Vitamin and Cofactor Responsive Encephalopathies and Seizures

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ABSTRACT

Early diagnosis and treatment for vitamin and/or cofactor responsive encephalopathies and seizures is critical for both seizure control and cerebral development and to prevent the kindling of intractable seizures with secondary brain injury. Recognition of these specific disorders is key to their management given their essential requirement for specific cofactors and their reduced responsiveness to standard anticonvulsant therapy. The overall goals of this review are: (1) to provide recognition of the clinical phenotypes of selected treatable metabolic etiologies of early-onset encephalopathies with seizures, (2) to highlight the appropriate diagnostic investigations for each, and (3) to outline the effective treatment strategies. Each condition will be described followed by an approach to vitamin-responsive infantile-onset seizure management.

Keywords: vitamin responsive; cofactor responsive; encephalopathies; epilepsy; transporters; energy metabolism

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1. Glucose Transporter Defect – Glut 1

Clinical Features have wide phenotypic variability, including infantile-onset seizures, which may be apneic episodes; episodic eye movements; generalized tonic clonic, clonic, myoclonic, atypical absence; and/or atonic in semiology. There is progressive microcephaly without treatment intervention, developmental delay, and speech delay. Varying degrees of cognitive impairment can occur ranging from learning disabilities to severe cognitive delays. Neurologic features include pyramidal spasticity, extrapyramidal and cerebellar signs, sleep disturbance, and headaches. There are at least three clinical phenotypes. Type I classic GLUT1 deficiency presents with seizures, microcephaly, developmental delay, spasticity, confusion, pyramidal, and extrapyramidal signs. Type 2 presents with developmental delay, dysarthria, dystonia, and ataxia. Type 3 is characterized by choreoathetosis, dystonia, paroxysmal eye and head movements, delay, dysarthria, and hypotonia. Proposed diagnostic criteria for GLUT1 deficiency syndrome includes seizures, developmental delay, complex movement disorder, and fasting EEG changes that improve somewhat postprandially [1].

Biochemical features are characterized by hypoglycorachia with a CSF glucose-to-blood glucose ratio < 0.4 X 3 (in the absence of infection), low CSF lactate, and reduced RBC glucose transport [2].

Pathology relates to impaired blood-brain barrier glucose transport by GLUT1. It is important to note that glucose serves not only as a key bioenergetic fuel for the brain, but it is also a signaling molecule.

Treatment consists primarily of early institution of the ketogenic diet as fatty acid oxidation becomes competent in the infant and has been initiated as early as 6-28 wks of age [3,4]. Ketogenic diets may contain long-chain or medium-chain triglycerides. Complications may include renal stones; therefore, maintenance of good hydration and monitoring of renal function and regular renal ultrasounds is important. The ketogenic diet has resulted in good control of seizures and motor symptoms [5, 6], although cognition may still be somewhat delayed, which may relate to delay in diagnosis and to the signaling role of glucose. Of note, phenobarb, which is often the first-line therapy in infantile seizures as well as diazepam, inhibits the GLUT1 transporter [7] and may thereby exacerbate the seizure disorder.

Genetics. This condition is autosomal dominant in transmission [8]. Affected individuals may have hemizygous or heterozygous mutations resulting in truncation of the GLUT1 protein. The gene (SLC2A1) is located on chromosome 1p35-p31.3. Rare cases of autosomal recessive inheritance have also been reported [9].

2. Creatine Deficiency Disorders

a) X-linked Creatine Transporter Defect

Clinical features include severe developmental delay or regression (or learning disabilities in females) and severe speech delay; seizures; behavioural problems with autistic features; hypotonia; midfacial hypoplasia; and gastrointestinal disturbances, including constipation, megacolon, gastric and duodenal ulcers, and bowel perforations. Failure to thrive and recurrent vomiting and motor delay have also been described [10]. Boys are most severely affected given the X-linked pattern of inheritance. It has a prevalence of 0.3-3.5 % in males. EEG in one patient showed slow, diffuse hypersynchronisms with abnormal multifocal spikes [10]. Carrier females may have borderline to moderate cognitive delays depending on their X-chromosome lyonization pattern [11].

Biochemical features include markedly decreased or absent creatine signal on 1H-MRS brain with severe depletion of creatine/phosphocreatine in the brain [12]. There was increased creatine in the plasma and urine and the guanidi-
noacetic acid (GAA) was normal in one child [12]. In another child, plasma creatine concentrations were consistently low [10]. There is also an increased urine creatine/creatinine ratio [13]. Creatine uptake can be measured in cultured skin fibroblasts and is decreased.

Treatment consists of creatine supplementation, though this does not correct the cerebral creatine deficiency. Dietary L-arginine, which is the precursor for creatine, was shown in one study to lead to improvement in neurological, language, and behavioral status and increased brain creatine in a 9-year-old boy after one year of therapy [14].

Genetics. This condition is X-linked in inheritance. The gene is SLC6A8 and maps to Xq28.

b) L-Arginine: Glycine Amidinotransferase (AGAT) Deficiency
Clinical features include severe developmental delay with regression, autonomic behavior, hypotonia, and severe expressive and cognitive speech delay [15].

Biochemical features include severe depletion of creatine/phosphocreatine in the brain as demonstrated by a markedly decreased or absent creatine signal on 1H-MRS brain. The AGAT enzyme catalyzes the transfer of a guanido group from arginine to glycine forming guanidinoacetic acid, the precursor of creatine. Blood and urine guanidinoacetate is decreased [16]. Low plasma and urine GAA and creatine at birth are indicative of AGAT deficiency [17].

Treatment consists of oral creatine (e.g. 100-400 mg/kg/day), which improves cerebral creatine levels and neurological outcomes [18,19]. Early intervention (e.g. creatine supplementation at 2 months of age before onset of symptoms) has been shown to prevent phenotypic expression of the disease [17].

Genetics. This is an autosomal recessive condition with GAMT gene locus at 15q12.

c) Guanidinoacetate Methyltransferase (GAMT) Deficiency
Clinical features include severe developmental delay with regression; autistic features; severe expressive and cognitive speech delay; intractable seizures (generalized tonic, clonic, and absence); pyramidal signs; and hypotonia and movement disorder, such as ataxia, myoclonus, and/or dystonia [20-22].

Biochemical features are characterized by severe depletion of creatine/phosphocreatine in the brain as demonstrated by a markedly decreased or absent creatine signal on 1H-MRS brain. The GAMT enzyme converts guanidinoacetate to creatine with S-adenosylmethionine (SAM) as the methyl donor. Low CSF creatine and creatinine has been documented [22]. Plasma creatinine is in the low to normal range, and the 24-hour urine creatinine excretion is markedly decreased. The accumulation of guanidinoacetate in the brain and body fluids may be responsible for the intractable seizures and movement disorder. Urine excretion of GAA is markedly increased [22].

Pathology in the brain is characterized by marked myelination delay.

Treatment consists of oral creatine, which is partially successful. In one patient, a diet with arginine restriction and supplementation with ornithine and creatine decreased the formation of GAA and improved clinical outcomes affecting developmental milestones and sensorineural hearing loss [23-25].

Genetics. This is an autosomal recessive disorder [21] with GAMT gene locus at 19p13.3.

3. Serine Deficiency Disorders
Clinical features of this group of disorders include congenital microcephaly, early onset seizures, hypotonia, and moderate to severe developmental delay with symmetric postnatal growth retardation and hypogonadism [26].

The 3-phosphoglycerate dehydrogenase (3-PHGDH) deficiency may also include congenital cataracts. An adult man with congenital cataracts, mild psychomotor retardation, slight cerebellar ataxia, and a chronic axonal sensorimotor polyneuropathy with 3-PHGDH deficiency has also been described, which expands the spectrum [27]. A mild form has been described in two siblings with juvenile onset of absence seizures and mild developmental delay with favorable response to serine supplementation with cessation of seizures, normalization of their EEG, and improvement in behavior [28].

3-phosphoserine phosphatase deficiency has been described in a Belgian boy who had pre- and postnatal growth retardation, moderate psychomotor retardation, and facial features suggestive of Williams syndrome with reduced phosphoserine phosphatase activity in lymphoblasts and fibroblasts to 25 % of normal [29].

Biochemical features are characterized by low fasting plasma and CSF serine and glycine. This group of disorders involve rare defects in the biosynthesis of L-serine. Characterized defects include deficiency of 3-phosphoglycerate dehydrogenase, which can be detected on the basis of decreased enzymatic activity in fibroblasts. The 3-phosphoserine phosphatase deficiency can be detected in lymphoblasts and fibroblasts and is reduced to 25 % of normal values in affected patients.

Pathology arises from the deficiency of L-serine, a precursor for nucleosides, phospholipids, and the neurotransmitters glycine and D-serine. L-serine appears to be essential for normal brain function, as it plays a role in the biosynthetic reactions of brain proteins, glycine, cysteine, serine phospholipids, sphingomyelins, and cerebrosides. Disturbances of serine-glycine metabolism in relation to N-methyl-D-aspartate-receptor activation may also play a role in psychiatric disease.

The 3-phosphoglycerate dehydrogenase deficiency results in dysmyelination of the developing brain and requires antenatal treatment. In one patient with the PHGDH gene defect who was detected prenatally on the basis of a reduction of fetal head circumference between the 20th to 26th week of gestation from the 75 % to the 29 %, L-serine at 190 mg/kg/day in 3 divided doses was given to the mother which led to a fetal head circumference increase to the 76 % percentile at 31 weeks gestation [30]. At birth, the girl’s head circumference was normal. Within 12 hours after birth, the serine concentration in plasma dropped to a severely deficient value, and the CSF serine was also depleted. MRI was normal but EEG showed discrete seizure activity. After initiation of L-serine at 400 mg/kg/day, the seizure activity decreased and was replaced by normal cerebral activity. At one year and at 4 years of age, this girl had normal growth and psychomotor development. The follow up MRI brains at 12 and 14 months were normal.

Treatment in 3-PHGDH deficiency consists of administration of oral serine (200 mg/kg/day divided into 3 doses) with or without glycine [26, 31-33], which may improve seizure control and cerebral growth. In phosphoserine phosphatase deficiency, treatment with oral serine led to normalization of serine levels and some improvement in head growth [29].

Genetics. 3-PHGDH deficiency is an autosomal recessive disorder and the PHGDH gene is located at 1p12.
3-phosphoserine phosphatase deficiency is presumed autosomal recessive in inheritance and the gene is at locus 7p11.2.

4. Biotin-Responsive Disorders

a) Biotin Deficiency

**Biochemistry.** Biotin is a cofactor in the metabolism of fatty acids and leucine and in gluconeogenesis. It is responsible for the transfer of CO2 in several carboxylase enzymes, including acetyl-CoA carboxylase alpha and beta, methylcrotonyl-CoA carboxylase, propionyl-CoA carboxylase, and pyruvate carboxylase. Sources of biotin include royal jelly, brewer’s yeast, Swiss chard, tomatoes, romaine lettuce, carrots, almonds, eggs, and onions. Deficiency states are rare and relatively mild. Causes of biotin deficiency include excessive consumption of raw egg whites (avidin), gastrectomy, aichlorhydria, extensive burns, and epilepsy. Clinical deficiency states are characterized by anorexia, decreased growth, alopecia, perosis, and fatty liver and kidney syndrome.

b) Biotinidase Deficiency (Late-Onset Multiple Carboxylase Deficiency)

**Clinical features** include variable phenotypes depending upon the degree of residual enzymatic activity and affects ~1/60,000 newborns. There are severe forms (< 10 % residual activity); partial forms (10-30% activity) where symptoms are triggered by metabolic stressors, such as prolonged infection; and asymptomatic cases. Clinical and biochemical consequences of severe biotin deficiency have been documented to occur within 12 days of birth [34]. Early infancy onset seizures are the most frequent initial symptom and may present as Othahara syndrome [35] or infantile spasms [36]. The primary features include hypotonia; cognitive delay; ataxia, which may be intermittent; sensorineural hearing loss; optic atrophy; rash; alopecia; and recurrent infections [36-41]. Older children and adolescents with profound biotinidase deficiency exhibit motor limb weakness, spastic paraparesis, and decreased visual acuity. Wolff et al [43] reported two unrelated asymptomatic adults with biotinidase deficiency only because their affected children were identified by newborn screening.

**Biochemical features** are characterized by ketoadicidosis and lactic acidosis. Urine organic acids demonstrate 3-hydroxy isovaleric acid, ß-methylcrotonylglycine, and 3-hydroxypropionic acids.

**Pathology** is characterized by cerebellar atrophy and may include basal ganglia calcifications [45]. Imaging also demonstrates low cerebral volume with ventriculomegaly and widened extracerebral CSF spaces [46].

**Treatment** with oral biotin supplementation (5-10 mg/day) leads to rapid clinical and biochemical improvement; however, there may be residual CNS injury, including developmental delay, ataxia, sensorineural hearing loss, and visual defects depending in part on the time of treatment intervention. Suormala et al [47] suggested treatment with biotin for all patients with residual activities below 10 %. Wolf [42] suggests that all individuals with profound deficiency should have lifelong treatment with biotin. Annual vision and hearing evaluations should be conducted, and raw eggs should be avoided, as they contain avidin, which binds biotin and decreases the bioavailability of biotin.

**Genetics.** Inheritance is autosomal recessive due to mutations in the BTD gene, which is located at gene locus 3p25.1. Because of the importance of early treatment intervention and the response to biotin therapy, screening for biotinidase deficiency is now part of many newborn screening programs [48].

5. Folate-responsive Disorders

a) Folate Deficiency

**Biochemistry.** Folic acid is important in the synthesis of DNA (thymine and purine bases) and in cell division. Sources of folic acid include leafy green vegetables, such as spinach and lettuce, dried beans, peas, fortified cereals, and sunflower seeds. Folate deficiency may be seen in individuals taking medications that interfere with folate metabolism such as methotrexate, trimethoprim, sulfonamides, dilantin, primidone, and metformin. It may also occur in malabsorption syndromes, including celiac disease, liver disease, and renal disease.

**Clinical manifestations** include diarrhea, anorexia, weight loss, palpitations, weakness, headaches, irritability, behavioral disorders, and megaloblastic anemia. Folate deficient mothers may bear children with low birth weight, pre-maturity, and neural tube defects.

Folic acid responsive disorders include hereditary folate malabsorption (SLC46A1), the cerebral folate transporter defect FOLR1, 5,10-methylenetetrahydrofolate reductase deficiency, and homocystinuria due to cystathione ß-synthase deficiency.

b) Folic Acid Transport Defect (Hereditary Folate Malabsorption) SLC46A1

**Clinical features** include early infancy onset with megaloblastic anemia, pancytopenia, diarrhea, vomiting, seizures, cognitive delay, drowsiness, ataxia, athetosis, and peripheral neuropathy.

**Biochemical features** are characterized by a defect in the intestinal and blood-brain barrier transport of folate [49]. Folate deficiency is demonstrable in RBCs, serum, and the CSF.

**Pathology** is characterized by basal ganglia calcifications [50, 51].

**Treatment** involves parenteral administration of folic acid, which restores normal growth and corrects hematologic abnormalities but has less effect on development and seizures. Corbeel et al [52] also gave methione and Vitamin B12 because of concurrent low plasma methionine, and the seizures were controlled. Peripheral neuropathy improved with intramuscular folic acid therapy [54].

**Genetics.** Inheritance is autosomal recessive due to mutations in the SLC46A1 gene at 17q11.2 [54-56].

c) Cerebral Folate Transport Defect FOLR1

**Clinical features** include late infantile onset of severe developmental regression, seizures, and progressive movement disorder characterized by ataxia and/or atethosis [57].

**Biochemical features** are characterized by a defect in cerebral folate transport due to mutations in the folate receptor 1 gene coding for folate receptor alpha, which results in severe folate deficiency in the CSF [57].

**Neuroimaging** is characterized by severe hypomyelination affecting periventricular and subcortical white matter. On brain MRS, there are decreased choline and inositol peaks in the parieto-occipital white matter [57].

**Genetics.** Inheritance is autosomal recessive due to mutations in the FOLR1 gene at 11q13.4.
6. Pyridoxine (Vitamin B6) and Pyridoxal-5'-Phosphate (PLP) – Responsive Disorders

Functions. Pyridoxine is converted into pyridoxal 5'-phosphate (PLP), its biologically active form. Pyridoxine has a number of important cellular functions. It assists in balancing cellular sodium and potassium, promotes RBC production, decreases the formation of homocysteine, and prevents exocma and psoriasis. It is a precursor for pyridoxal 5'-phosphate, a cofactor for aromatic amino acid decarboxylase, which converts 5-hydroxytryptophan into serotonin and L-DOPA into dopamine, noradrenaline, and adrenaline. Dietary sources include dragon fruit, grains, and nuts.

Pyridoxine may be given with isoniazid at 10-50 mg/day to prevent peripheral neuropathy and CNS toxicity during tuberculosis therapy. In high doses, it may lead to sensory neuropathy and ataxia.

a) Pyridoxine Deficiency

Clinical features include chelitis, conjunctivitis, sideroblastic anemia, neonatal onset seizures, irritability, and confusion.

Biochemical features are characterized by impairment in the decarboxylation of glutamate to GABA and an impairment of the transamination of glutamate to alpha-ketoglutarate (Kreb's cycle intermediate).

b) Pyridoxine Dependent Epilepsy (Antiquitin Deficiency) - α-Amino Adipic Semialdehyde (αAASA) Dehydrogenase Deficiency

Clinical features include seizure onset, usually on day one of life but may be delayed up to 3 weeks or even later. Seizures may be prolonged with recurrent episodes of status, which is typical but may also be recurrent, self-limited events, including partial seizures, generalized seizures, atonic, and myoclonic seizures. Infantile spasms may also occur. Mothers may complain of intrauterine seizures. In the classic presentation, neonatal or early infantile seizures are clonic, generalized tonic, and/or myoclonic and are resistant to standard anticonvulsants but respond completely with cessation of clinical and electrographic seizures to 50-100 mg of intravenous pyridoxine within minutes. A transient coama concomitant with seizure cessation is characteristic for pyridoxine-dependent epilepsy (PDE) but does not always occur [67,68]. Seizures usually recur when pyridoxine is stopped, either incidentally or for diagnostic withdrawal, for which time intervals between 1 and 51 days have been reported [69,70]. EEG patterns may vary from normal to high voltage delta activity, focal spike wave discharges, burst suppression patterns, and, rarely, hypersarrhythmia [71-73]. Other features may include respiratory distress, acidosis, sleeplessness, irritability, fluctuating tone, abdominal distension, and vomiting. Despite early treatment and good seizure control, many will have mild to severe developmental delay with speech delay. Atypical presentations may include late onset of seizures up to 3 years of age [74,75], autism, and partial response to common anticonvulsants, especially Phenobarbital with delayed response to pyridoxine [75].

Screening should be performed in neonates, infants, and older children with unexplained, intractable, or poorly controlled seizures, especially in combination with encephalopathy, long lasting focal seizures, and status epilepticus. With available biomarkers, patients with later onset and milder and atypical courses should be considered for screening, particularly if parents are consanguineous and there is a history of partial or transient pyridoxine responsiveness.

Biochemical features are characterized by an increase in plasma homocysteine, decreased plasma methionine, decreased folate in serum and RBCs, homocystinuria, and decreased MTHFR activity in fibroblasts or leukocytes. Decreased S-adenosylmethionine and demyelination have been documented [63].

Treatment includes folinic acid, methylenetetrahydrofolate, betaine, and methionine supplementation [60, 62].

Genetics. Inheritance is autosomal recessive due to mutations in the MTHFR gene at 1p36.22 [64-66].
of ATQ deficiency [86]; and (iv) possibly the primary toxicity of pipelic acid, aASA, and the P6C/PLP complex. PLP acts as a cofactor in numerous enzyme reactions facilitating transamination and decarboxylation of amino acids and neurotransmitter precursors.

**Treatment** consists of supplementation with oral pyridoxine 30 mg/kg/day divided in three doses. Oral pyridoxal phosphate (PLP) up to 30 mg/kg/day divided in three doses can be alternatively given as both patients with antiquitin or with PNPO (pyridoxamine 5'-phosphate oxidase) deficiency will respond, whereas PNPO deficient patients will only respond to PLP and not to pyridoxine. An initial trial is given with 100 mg intravenously of pyridoxine, which may result in respiratory arrest in responders. Thus, treatment should be performed with respiratory support if needed. Not all patients with PDE have immediately shown the expected clinical or EEG responses; therefore, Stockler et al [86] suggests that neonates with therapy resistant seizures should receive oral pyridoxine until PDE is fully excluded by biochemical or mutational analysis. Scharer et al [87] has described three different phenotypes in pyridoxine treated patients: (i) complete seizure control and normal developmental outcome, (ii) complete seizure control and developmental delay or intellectual disability, and (iii) incomplete seizure control and developmental delay or intellectual disability. Long-term treatment doses vary between 15-30 mg/kg/day in infants or up to 200 mg/day in neonates and up to 500 mg/day in adults [86]. Folinic acid may have an additional benefit as an add-on treatment. Prenatal treatment with maternal pyridoxine supplementation may possibly improve outcomes [86]. Though there is a good rationale for a lysine-restricted diet, the effect on PDE outcome is yet to be determined and will require multicentre studies. Lysine restricted diets have potential side effects and risks and are a burden for families.

**Genetics.** Inheritance is autosomal recessive due to mutations in the antiquitin (ALDH7A1) gene at locus 5q31 [88,89].

**Patients at Risk for PDE.** As recommended by Goutieres and Aicardi [90], pyridoxine dependency should be considered to be the cause of intractable seizures in the following situations:

1. Seizures of unknown etiology in a previously normal infant without an abnormal gestational or perinatal history
2. The occurrence of long-lasting focal or unilateral seizures
3. Signs of encephalopathy, such as irritability, restlessness, crying, and vomiting preceding the actual seizures
4. A history of severe epilepsy in a sibling, often leading to death during status epilepticus
5. Parental consanguinity

In order NOT to miss milder and atypical presentations, Stockler et al [86] recommends that the following patients should also be considered for screening:

1. Infants and children with seizures that are partially responsive to pharmacological anticonvulsive drugs (e.g. phenobarbital), particularly if associated with developmental delay and intellectual disability
2. Neonates with hypoxic ischemic encephalopathy and difficult to control seizures
3. Patients with a history of transient or unclear response to pyridoxine
4. Patients with a history of response to folic acid and/or with the characteristic unidentified peak ‘X’ on CSF monoamine analysis

5. Seizures in any child under the age of one year without an apparent CNS malformation.

**Other Pyridoxine-responsive Disorders that Include Seizures Responsive to Pyridoxine or its Vitamers** are (i) Pyridoxal phosphate response encephalopathy due to deficiency of pyridoxamine 5'-phosphate oxidase deficiency (PNPO), which responds only to pyridoxal 5-phosphate; (ii) hypophosphatasia due to tissue non-specific alkaline phosphatase (TNSALP) deficiency with seizures and lethal bone disease; (iii) familial hyperphosphatasia with mental retardation, seizures, and neurological deficits (Mabry syndrome) due to a defect in phosphatidylglycerol glycan anchor biosynthesis class V (PIGV) [91-94]; and (iv) hyperprolinemia type 2 due to P5CD deficiency with non-progressive developmental delay with intellectual disability, mild ataxia, and occasional seizures.

c) **Folinic Acid Responsive Seizures (FARS) are Genetically Identical to Antiquitin Deficiency**

**Clinical features** include intractable seizures and encephalopathy.

**Biochemical features** are characterized by two characteristic yet unidentified peaks (peak X) in the HPLC chromatogram for CSF monoamine neurotransmitter analysis. Two patients with the FARS peak had increased levels of alpha-AASA and pipelic acid in CSF and known or, presumably, pathogenic mutations in the ATQ gene.

**Treatment.** Patients have shown an improvement of seizures upon administration of folic acid (3-5 mg/kg/day). Two patients with the CSF marker of FARS responded clinically to pyridoxine. Improved outcomes have been seen with pyridoxine and folic acid together.

**Genetics.** FARS has been shown to be genetically identical to ATQ deficiency [95].

d) **Pyridoxamine 5'-Phosphate Oxidase (PNPO) Deficiency**

**Clinical features** include neonatal onset seizures that may be clonic, myoclonic, and frequently status epilepticus. Birth is often premature with seizure onset on day 1 or in utero. There may be rotatory eye movements, orobuccal rhythmic movements, myoclonus, hyperexcitability, and hypersalivation. EEG reveals a severe burst suppression pattern or myoclonic epilepsy [96-99]. Without treatment with pyridoxal-5'-phosphate (PLP), there is severe developmental delay, intractable seizures, and dystonia.

**Biochemical features** are characterized by hypoglycemia, early lactic acidosis, pancytopenia, and coagulopathy. PLP-responsive epileptic encephalopathy is caused by deficiency of pyridoxamine 5'-phosphate oxidase (PNPO). The CSF and urine biochemical profiles are consistent with a reduction of PLP-dependent enzyme aromatic L-amino acid decarboxylase (AADC) activity characterized by (1) build up of metabolites of L-DOPA, including markedly elevated CSF 3-methoxytyrosine and increased urinary excretion of vanillic acid (VLA) and (2) markedly decreased concentration of dopamine metabolite, homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF. The CSF amino acid profile demonstrates elevated glycine, threonine, taurine, and histidine and low arginine [98].

**Pathophysiology** relates to the disturbance in neurotransmitter metabolism.

**Neuroimaging** demonstrates progressive hypomyelination and global cerebral atrophy.
Treatment consists of pyridoxal-5'-phosphate (PLP), which brings about a rapid clinical response.

Genetics. Inheritance is autosomal recessive with mutations in the PNPO gene at locus 17q21.32.

7. Approach to Unexplained Frequent or Intractable Neonatal Seizures

The classic approach has been to try each of the vitamers in sequence and to ascertain the clinical and EEG response.

1. Pyridoxine 100 mg bolus IV with EEG
   Then 10 mg/kg q8h po X 24 hrs
   If no definite response (EEG normalization or Sz control)
2. Folinic acid 5 mg/kg q 24 hrs po X 3 days
   If no definite response
3. PLP 10 mg/kg q 8h po X 3 days

However, if seizures are frequent and intractable, or there is epileptic encephalopathy with status, a more immediate and preferable therapeutic approach would be to initiate treatment with a combination of oral PLP with folinic acid in order to achieve earlier seizure control and to thereby avoid further ongoing kindling of seizures. The PLP would treat both the antiquitin defect as well as PNPO deficiency. Serum, urine, and CSF biomarkers should be sent followed by specific gene testing for the suspected disorder. Therapy with PLP and folinic acid should be continued until the specific defect is identified, at which time the treatment could be modified according to the identified disorder. As both urine and plasma αAASA and plasma piperidolic acid are informative in both the untreated and treated states of antiquitin deficiency [86], initiation of therapy with pyridoxine should NOT be delayed for diagnostic purposes, and diagnostic samples can be taken any time before and after treatment. In this way, there would be no delays in initiating treatment, as PLP would treat both the antiquitin defect as well as PNPO deficiency.

Work-up

<table>
<thead>
<tr>
<th>Work-up</th>
<th>Test</th>
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<tbody>
<tr>
<td>Serum</td>
<td>glucose, lactate, NH3, quantitative amino acids, acylcarnitines, biotinidase assay, α-amino adipic semialdehyde (αAASA)<em>, P6C</em>, piperidolic acid**</td>
</tr>
<tr>
<td>Urine</td>
<td>amino acids, organic acids, αAASA*, sulfocysteine</td>
</tr>
<tr>
<td>CSF</td>
<td>glucose, lactate, amino acids (glycine), neurotransmitters + Peak X (Keith Hyland’s lab) αAASA*, piperidolic acid</td>
</tr>
<tr>
<td>Gene testing</td>
<td>as indicated by screens -&gt; e.g. antiquitin sequencing</td>
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</tbody>
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* Because αAASA and P6C are unstable, samples should be frozen immediately after collection.
** Elevated piperidolic acid may also be seen in other inborn errors of metabolism, e.g. generalized peroxisomal dysfunction, hyperlysinsima, and defects of proline metabolism and in liver disease.

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Competing interests
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Author contributions
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Supplementary material
Supplementary material is available at JICNA online.

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