The third patient also presented with these findings, although a high pitched cry was not observed. The diagnosis was suspected after proton-MRS revealed a GABA peak in the basal ganglia. All three patients had biochemical findings (i.e. elevated GABA levels in the plasma and CSF) and molecular confirmation revealing compound heterozygosity in the 4-aminobutyrate aminotransferase (*ABAT*) gene [137]. In the reported sibship, there was no improvement in clinical or biochemical parameters after administration of pyridoxine, the precursor of the coenzyme of GABA transaminase, or picrotoxin, a GABA antagonist [136].

5.3.6. Dihydropyrimidine dehydrogenase deficiency—Dihydropyrimidine dehydrogenase deficiency is an inborn error of pyrimidine metabolism, where uracil and thymine are not catalyzed appropriately. Individuals with severe deficiency can present with neonatal seizures, motor and mental disability, hypertonia, hyperreflexia, microcephaly and autistic features [138]. Neuroradiological findings may include diffuse cerebral atrophy and white matter hyperintensities [139]. Dihydropyrimidine dehydrogenase deficiency is inherited in an autosomal recessive manner with mutations (93%) and deletions (7%) in the *DPYD* gene identified [140]. There is no genotype–phenotype correlation as individuals with the same mutation can have a wide range of variability in clinical symptoms. Elevations in uracil and thymine are much higher in the urine compared to plasma and CSF [141]. There is no treatment available, and death occurs early in infancy for those who are severely affected [105].

5.3.7. Congenital disorders of glycosylation—Congenital disorders of glycosylation (CDG) refer to the class of enzymes responsible for the glycosylation of proteins and lipids, of which there are at least 29 different types recognized. The presentation can be variable depending on the type of CDG, but in general, multiple organ systems are affected and symptoms may include hypotonia, seizures, developmental delay and abnormal brain imaging. Other associated findings may include inverted nipples, abnormal fat pad distribution, eye abnormalities (e.g. optic atrophy, strabismus, nystagmus), microcephaly, neurological abnormalities (e.g. sensorineural hearing loss, stroke-like episodes), hepatic changes (e.g. fibrosis, hepatomegaly), cardiomyopathy, hematological abnormalities, pulmonary hypoplasia, musculoskeletal findings (e.g. arthrogryposis, contractures), gastrointestinal and dermatological changes (e.g. ichthyosis). Transferrin isoelectric focusing is used to determine the number of sialylated N-linked oligosaccharide residues linked to serum transferrin, the specific type is ascertained by molecular genetic testing. Most types of CDG are inherited in an autosomal recessive manner, with the exception of MAGT1-CDG which is X-linked. CDG type 1a is the most prevalent by far with over 700 reported cases, followed by type 1c with 30 reported cases. Only type 1b is treatable with mannose administration [142].

5.3.8. Mitochondrial glutamate transporter defect—Mitochondrial glutamate transporter defect is characterized by severe neonatal myoclonic epilepsy with burst suppression pattern on EEG and retinitis pigmentosa. Other features may include abnormal visual evoked potentials, hypotonia, progressive microcephaly and spasticity. Oxidation of glutamate is impaired and diagnosis is based on measurement of defective glutamate oxidation in skin fibroblasts or molecular testing. This disorder is inherited in an autosomal recessive manner, and mutations have been identified on the *SLC25A22* gene in two consanguineous families [143,144].

5.3.9. Menkes disease—In Menkes disease, symptoms arise due to a defective ATPase, copper-transporting, α polypeptide (*ATP7A*), which is localized to the Golgi network. Copper is not absorbed properly through the gastrointestinal system, which results in low copper concentrations in some tissues. Affected infants present at 2–3 months of life with loss of developmental milestones, hypotonia, seizures, and failure to thrive. Associated findings include neurologic changes and characteristic pili torti findings of the hair, which is often short, sparse, coarse and twisted. Subcutaneous copper injections given in the first ten days of life may normalize developmental outcome and improve neurologic symptoms in some [145]. Biochemical findings include low serum copper and ceruloplasmin levels, with reduced urinary excretion of deoxypyridinoline. *ATP7A* protein defects are inherited in an X-linked manner. Molecular testing of the *ATP7A* gene identifies 80% mutations through sequence analysis and 15% of mutations through deletion/duplication analysis [146].

5.3.10. Peroxisomal biogenesis defects—The peroxisomal biogenesis defects include the Zellweger syndrome spectrum (ZSS) which spans a continuum from severe Zellweger syndrome to neonatal adrenoleukodystrophy, to the more mild infantile Refsum disease. In the newborn period, affected individuals may present with hypotonia, failure to thrive, seizures, developmental delay, hepatic cysts with dysfunction, and dysmorphic features. Infants with Zellweger syndrome usually die during the first year, while those with neonatal adrenoleukodystrophy and infantile Refsum disease have a variable course which tends to be slowly progressive and may include sensorineural hearing loss, retinal dystrophy, and intracranial bleeding. Plasma very long chain fatty acids are increased. Mutations in peroxisomal biogenesis factor 1 (*PEX1*) comprise 58–68% cases of ZSS, while mutations in *PEX6*, *PEX26*, *PEX10* and *PEX12* account for another 26% of cases. Sequence analysis detects approximately 95% of all mutations, based on the assumption that large deletions and intronic mutations would be missed, although they do not seem to occur commonly with *PEX* genes [147].

D-bifunctional enzyme deficiency is an autosomal recessive condition responsible for 15% of individuals with Zellweger syndrome spectrum. Affected individuals often present with hypotonia and severe intractable seizures in the first few days of life, and most die in the first few years of life. They usually have elevated very long chain fatty acid levels, and no mutations in *PEX* genes. Some patients were found to have normal to mild elevations in very long chain fatty acids, and further evidence for a peroxisomal defect was garnered through neuroradiologic findings (i.e. cerebral and cerebellar leukencephalopathy, perisylvian polymicrogyria, frontoparietal pachygyria, and a pattern of posterior to anterior demyelination with white matter disease). Subsequently, molecular confirmation was attained through mutations identified in the *HSD17B4* gene, which encodes 17-beta-hydroxysteroid dehydrogenase IV, involved in peroxisomal fatty acid beta-oxidation [148,149]. In a series of 110 patients with clinical and biochemical diagnosis of D-bifunctional protein deficiency, results from mutational analysis of the *HSD17B4* gene suggest that the amount of residual enzyme activity correlates with the severity of the phenotype [150]. In one case, vigabatrin was effective in treating severe seizures [151].

5.3.11. Mitochondrial encephalopathy—The most frequent mitochondrial encephalopathy is Leigh syndrome, or subacute necrotizing encephalomyelopathy, which is a clinical and radiological diagnosis characterized by focal bilaterally symmetric lesions in the deep gray matter, including brain stem, thalamus, dentate nuclei, optic nerves, and basal ganglia. Pathologic findings include demyelination, gliosis, necrosis with spongiotic vacuolization, and capillary proliferation. These brain lesions generally indicate an impairment of energy supply, and are accompanied by lactic acidosis, due to a defect in the mitochondrial respiratory chain. Signs and symptoms reflective of brain stem and/or basal ganglia disease usually present between 3 and 12 months of age, with exacerbations often precipitated by viral illnesses. Each episode of decompensation is accompanied by elevated lactate levels in the plasma and CSF, followed by psychomotor retardation or regression. The most common causes of Leigh syndrome include defects in complex I, complex IV, multiple respiratory chain defects, and *MT-ATP6* which encodes a subunit of complex V [152]. An estimated 10–20% of individuals with Leigh syndrome carry mutations in *MT-ATP6*, with another 10–20% found to have mutations in other mitochondrial genes [153]. While the presence of other symptoms (e.g. seizures, ataxia, myopathy, blindness, cardiomyopathy, stroke) depends on the causative mutation and gene, there are no clear genotype-phenotype correlations. Mutations in numerous mitochondrial and nuclear genes have been identified as pathogenic for Leigh syndrome. In most of the early-onset mitochondrial disorders, muscle histochemistry is usually unrevealing, but investigation of the muscle biopsy for respiratory chain activity may lead to a diagnosis [152].

6. Chromosomal causes

6.1. 1p36 deletion syndrome

1p36 deletion syndrome is a recently characterized entity associated with terminal deletions of variable size in the 1p36 region. Distinct craniofacial features include microcephaly, brachycephaly, large and late closing anterior fontanelle, prominent forehead, straight eyebrows, short palpebral fissures, deep set eyes, broad nasal bridge, midface hypoplasia, pointed chin, low-set and posteriorly rotated malformed ears. Congenital heart defects and vision problems are common [154]. All individuals have moderate to profound developmental delay with significantly impaired expressive speech. Seizures are present in 50–75% of cases, with median age of onset at 3 months [155,156]. Different seizure types have been observed with a spectrum of EEG abnormalities ranging from hypsarrhythmia to asymmetry of slow wave activity. Epilepsy is usually well controlled with conventional anticonvulsants, but there are some reports of refractory cases of infantile spasms treated with vigabatrin and/or steroids [156,157]. Some experts advocate the short term use of corticotropin [158] or steroids for effective control of infantile spasms [157]. Brain MRI findings may include cortical atrophy and thin corpus callosum.

6.2. 4p- (Wolf-Hirschhorn) syndrome

Wolf-Hirschhorn syndrome is characterized by deletion of the critical region of chromosome 4p16.3. Craniofacial findings include microcephaly, ocular hypertelorism, epicanthal folds, iris coloboma, prominent glabella with a “Greek warrior helmet” appearance, cleft lip and/or palate, severe cognitive impairment, and high seizure prevalence. Seizures typically present within the first two years of life as clonic, tonic, unilateral with or without generalization, or generalized tonic-clonic seizures from the onset. They are frequently triggered by fever, and tend to occur in the early years despite adequate anti-epileptic treatment in over half of patients. The evolution of the seizure phenotype changes between the ages of 1 and 5 years to absence seizures accompanied by a myoclonic component triggered by eye closure. Seizures are effectively controlled by anti-epileptic drugs for generalized onset seizures (e.g. valproate, topiramate, levateracetam, zonisamide), or with ethosuximide if an absence component is present. The generalized or absence seizures may worsen with carbamazepine. The long term prognosis for seizure control is good, as they tend to disappear with age [154,159,160].

6.3. Ring chromosome 14 syndrome

The incidence of seizures in individuals found to have ring chromosome 14 is nearly 100%, with onset in infancy. A series of 20 patients defined a recognizable phenotype including psychomotor delay, variable cognitive disability, postnatal growth deficiency, microcephaly, hypotonia and retinal abnormalities. Distinct facial features (Fig. 5) include a long face, full cheeks, high forehead, downslanting short palpebral fissures, hypertelorism, short nose with bulbous tip, long philtrum and small mouth with downturned corners [161,162]. Various seizure types have been described, most of them intractable [163]. Reported seizure types include generalized tonic-clonic [164], myoclonic [165], minor motor seizures [166], complex partial seizures secondary to generalized attacks [167], and status epilepticus [168]. EEG findings vary from normal to epileptiform discharges predominantly of the multifocal type [164].

6.4. Ring chromosome 20 syndrome

Similar to ring chromosome 14, seizures tend to occur in almost all affected individuals. Chromosomal mosaicism is generally present [169]. Individuals with a higher percentage of affected cells appear to be more cognitively impaired, but a correlation with epilepsy has not

been established [170]. Since the level of mosaicism in lymphocytes may be low, it has been recommended to look at a minimum of 100 mitoses, when karyotyping is performed [171]. Early in life, patients lack any distinct dysmorphic features, leading to a delay in diagnosis. Unique clinical features include episodes of non-convulsive status reflected by a prolonged confusional state and focal seizures associated with oroalimentary automatisms and hypertonia [172]. These seizures may be mistaken as behavioral abnormalities, particularly in children, and may be triggered by hyperventilation, specific mental activities or adverse psychological situations [171]. Seizure onset ranges from infancy to age 17 years, and seizures tend to be refractory to anticonvulsant therapy [170,173].

6.5. 17p13.3 del (Miller Dieker) syndrome

Larger deletions of the 17p region contribute to the phenotype of Miller Dieker syndrome which is characterized by lissencephaly, severe cognitive impairment, microcephaly, distinct facial features, hypotonia, spasticity, and epilepsy. Typical facial features include prominent forehead, bitemporal narrowing, short nose with upturned nares, protruding upper lip, thin vermilion border of the upper lip, and micrognathia. Smaller deletions or point mutations in the Lissencephaly-1 (*LIS1*) [42] gene cause isolated lissencephaly [174]; other clinical features may include severe developmental delay, cognitive impairment and seizures [175]. Seizures begin in the first year of life; half of affected individuals have infantile spasms, while other types (e.g. partial, tonic, myoclonic, tonic-clonic) have also been observed. Prognosis is grim and seizures are generally refractory to anti-epileptic medications [175,176].

6.6. Inv dup 15 syndrome

Inv dup (15) is the most common abnormality of the group of supernumerary abnormal chromosomes [177], with an incidence of 1:30,000 at birth [178]. This rearrangement results in tetrasomy 15p and partial tetrasomy 15q, and both standard cytogenetics and FISH analysis must be used with probes from proximal chromosome 15 and from the PWS/AS critical region [179]. Common clinical features include moderate to profound intellectual disability, severe epilepsy, diffuse hypotonia and autistic behavior [180]. Dysmorphic features may not be present, or may include epicanthus, downslanting palpebral fissures, low-set ears, and skin pigmentary changes [160]. Most affected individuals have refractory seizures with very poor outcome; although other seizure types have been observed (e.g. West syndrome [180], myoclonic, complex partial seizures [4], and adult-onset generalized epilepsy [181]).

6.7. Down syndrome

Down syndrome, or trisomy 21, is the most commonly recognized chromosomal abnormality in children. The combination of cognitive impairment and distinct facial features usually leads to the diagnosis. Clinical features include small ears, conductive hearing loss, upslanting palpebral fissures, epicanthal folds, iris Brushfield spots, protruding tongue, 5th finger clinodactyly, and single transverse palmar creases. Affected individuals may also have congenital heart defects, Hirschsprung disease, duodenal atresia, Alzheimer disease, and leukemia. Seizures occur in 6% of individuals affected with Down syndrome [176]. All major seizure types have been reported, although reflex epilepsies [182] and infantile spasms [183,184] appear to be the most common. Most cases of seizures appear either within the first year of age, or in the third decade of life [185]. No significant differences among seizure treatments have been reported in this population [186].

7. Work-up and management of genetic epileptic encephalopathies

The work-up for patients presenting with seizures should begin with a detailed history and physical examination. Dysmorphic facial features in conjunction with specific physical findings may lead to recognition of a syndrome for which genetic testing is available, as discussed in the section on syndromes associated with epilepsy. Metabolic conditions may also be suggested by newborn screening or physical examination. For example, the presence of abnormal fat pads and inverted nipples suggest congenital disorders of glycosylation, while hepatosplenomegaly, hypotonia, and dysmorphic features suggest lysosomal or peroxisomal disorders. If the physical examination does not reveal a recognizable syndrome, it is reasonable to proceed with array comparative genomic hybridization (CGH) to assess for copy number variations that may explain the phenotype [187]. Array CGH has been helpful in detecting chromosomal causes of epilepsy in 10–30% of patients with seizures [188–190].

Neuroimaging and an ophthalmology exam may yield further clues. Brain MRI may reveal structural anomalies or disease processes (e.g. hypoxic ischemic encephalopathy) that are associated with seizures. A brain MRS should be considered at the time MRI is undertaken, as it may uncover valuable diagnostic clues, without the need for additional anesthesia or invasive testing (e.g. lumbar puncture). Numerous publications have demonstrated the powerful utility of the MRS in the diagnosis and monitoring of IEMs [137,191–198]. Evaluation by a neuro-ophthalmologist may reveal signs of metabolic disease seen with some types of seizures. Some of the conditions in which retinitis pigmentosa and seizures can be observed include mitochondrial disease [199,200], congenital disorders of glycosylation [201], and peroxisomal biogenesis defects. Additionally, the macular cherry red spot in conjunction with seizures may be seen in sialidosis and gangliosidosis (e.g. Tay Sachs). Optic atrophy, macular degeneration and retinitis pigmentosa has been described in neuronal ceroid lipofuscinosis [202], a condition predominated by myoclonus and epilepsy.

Furthermore, it is certainly worth considering metabolic testing in patients with unrevealing physical examination and neuroimaging. Basic metabolic investigations should include ammonia, lactate, pyruvate, quantitative plasma amino acids, quantitative urine organic acids, carnitine levels, and an acylcarnitine profile. These tests can be sensitive to one's metabolic state (e.g. fasting, illness), and proper specimen retrieval and handling is important (e.g. lactate levels may be falsely elevated if specimen is not placed immediately on ice and analyzed quickly).

Neonates with intractable seizures not responding to antiepileptic treatment with normal initial metabolic investigations should have a therapeutic trial of pyridoxine, folinic acid, and pyridoxal phosphate. Initial administration of 100 mg of pyridoxine should be given intravenously during EEG monitoring followed by oral administration of pyridoxine 30 mg/kg daily for five to seven days. If responsive, cessation of spike activity occurs with concurrent seizure remission as monitored by video EEG. Folinic acid should also be given simultaneously at 3–5 mg/kg/day. There have been reports of patients with folinic acid responsive epilepsy who have initially responded to pyridoxine, and subsequently had recurrence of seizures that remitted with the addition of folinic acid [71]. Pyridoxal phosphate 50 mg/kg for three days should be considered in cases unresponsive to pyridoxine [203].

If the array CGH and metabolic work-up are negative, molecular testing for *SCN1A* and other channelopathies should be pursued. It is worthwhile to note that submicroscopic copy number variants of known seizure and encephalopathy genes (e.g. *UBE3A*, *MECP2*, *CDKL5*, *FOXG1*, *MBD5*, as well as various channelopathy genes) have been reported

[204,205]; which further emphasizes the need for array CGH in the work-up of these patients. Epilepsy gene panels are now available.

As discussed in the section on IEMs presenting with intractable seizures in the neonatal period, additional investigations to be considered include plasma glycosylated transferrin; plasma very long chain fatty acid analysis; cerebrospinal fluid lactate, folate, glucose, amino acids, neurotransmitters; plasma and/or urine guanidinoacetate; plasma and/or urine S-sulfocysteine; urine for purine and pyrimidines; muscle biopsy for histochemistry and mitochondrial respiratory chain activities. Any possible diagnosis is worth considering for testing since current research has shown that effective pharmacologic intervention is dependent on the correct diagnosis for the cause of the seizures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Supplementary material

Supplementary data associated with this article can be found, in the online version, at [doi: 10.1016/j.ejmg.2011.12.010](https://doi.org/10.1016/j.ejmg.2011.12.010).

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Fig. 1. FOXG1 Deletion. Frontal and side profile depicting microcephaly, wide and round face, sloping forehead, bitemporal narrowing, full cheeks, flat midface, large ears, and micrognathia.

Fig. 2. Mowat Wilson Syndrome. Characteristic facial features include bitemporal narrowing, hypertelorism with downslanting palpebral fissures, square jaw with micrognathia, pointed chin, malar hypoplasia, open mouth, rounded nasal tip, broad nasal bridge, columella extended below nasal tip, unusual ears with thick cupped helices and upturned fleshy lobes.

Fig. 3. Microcephaly Capillary Malformation Syndrome. Multiple round 1–2 cm capillary malformations (port wine stains) on the skin at birth. Facial features can include ptosis, hypertelorism, short nose, and downturned mouth, a low frontal hairline, flat nasal bridge, bilateral epicanthus, hypertelorism, thin upper lip and interrupted eyebrows. MRI shows a very simplified gyral pattern with widened extra-axial spaces suggesting atrophy, relative sparing of the cerebellum, severe hypomyelination, thin corpus callosum, and thin optic tracts.

Fig. 4. MCAP Syndrome Neuroimaging. A. Megalecephaly with thick corpus callosum. Cerebellar tonsillar ectopia after surgical decompression. B. Bilateral perisylvian polymicrogyria. C. MCAP Syndrome features a spectrum of anomalies including primary megalecephaly, prenatal overgrowth, brain and body asymmetry, cutaneous vascular malformations, digital anomalies (primarily syndactyly and/or postaxial polydactyly), and connective tissue dysplasia involving the skin, subcutaneous tissue, and joints.

Fig. 5.
Ring Chromosome 14 Syndrome. Distinct facial features included a long face, full cheeks, high forehead, downslanting short palpebral fissures, hypertelorism, short nose with bulbous tip, long philtrum and small mouth with downturned corners.

Table 1

Inborn errors of metabolism that can present in the neonatal period with intractable seizures

Condition	Other findings	Biochemical findings	Gene
Pyridoxine-responsive seizures* (α -aminoadipic semialdehyde dehydrogenase or antiquitin deficiency)	Treat with pyridoxine	Increased α -aminoadipic semialdehyde (AASA), piperidine-6-carboxylate (P6C) and pipecolic acid in CSF, blood and urine	<i>ALDH7A1</i>
Folinic acid responsive seizures* (α -aminoadipic semialdehyde dehydrogenase or antiquitin deficiency)	Treat with folinic acid and pyridoxine	Increased α -AASA in CSF, urine	<i>ALDH7A1</i>
Pyridoxine 5'phosphate oxidase deficiency*	Treat with pyridoxal-P	Presence of urine vanillic acid, CSF decreased homovanillic acid, 5-hydroxyindoleacetic acid, pyridoxal 5'-phosphate and increased L-DOPA and 3-methoxytyrosine	<i>PNPO</i>
Multiple carboxylase deficiency* (Holocarboxylase synthetase or Biotinidase deficiency)	Treat with biotin	Increased lactic acid, and urine/plasma levels of derivatives of 3-methylcrotonyl-coenzyme A and propionyl-CoA	<i>BTD</i> <i>HLCS</i>
GLUT-1*	Treat with ketogenic diet	Low CSF to plasma glucose ratio	<i>SLC2A1</i>
3-Phosphoglycerate dehydrogenase deficiency*	Treat with serine	Decreased serine in plasma and CSF	<i>PHGDH</i>
Primary hyperinsulinemic hypoglycemia*	Treat with glucose	Plasma: decreased glucose, free fatty acids; increased insulin, C-peptide, cortisol, growth hormone Urine: negative ketone bodies, reducing substances; increased C-peptide	<i>ABCC8</i> <i>KCNJ11</i> <i>GLUD1</i> <i>GCK</i> <i>HADH</i> <i>SLC16A1</i> <i>HNF4A</i>
Congenital magnesium malabsorption*	Treat with magnesium	Decreased magnesium and calcium in plasma	<i>TRPM6</i>
Cerebral creatine disorders (Guanidinoacetate methyltransferase deficiency*)	Treat with oral creatine, and dietary supplementation of ornithine; restriction of arginine; extrapyramidal movement disorder in half	Low plasma creatine and increased guanidinoacetate levels	<i>GAMT</i>
Nonketotic hyperglycinemia	Severe hypotonia, hiccups	CSF to plasma glycine ratio >0.08	<i>GLDC</i> <i>AMT</i> <i>GCSH</i>
D-2-hydroxyglutaric aciduria (D-2-hydroxyglutaric acid dehydrogenase deficiency)	Severe hypotonia, cerebral visual failure, cardiomyopathy in a third of cases	Increased levels of D2-hydroxyglutaric acid in urine, plasma and CSF	<i>D2HGDH</i> <i>IDH2</i>
Pyruvate carboxylase deficiency	Cystic periventricular leukomalacia and widespread demyelinated white matter on brain imaging	Increased lactic acid, ammonia, citrulline, and lysine in plasma	<i>PC</i>
Sulfite oxidase defect and/or molybdenum cofactor deficiency	Lens dislocation may be present	Increased S-sulfocysteine in plasma, urine; with molybdenum cofactor deficiency, low plasma uric acid and high urine purines (i.e. xanthine, hypoxanthine)	<i>SUOX</i> <i>MOCOS1</i> <i>MOCOS2</i> <i>GPHN</i>

Condition	Other findings	Biochemical findings	Gene
4-Aminobutyrate aminotransferase (GABA Transaminase) deficiency	Hypotonia, hyperreflexia, high pitched cry	Increased GABA in plasma or CSF	<i>ABAT</i>
Dihydropyrimidine dehydrogenase deficiency	Hypertonia, hyperreflexia	Increased uracil and thymine in urine	<i>DPYD</i>
Congenital disorders of glycosylation *	Type 1b is treatable with mannose	Abnormal transferrin isoelectric focusing	29 different enzymes and associated genes are recognized
Mitochondrial glutamate transporter defect	Abnormal visual evoked potential, hypotonia, progressive microcephaly, spasticity	Defective glutamate oxidation in skin fibroblasts	<i>SLC25A22</i>
Menkes disease	Pili torti observed in hair, regression, skin laxity	Serum copper and ceruloplasmin levels are low, reduced deoxypyridinoline in urine	<i>ATP7A</i>
Peroxisomal biogenesis defects: Zellweger syndrome spectrum (ZSS) D-Bifunctional protein deficiency (DBPD)	Hypotonia, progressive white matter disease, dysmorphic features may be present	Increased very long chain fatty acids, decreased plasmalogen levels in neonatal adrenoleukodystrophy	ZSS genes: <i>PEX</i> 1,2,3,5,6,10,12,13,14,16,19,26 DBPD gene: <i>HSD17B4</i> Numerous genes reported
Mitochondrial (e.g. Leigh disease)	Focal bilaterally symmetric lesions in deep gray matter, dystonia, developmental regression	Lactic acidosis, mitochondrial respiratory chain deficiencies in complex I-V	

* Treatable conditions.