

Neonatal Vitamin-responsive Epileptic Encephalopathies

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The treatment of neonatal seizures generally relies on the use of one or more anticonvulsant medications along with evaluation and management of any underlying etiology. In some circumstances, neonatal seizures are refractory to therapy and result in poor outcomes, including death. Certain rare vitamin-responsive inborn errors of metabolism may present as neonatal encephalopathy with anticonvulsant-resistant seizures. Therefore, it is vital for the clinicians of caring for seizing encephalopathic newborns to consider these particular disorders early in the hospital course. Pyridoxine-dependent seizures are due to deficiency of α -aminoacidic semialdehyde dehydrogenase (antiquitin) which is encoded by *ALDH7A1*. Seizures in infants who are pyridoxine-dependent must be treated using pharmacologic doses of pyridoxine (vitamin B₆), and life-long therapy is required. Despite medical therapy, developmental handicaps, particularly in expressive language, are common. Folinic acid-responsive seizures are treated with supplements of folinic acid (5-formyltetrahydrofolate). Recently, patients with this condition were also demonstrated to be antiquitin deficient. Pyridoxal phosphate-dependent seizures result from a deficiency of pyridox(am)ine 5'-phosphate oxidase which is encoded by *PNPO*. Patients with this cause of seizures respond to pyridoxal phosphate but not to pyridoxine. This review discusses our current understanding of these three neonatal vitamin-responsive epileptic encephalopathies and a diagnostic and treatment protocol is proposed. (*Chang Gung Med J* 2010;33:1-12)



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Neonatal seizures are common clinical problems confronting pediatricians, neonatologists and pediatric neurologists. Seizures presenting in a newborn represent a symptom of underlying central nervous system dysfunction that may result from a variety of causes including developmental anomalies of brain structure, infectious or inflammatory condi-

tions, cerebrovascular disease, trauma, or metabolic disturbance. The treatment of neonatal seizures generally relies on the use of one or more anticonvulsant medications (typically phenobarbital) along with appropriate evaluation and management, when possible, of any underlying etiologies. Despite these measures, in some circumstances, neonatal seizures are

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refractory to therapy and poor outcomes, including death, may ensue. Certain rare inborn errors of metabolism that are clinically responsive to specific vitamin therapy may present as a neonatal encephalopathy with anticonvulsant-resistant seizures. As such, it is vital for the clinicians caring for seizing encephalopathic newborns to consider these particular disorders early in the hospital course. This review discusses our current understanding of three neonatal vitamin-responsive epileptic encephalopathies: pyridoxine-dependent seizures, folinic acid-responsive seizures, and pyridoxal phosphate-dependent seizures, and protocols for the diagnoses and treatment of these disorders are proposed.

Pyridoxine-dependent seizures

Brief history of the disorder

Pyridoxine-dependent seizures (PDS) is the best understood of the neonatal vitamin-responsive epileptic encephalopathies, particularly due to the relatively recent discovery of its underlying biochemical and genetic bases and the publication of several case reports. Classically, patients with PDS present with neonatal seizures that are intractable to treatment with conventional anticonvulsants and only come under control once pharmacologic doses of pyridoxine are administered and then continued on a regular basis. The disorder was first described in 1954 by Hunt and colleagues when they reported their evaluation and care of a newborn with pharmacoresistant seizures that eventually came under control after regular treatment with a multivitamin preparation.⁽¹⁾ The clinicians caring for this infant consecutively eliminated components of this proprietary product and subsequently deduced that pyridoxine (vitamin B₆) was the factor responsible for controlling the infant's epileptic seizures. As one of the mother's previous pregnancies resulted in a newborn who succumbed to intractable seizures, the familial nature of PDS was suggested. During the last half of the 20th century approximately 100 cases were reported,⁽²⁻⁵⁾ and the published accounts during the past two decades have primarily focused on atypical clinical presentations,⁽⁶⁻⁹⁾ neurodevelopmental features,⁽¹⁰⁻¹⁴⁾ electroencephalogram (EEG) findings,⁽¹⁵⁻¹⁷⁾ imaging characteristics,^(11,17,18) and most recently mutations in the *ALDH7A1* gene which are responsible for the biochemical abnormalities underlying PDS.^(13,19-26)

Epidemiology

Only a handful of epidemiologic studies have been performed.^(10,11,27-29) A study conducted in the United Kingdom and the Republic of Ireland showed a point prevalence of 1:687000 for definite and probable PDS cases,⁽²⁷⁾ and a survey conducted in the Netherlands estimated a birth incidence of 1:396000.⁽²⁸⁾ Even with the recent increase in clinical recognition, PDS is probably underdiagnosed. Conceivably the incidence is higher, as supported by a study from a center in Germany where pyridoxine administration is part of a standard treatment protocol for neonatal seizures. In that study, the reported birth incidence of probable cases was 1:20000.⁽²⁹⁾

Clinical features

PDS is due to an autosomal recessive inborn error of metabolism, and affected patients are dependent upon regular pharmacologic doses of pyridoxine. Untreated, the disorder results in death from status epilepticus. Retrospectively, this adverse situation has been reported in individuals who succumbed prior to the birth and ensuing PDS diagnosis in a younger sibling.^(2,5) The disorder may present within hours of birth as an epileptic encephalopathy that may mimic hypoxic-ischemic encephalopathy.^(2,5,11,27) In addition, some mothers may report having experienced unusual fetal movements that likely represent intrauterine fetal seizures. Other cases may present with seizures at a later time during the first several weeks of life. Even more unusual are examples of patients with PDS that develop clinical features after 2 months of age, and these are considered to be late-onset cases.^(5,8,9) Universally, all patients with PDS have clinical seizures which either recur serially or evolve into status epilepticus despite treatment with large doses of one or more conventional anticonvulsants. In most instances, the institution of either parenteral or oral pyridoxine rapidly results in seizure control and improvement in the encephalopathy. Along with the late-onset cases, other atypical forms of PDS have been described, including patients whose seizures initially respond to anticonvulsants but who then develop recurrence weeks to months after the initial resolution and then become intractable, and infants whose seizures are not controlled by initial large doses of pyridoxine but who subsequently respond to a second trial days after the initial doses.^(2,6-9) Pyridoxine treatment must continue,

or clinical seizures will reappear within days. In patients with PDS, pyridoxine-deficiency is not present, and it is important to point out the distinction between pyridoxine-dependency and pyridoxine-deficiency to parents, therapists, teachers and others providing care to these patients.

Types of clinical seizures

The semiology of seizures and associated clinical features in patients with PDS is quite varied. In the newborn, the condition may present with encephalopathy, infrequently with gastrointestinal symptoms such as emesis and abdominal distention, and is associated with recurrent partial motor seizures, generalized tonic seizures or myoclonus. Subsequently, complex partial seizures, infantile spasms and other myoclonic seizures as well as a mixed seizure pattern may emerge. It is not uncommon in untreated cases for status epilepticus to develop at some point. In patients with late-onset PDS, similar seizure types may occur as well as infantile spasms as the initial clinical presentation, generalized clonic seizures, atonic seizures, visual seizures and intermittent attacks of status epilepticus.^(2,5,10,11,13,14,27) In all instances, a high risk of status epilepticus occurs with the discontinuation of pyridoxine therapy, thereby necessitating daily life-long pharmacologic doses of pyridoxine. With adherence to this regimen, the prognosis for seizure control in most patients with PDS is generally excellent, with only an occasional breakthrough seizure which may occur during acute illness such as gastroenteritis which causes a temporary reduction in pyridoxine bioavailability. However, some patients treated appropriately with pyridoxine supplementation continue to have recurrent seizures. It has been hypothesized that in these circumstances a secondary cause of epilepsy, such as mesial temporal sclerosis, hydrocephalus or other brain dysgenesis, may be responsible.^(2,10,30)

Neurodevelopmental outcome

A range of neurodevelopmental disabilities have been noted in patients with PDS. Expressive language deficits are common, and affected patients have also been described with non-verbal cognitive deficits, as well as motor developmental delay with associated persistent mild reductions in tone.^(2,5,10) In some severely affected patients, cerebral palsy and

significant intellectual handicaps have been described. In some older individuals, behavioral features typical of either obsessive-compulsive disorder or autistic spectrum disorder have been reported.⁽¹⁰⁾ It has been noted by several authors that early diagnosis and effective treatment of PDS results in better neurodevelopmental outcomes, and that individuals with late-onset PDS, in general, have better prognoses (including a few cases with reportedly normal development) than those with an early-onset of symptoms. However, the severity of the neurodevelopmental features of PDS likely has a multifactorial basis, which includes the time of clinical onset (fetal, vs. neonatal, vs. late-onset), the lag time to diagnosis and effective treatment, compliance with pyridoxine therapy, associated brain dysgenesis, and presently unknown associations between the *ALDH7A1* genotype and neurodevelopmental phenotype.^(2,5,10,13,14,27,31) From a few specific case reports in the literature, there is a suggested characteristic neuropsychological profile of PDS patients. Formal psychometric assessments conducted in these patients have shown reduction in the cognitive/verbal IQ, particularly in measures of expressive language, together with low normal motor/performance IQ.^(2,10-12)

EEG findings

While several researchers have reported EEG characteristics of PDS patients, defining a specific pattern of EEG abnormalities remains difficult.^(2,15-17) In PDS patients, EEGs are typically performed after several seizures have occurred as well as after the administration of anticonvulsant therapy, typically phenobarbital if not additional medications. Both of these factors may affect the EEG and thus modify any presumed disease-specific pattern. With this in mind, abnormal background activity together with a variety of paroxysmal features have been described including generalized and multi-focal epileptiform activity, discontinuous patterns including burst-suppression, bursts of high voltage slow waves, and hypsarrhythmia in patients with infantile spasms. It is important to emphasize that in some untreated patients, as well as in many pyridoxine-treated patients, it is not uncommon for the interictal EEG to be normal or to demonstrate only minimal epileptiform activity. Therefore, clinicians must realize that a clinical diagnosis of PDS should not be made solely by examining the concurrent effects of pyridoxine

administration on the interictal EEG. Positive results of clinical effectiveness of pyridoxine treatment, as well as biochemical and/or genetic confirmation of PDS, are necessary.

Neuroimaging findings

While a variety of abnormal neuroradiologic features have been described in patients with PDS, it is not uncommon for affected patients to have normal imaging study results. Of the various neuroimaging findings described, none can be concluded to be specifically pathognomonic of the disease. However, certain abnormalities have been noted in a number of patients including the thinning of the isthmus of the corpus callosum and mega cisterna magna, while varying degrees of cerebral atrophy have been described in late-diagnosed or inadequately treated patients. Progressive hydrocephalus necessitating shunting has also been reported.^(2,11,17,18)

Nutritional, biochemical and genetic aspects

The term pyridoxine connotes the six vitamers of vitamin B₆: the alcohol pyridoxine (sometimes noted as pyridoxol in older reports in the literature), the aldehyde pyridoxal, the amine pyridoxamine, and their respective 5'-phosphorylated esters (Fig. 1). These substances are widely available in both animal- and plant-derived foods, and while vitamin B₆ is an essential nutrient in humans, clinical pyridox-

ine-deficiency states are extremely rare.^(32,33) Importantly, both pyridoxine phosphate and pyridoxamine phosphate are converted to the active cofactor pyridoxal phosphate (PLP) by pyridox(am)ine 5'-phosphate oxidase. PLP plays numerous roles in over 140 metabolic reactions making up at least 4% of all classified enzyme activities including transamination of amino acids, decarboxylation reactions, modulation of the activity of steroid hormones and regulation of gene expression.^(34,35) From a neurologic perspective, abnormalities of pyridoxine homeostasis may result in alterations in dopaminergic, serotonergic, glutaminergic and gabaergic neurotransmission.

Mutations in the *ALDH7A1* gene which encodes the protein antiquitin, an aldehyde dehydrogenase that functions within the cerebral lysine catabolism pathway (Fig. 2), have recently been demonstrated to be the molecular cause of PDS.⁽²²⁾ Homozygous or compound heterozygous *ALDH7A1* mutations have been described in several patients with neonatal-onset PDE and in a few individuals with late-onset PDS.^(13,19,21,22,24,26,31) It has also been demonstrated that affected patients have elevations in α -amino adipic semialdehyde (AASA) in their plasma, urine and cerebrospinal fluid (CSF). While these biochemical findings persist even after years of effective treatment, elevations of the indirect biomarker pipercolic acid (PA), may also be detected in the plasma and CSF, but in some patients the levels normalize after

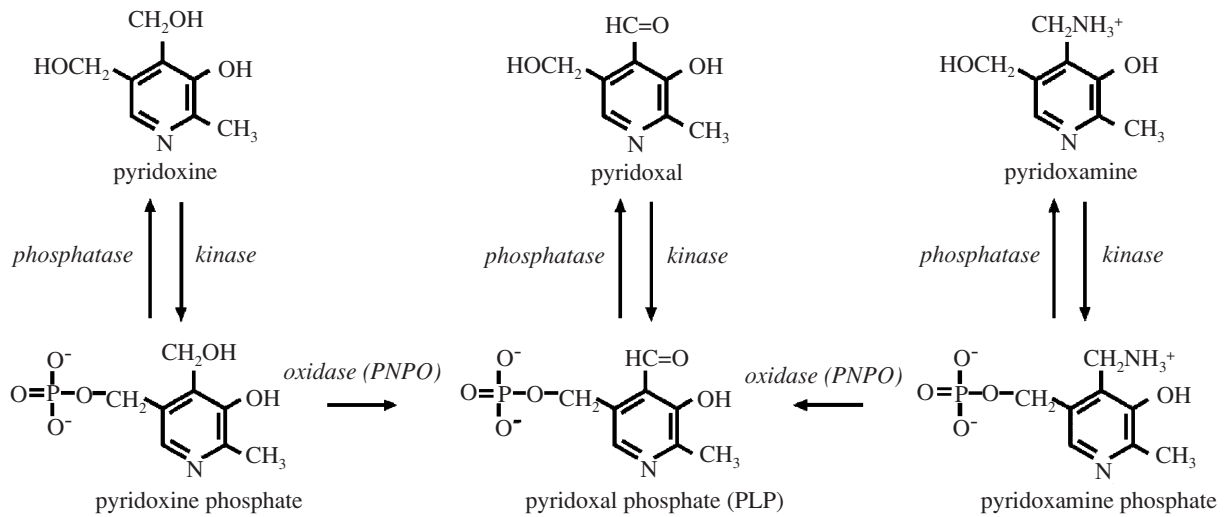


Fig. 1 The six vitamin B₆ vitamers and the enzymatic reactions leading to their interconversion.

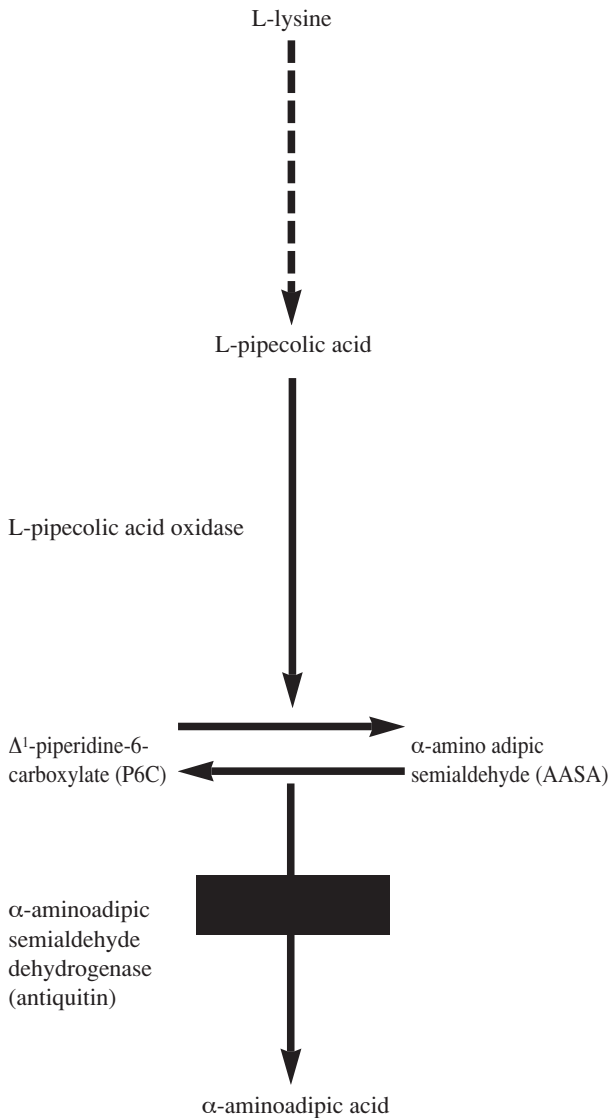


Fig. 2 Cerebral lysine metabolic pathway. The bar indicates the site of the block of α -amino adipic semialdehyde dehydrogenase (antiquitin) in patients with pyridoxine-dependent seizures.

effective long-term therapy.^(20,22,23,25) AASA is in equilibrium with Δ^1 -piperidine-6-carboxylate (P6C) which through a Knoevenagel condensation reaction with PLP inactivates this vital cofactor.⁽²²⁾ Therefore, mechanistically, accumulation of AASA results in an intracellular reduction in PLP; curiously, while patients with PDS are not systemically pyridoxine-

deficient, from a cellular physiology perspective, they are PLP-deficient. Consequently, an imbalance between the excitatory neurotransmitter glutamic acid and the inhibitory neurotransmitter GABA may result in the development of encephalopathy and intractable epileptic seizures.

The clinical diagnosis of PDS

The diagnosis of PDS is made by clinical observation, where an infant with anticonvulsant-resistant seizures is offered a trial of pyridoxine that results in an often dramatic cessation of these events. The most convincing clinical demonstration of the effectiveness of pyridoxine therapy is to administer intravenous pyridoxine at a time when the patient is actively experiencing seizures and is undergoing continuous EEG monitoring.^(2,4) By taking these measures, both clinical and electrographic evidence of pyridoxine's effectiveness is demonstrated, generally within minutes of a single dose of 20-100 mg, however in some instances higher doses are required. Therefore, if a patient does not respond to an initial dose of 100 mg, up to 500 mg of intravenous pyridoxine should be administered in sequential doses of 100 mg every 5-10 minutes before concluding that the infant's clinical and electrographic seizures are not responsive to the vitamin. Ideally this trial should take place within an intensive care unit setting, as profound central nervous system depression with associated changes in the EEG have been noted in some PDS patients after the initial treatment with pyridoxine.^(2,3,7) An alternate diagnostic approach is suggested for patients who are experiencing frequent short anticonvulsant-resistant seizures. In those cases, oral pyridoxine (up to 30 mg/kg/day) should be prescribed, and patients with PDS should have a resolution of clinical seizures within 3 to 7 days.^(2,4)

As patients with PDS have a life-long dependence on pyridoxine supplementation, a definitive clinical confirmation of the diagnosis requires additional steps. The patient must manifest continued control of seizures on pyridoxine monotherapy after the sequential withdrawal of all anticonvulsants, followed by seizure recurrence once pyridoxine is withdrawn, and then regained control of seizures once pyridoxine is reintroduced. Clearly, many parents and clinicians have been reluctant to take the step of withdrawing pyridoxine. Therefore, epidemiologic studies and case series have reported such instances

as possible PDS cases.^(2,10,27) However, one needs to be cautious in diagnosing all patients treated in this manner with PDS. Patients have been reported with seizures that cease in response to pyridoxine therapy, but in whom seizures do not recur after the vitamin is discontinued. The term pyridoxine-responsive seizures (PRS) has been coined to describe patients with this particular condition.^(2,27) Therefore, some patients with possible PDS may actually have PRS.

The diagnosis of PDS via biochemical and genetic testing

The recent discovery of the biochemical and genetic abnormalities which underlie PDS has led to changes in our approach in diagnosing this condition. In PDS patients, documentation of elevated levels of PA in plasma samples, taken either prior to treatment or within several months after therapy has been initiated, can serve as indirect confirmatory evidence of PDS.^(23,25) The demonstration of elevated levels of AASA in the plasma, cerebrospinal fluid or urine is a more specific biochemical confirmation of the inborn error of metabolism that underlies PDS.^(20,22) However, assays of AASA are currently not available, except on a research basis. An absolute diagnosis of PDS can be accomplished via testing of the *ALDH7A1* gene in patients clinically suggested of having the disorder. The demonstration of either homozygous or compound heterozygous mutations in both *ALDH7A1* alleles will affirm the diagnosis.^(19,22,24,26,31) Therefore in these cases, the withdrawal of pyridoxine to clinically verify the diagnosis would not be necessary. Both biochemical and genetic testing is recommended, as a few individuals with elevated PA and/or AASA levels did not demonstrate mutations of one or both *ALDH7A1* alleles,^(19,24) and diagnosed PDS patients treated for an extended period of time may have a normalization of PA levels.^(23,24)

The management of PDS

Once a clinical diagnosis of PDS has been made, patients require life-long pyridoxine treatment to prevent recurrent seizures. The recommended daily allowance of pyridoxine for healthy individuals is 0.5 mg for infants and 2 mg for older children and adults, however, patients with PDS generally require higher (i.e. pharmacologic) doses. While the optimal dose of pyridoxine has not been firmly established,

the daily administration of 50 to 200 mg (given once daily or in two divided doses) is generally effective in preventing seizures in most patients.⁽²⁾ Once diagnosed, it is not uncommon for PDS patients to remain on the same amount of pyridoxine for many years, despite continued growth that effectively reduces the mg/kg/day dose. A recent study of six children with PDS demonstrated that a higher daily pyridoxine dose resulted in an increase in IQ scores, with the expressive language scores showing the least amount of improvement.^(2,11) Any additional increase in IQ was generally not seen with doses higher than 15 to 18 mg/kg/day. As megavitamin therapy with pyridoxine is known to cause dorsal root ganglionopathy,⁽³⁶⁾ and sensory neuropathy has been reported in a few PDS patients,^(30,31) parents must be cautioned about the overzealous use of pyridoxine. Therefore it has been suggested that patients with PDS should receive approximately 15 to 18 mg/kg/day, with a maximum daily dose of 500 mg. As individuals with PDS are at an increased risk of seizure recurrence when experiencing febrile illnesses, particularly gastroenteritis, the pyridoxine dose may be doubled for several days during this period. Unless a secondary cause of seizures is present, patients with PDS do not require the concurrent use of anticonvulsants. However, some patients may be prescribed certain anticonvulsants, specifically for psychotropic effects, as well as neuroleptics and mood stabilizers for the management of associated neurodevelopmental and behavioral symptoms.⁽¹⁰⁾ As deficits in expressive language are expected in PDS patients, these children should be offered early intervention services that focus on language skills. Older patients will benefit from special education and a variety of physical, occupational and speech therapy services.

While the neurodevelopmental outcome of PDS patients is multifactorial, still the early diagnosis and treatment of these patients is vital. As PDS is an autosomal recessive disorder, there is a 25% recurrence risk in subsequent pregnancies. Therefore, it has been suggested that during subsequent pregnancies, mothers should take a daily dose of pyridoxine of 50 to 100 mg during the last half of gestation.^(2,37) In some cases, affected newborns treated prenatally with pyridoxine followed by postnatal therapy had better neurodevelopmental outcomes when compared with their older affected siblings.^(2,16) However, this

has not been universally observed suggesting that genotype may play a role in the neurodevelopmental outcomes of patients with PDS.⁽³¹⁾ For at risk infants who received both *in utero* and postnatal pyridoxine therapy, parents and health care providers are faced with the decision of whether or not to withdraw pyridoxine supplementation in order to determine if the newborn will experience seizures, and therefore meet the clinical criteria for PDS. In the future when biochemical and *ALDH7A1* gene testing become more clinically available, the at risk newborn treated prenatally with pyridoxine may be tested for PDS biomarkers and/or genotype, so that pyridoxine therapy may be either maintained or safely discontinued.

Folinic acid-responsive seizures

Clinical features

In 1995, Hyland and colleagues reported the first cases of neonatal epileptic encephalopathy in which intractable neonatal seizures responded to treatment with folinic acid (5-formyltetrahydrofolate),⁽³⁸⁾ and during the following decade a total of seven cases have been reported.⁽³⁹⁻⁴¹⁾ These infants all presented with seizures and encephalopathy within the first 5 days of life, and the seizures were resistant to anticonvulsant therapy. In the first case, by chance it was discovered that folinic acid administration at a dose of 2.5 mg twice daily led to marked improvement in seizure control.^(38,41) Over time, some breakthrough seizures developed that responded to higher daily doses of folinic acid. As this infant, as well as two other reported cases, had a family history of a deceased older sibling with intractable neonatal seizures, the familial nature of this vitamin-responsive neonatal epileptic encephalopathy was established. As part of the diagnostic evaluation of the first described cases, CSF analysis of neurotransmitter metabolites via high performance liquid chromatography with electrochemical detection was conducted and revealed a previously unrecognized pattern of peaks that included two unidentified substances, a pattern that was also present in subsequently diagnosed cases.⁽³⁸⁻⁴¹⁾ In particular, these cases point out the utility of conducting a metabolic analysis of CSF in infants with unexplained epileptic encephalopathy.

Relationship of folinic acid-responsive seizures to PDS

In some of these cases, the patients had actually

demonstrated a variable degree of clinical response to pyridoxine. Recently, it was discovered in two additional infants with epileptic encephalopathy whose seizures responded to a combination of pyridoxine followed by the addition of folinic acid that not only was the characteristic pattern of peaks present on CSF analysis, but that these children also had AASA and PA elevations in CSF as well as mutations in *ALDH7A1*. CSF and DNA specimens from the previous seven reported cases of folinic acid-responsive seizures were then studied and similar abnormalities were demonstrated,⁽⁴²⁾ hence, folinic acid-responsive seizures are identical to PDS. While the identity of the two characteristic CSF peaks remains unknown, as does the biochemical mechanism of folinic acid, the discovery that these two vitamin-responsive disorders are identical clearly changes our approach to the diagnosis and management of infants with intractable seizures. As described in some of the recent cases, as well as in some earlier reports,^(2,7) patients with PDS may show initial unresponsiveness or only partial responsiveness to pyridoxine. While this may have been due to the pyridoxine treatment protocol that was used, it is possible that the early simultaneous use of both pyridoxine and folinic acid may have led to a more rapid clinical diagnosis of vitamin-responsive epileptic encephalopathy. In addition, continuous combination therapy with both cofactors together with a low lysine diet may lead to better long-term outcomes.⁽⁴²⁾ These are presently unanswered questions that will require controlled long-term therapeutic trials.

Pyridoxal phosphate-dependent seizures

Biochemical features

Neonatal epileptic encephalopathy in a patient that clinically responded to PLP rather than to pyridoxine was first described in 2002 by Kuo and Wang.⁽⁴³⁾ Shortly thereafter, additional cases were reported together with characteristic metabolic changes in the CSF, plasma and urine that suggested dysfunction in several PLP-dependent enzymes. These metabolic alterations included increases in CSF L-DOPA and 3-methoxytyrosine, together with decreased levels of CSF homovanillic acid and 5-hydroxyindoleacetic acid and urinary excretion of vanillic acid, all indicating dysfunction of aromatic L-amino acid decarboxylase activity; increased plasma and CSF levels of threonine demonstrating

threonine dehydratase dysfunction; and increased plasma and CSF glycine levels signifying reduced activity of glycine cleavage enzyme.⁽⁴⁴⁾ It was hypothesized that this disorder was secondary to the deficiency of the enzyme pyridox(am)ine 5'-phosphate oxidase which converts both pyridoxine phosphate and pyridoxamine phosphate to PLP. Patients with this enzyme deficiency would only be able to generate intracellular PLP through dietary sources of pyridoxal and PLP; hence the seizures are PLP-dependent. This hypothesis was subsequently proven when mutations in the *PNPO* gene, which encodes pyridox(am)ine 5'-phosphate oxidase, were demonstrated along with an autosomal recessive mode of inheritance.⁽⁴⁵⁾

Clinical features of PLP-dependent seizures

With the reporting of a few additional infants with PLP-dependent seizures, some clinical features can now be described and contrasted with the characteristics of patients with PDS (Table 1).⁽⁴⁶⁻⁴⁹⁾ In particular, affected patients are almost uniformly born premature and have immediate signs of encephalopathy and seizures, and lactic acidosis and hypoglycemia

are typically present. Clinical seizures may consist of myoclonus, clonic movements and ocular, facial and other automatisms; maternal reports of fetal seizures are also common. The seizures in these infants are resistant to anticonvulsants and pyridoxine, but come under clinical control with the enteral administration of PLP. The EEG demonstrates a burst suppression pattern, also characteristic of Ohtahara Syndrome and nonketotic hyperglycinemia both which may present in similar fashions. PLP treatment results in significant improvement in the EEG, but may first show a transient worsening with significant electrographic depression. Untreated, the disorder results either in death or in profound neurodevelopmental impairment, and brain imaging demonstrates cerebral atrophy and abnormal patterns of myelination. In treated patients, particularly those in whom the disorder was recognized early, many had near normal development. It is important to emphasize that the biochemical changes described above may not be present in all affected patients.⁽⁴⁷⁾ Given that biochemical and genetic testing may take an extended period of time to complete, clinicians caring for newborns with epileptic encephalopathy (particularly for

Table 1. Comparison of Clinical and Metabolic Aspects of PDS and PLP-dependent Seizures

	Pyridoxine-dependent seizures	Pyridoxal phosphate-dependent seizures
Prenatal signs	Occasional <i>in utero</i> fetal seizures	Fetal distress and <i>in utero</i> fetal seizures
Prematurity	Uncommon	Frequent
Postnatal signs	Seizures, gastrointestinal symptoms, encephalopathy	Seizures, encephalopathy
Blood chemistry	Normal	Hypoglycemia and lactic acidosis common
Blood and CSF amino acids	Normal	Elevated glycine and threonine
Urine vanillic acid	Absent	Present
CSF neurotransmitter metabolites	Normal	Increased L-DOPA and 3-methoxytyrosine; decreased homovanillic acid and 5-hydroxyindoleacetic acid
Blood and CSF pipercolic acid	Elevated	Normal
Blood, CSF and urine α -amino adipic semialdehyde (AASA)	Elevated	Normal

Modified from Hoffmann *et al.*⁽⁴⁷⁾

those born prematurely with signs suggestive of hypoxic-ischemic encephalopathy) should initiate prompt therapeutic trials of PLP.

Other pyridoxine and PLP-responsive epileptic disorders

Reports in the literature suggest that other epileptic conditions presenting during infancy are also responsive to pyridoxine and/or PLP. In Japan and Taiwan, pyridoxine or PLP have been used for the treatment of infantile spasms (West Syndrome) as well as some other epileptic syndromes.^(33,50) For the treatment of West Syndrome, the concomitant use of PLP and low dose ACTH has produced high rates of remission of infantile spasms without any reports of serious side effects.⁽⁵⁰⁾ Wang and colleagues compared the effectiveness of both pyridoxine and PLP in the treatment of 94 children between the ages of 8 months and 15 years with intractable idiopathic epilepsy.⁽⁵¹⁾ Eleven of the 94 children responded to PLP with complete seizure control. Of the 11 patients, six had recurrence when PLP was replaced with pyridoxine but again achieved seizure control when PLP therapy was re-instituted, suggesting that PLP was better than pyridoxine. The metabolic and genetic nature of these pyridoxine and PLP responders is not known. While some of the PLP responders may represent unreported phenotypes of pyridox(am)ine 5'-phosphate oxidase deficiency, and some of the pyridoxine responders may represent cases of PDS, it is also possible, as suggested by Baxter,⁽⁵²⁾ that both pyridoxine and PLP (as well as

pyridoxal) may have anticonvulsant effects in these patients, and were therefore not treating any specific metabolic defects. This may be the case for some of the reported patients with late-onset infantile spasms successfully treated with pyridoxine but in whom *ALDH7A1* mutations have not been found,⁽¹⁹⁾ or in some children classified as having PRS.^(2,27,52)

Proposed diagnostic and treatment pathway

In order to assure the best possible prognosis, the prompt diagnosis and treatment of patients afflicted with one of these neonatal vitamin-responsive encephalopathies is essential. For pediatricians, neonatologists and neurologists caring for newborns with seizures, these conditions should not be overlooked as a potential etiology. I would suggest that in a patient with neonatal seizures that are not easily controlled with a first-line anticonvulsant and in whom an obvious infectious, structural, traumatic or cerebrovascular cause is not established, steps should be taken promptly both to conduct biochemical and genetic testing and to initiate therapy with the three important cofactors discussed in this paper (Table 2). DNA should be banked for future gene testing of either *ALDH7A1* or *PNPO* and the urine, plasma and CSF should be collected for biochemical analyses of amino acids, neurotransmitter metabolites, vanillic acid, AASA and PA. The patient should be managed within the neonatal intensive care unit, and if the infant is clinically in status epilepticus or having frequent recurrent seizures, continuous EEG monitoring is recommended. The patient should be started

Table 2. Proposed Diagnostic and Treatment Steps for Anticonvulsant-resistant Neonatal Epileptic Encephalopathy (see text)

Diagnostic studies	CSF for neurotransmitter metabolites and amino acids Blood for amino acids, pipercolic acid, and α -aminoadipic semialdehyde (AASA) Urine for vanillic acid, and AASA Bank DNA for future confirmatory testing of either <i>ALDH7A1</i> or <i>PNPO</i> genes
Therapeutic trials	Pyridoxine 100 to 500 mg intravenously (continuous EEG monitoring recommended if infant is experiencing status epilepticus or frequent clinical seizures) PLP 30 mg/kg/day divided in three or four doses enterally, for three to five days Folinic acid 3 to 5 mg/kg/day enterally, for three to five days
Chronic therapy	For confirmed PDS: pyridoxine 15 to 18 mg/kg/day, and folinic acid 3 to 5 mg/kg/day For confirmed PLP-dependent seizures: PLP 30 to 50 mg/kg/day divided in four to six doses

on enteral PLP at 30 mg/kg/day in three or four divided doses, along with folinic acid at 3 to 5 mg/kg/day, and 100 to 500 mg of intravenous pyridoxine should be administered. Both PLP and folinic acid should be continued for 3 to 5 days and the infant's course should be monitored closely. With such a short term administration of these substances, toxic side effects should not be expected. If the patient has either PDS or PLP-dependent seizures, this treatment regimen should result in substantial clinical improvement. As PLP can be used to treat both PDS as well as PLP-dependent seizures, daily supplementation with pyridoxine would not be needed during this early diagnostic and treatment phase. If this therapeutic trial is successful, and a biochemical and/or genetic confirmation of either PDS or PLP-dependent seizures is established, then chronic therapy with pyridoxine 15 to 18 mg/kg/day and folinic acid 3 to 5 mg/kg/day (for PDS), or PLP 30 to 50 mg/kg/day divided in four to six doses (for PLP-dependent seizures) should be instituted. Unfortunately, in the United States and Europe, preparations of PLP are not readily available in hospital formularies and this can lead to a delay in instituting a therapeutic trial with this particular cofactor.^(32,47) Hopefully with the increasing recognition and understanding of both PDS and PLP-dependent seizures, the availability of PLP will improve. Tertiary care centers that include neonatal intensive units should consider adding PLP to their formulary.

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