# Folinic Acid–Responsive Seizures Are Identical to Pyridoxine-Dependent Epilepsy

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**Objective:** Folinic acid–responsive seizures and pyridoxine-dependent epilepsy are two treatable causes of neonatal epileptic encephalopathy. The former is diagnosed by characteristic peaks on cerebrospinal fluid (CSF) monoamine metabolite analysis; its genetic basis has remained elusive. The latter is due to α-aminoadipic semialdehyde (α-AASA) dehydrogenase deficiency, associated with pathogenic mutations in the *ALDH7A1 (antiquitin)* gene. We report two patients whose CSF showed the marker of folinic acid–responsive seizures, but who responded clinically to pyridoxine. We performed genetic and biochemical testing of samples from these patients, and seven others, to determine the relation between these two disorders.
**Methods:** CSF samples were analyzed for the presence of α-AASA and pipecolic acid. DNA sequencing of the *ALDH7A1* gene was performed.
**Results:** Both patients reported here had increased CSF α-AASA, CSF pipecolic acid, and known or likely pathogenic mutations in the *ALDH7A1* gene, consistent with α-AASA dehydrogenase deficiency. Analysis of CSF samples from seven other anonymous individuals diagnosed with folinic acid–responsive seizures showed similar results.
**Interpretation:** These results demonstrate that folinic acid–responsive seizures are due to α-AASA dehydrogenase deficiency and mutations in the *ALDH7A1* gene. Thus, folinic acid–responsive seizures are identical to the major form of pyridoxine-dependent epilepsy. We recommend consideration of treatment with both pyridoxine and folinic acid for patients with α-AASA dehydrogenase deficiency, and consideration of a lysine restricted diet. The evaluation of patients with neonatal epileptic encephalopathy, as well as those with later-onset seizures, should include a measurement of α-AASA in urine to identify this likely underdiagnosed and treatable disorder.

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Folinic acid–responsive seizures and pyridoxine-dependent epilepsy are two causes of treatable neonatal epilepsy and, therefore, are of particular interest to neurologists, neonatologists, and clinical geneticists.[1] Folinic acid–responsive seizures have been an enigmatic clinical and biochemical entity of unknown etiology. Patients present with seizures,[2–6] either myoclonic[6] or clonic,[5,6] apnea,[4,5] and irritability[2,4] within 5 days after birth. The electroencephalogram (EEG) shows a discontinuous background pattern with multifocal spikes or sharp waves.[3–6] Most patients develop brain atrophy and white matter abnormalities.[2–4,6] A characteristic pattern of peaks, reflecting two unidentified compounds, was recognized in the cerebrospinal fluid (CSF) when analyzed by high-performance liquid chromatography (HPCC) with electrochemical detection to quantify monoamine metabolites.[2,6] This led to the recognition of multiple other affected children[2–5] (Table 1). One child was serendipitously given folinic acid, and had persistent seizure cessation.[2,3] In others, the response to folinic acid was variable, including responsiveness to folinic acid alone or to combination therapy.[2–6] Interestingly, in the first report, one individual responded to pyridoxine alone.[2] Another was initially responsive to pyridoxine, but then became resistant and responded to folinic acid.[5] The response to treatment has been variable. All surviving patients were developmentally delayed, and 5 of 10 reported cases were

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*Table 1.* **Published Cases of Folinic Acid–Responsive Seizures**

| Case No. | Seizure Onset | Pyridoxine Response | Folinic Acid Response | Outcome | Publications |
|---|---|---|---|---|---|
| 1 | Day 5 | Partial response[a] | Complete response[a] | Developmental delay, hydrocephalus, brain atrophy | Hyland and colleagues[2]: Case 1 Torres and colleagues[3]: Case 1 |
| 2 | 6 hours | Not done | Partial response[a] | Death at 2.5 months | Hyland and colleagues[2]: Case 2 |
| 3 | 8 hours | Complete response[b] | Not done | Mild developmental delay | Hyland and colleagues[2]: Case 3 |
| 4 | 2 hours | No response to single-dose intravenous administration | Complete response[a] | Developmental delay, brain atrophy | Torres and colleagues[3]: Case 2 |
| 5 | Day 2 | Not done | Response after 5 days[b] | White matter abnormality: frontal and parietal, hypotonia, developmental delay | Torres and colleagues[3]: Case 3 |
| 6 | 9 hours | Not done | Complete response after 24 hours[a] | White matter abnormality, developmental delay, deceased | Frye and colleagues[4]: Case 1 |
| 7 | 7 hours | Initial response, then recurrences[a] | Complete response, but recurrences[a] | Moderate-to-severe mental retardation | Nicolai and colleagues[5]: Case 1 |

Response to treatment with either folinic acid or pyridoxine and neurodevelopmental outcome in patients previously published with folinic acid–responsive seizures.[2-5] This table does not include three untreated siblings, all of whom had died.
[a]Treatment included other medications.
[b]Monotherapy.

deceased, including 2 treated with folinic acid.[2–5] The cause of the condition has remained unresolved. The chemical identity of the diagnostic compounds has not been determined, and no abnormality of folate metabolism or transport has been identified.[2,6]

Pyridoxine-dependent epilepsy is another treatable cause of early infantile epileptic encephalopathy.[7–10] Seizures usually develop within hours to days after birth[8]; late-onset variants have also been noted.[11] Multiple seizure types have been described.[8] Irritability, restlessness, and vomiting may occur.[8] The EEG often shows burst suppression, hypsarrhythmia, or multifocal spike-wave discharges. In the classic description, seizures are often resistant to anticonvulsants but cease within an hour of administration of 50 to 100mg pyridoxine intravenously. Until recently, diagnostic criteria included: (1) complete cessation of seizures with pyridoxine, (2) seizure recurrence with pyridoxine withdrawal, and (3) seizure cessation after reintroduction of pyridoxine. Few patients underwent a formal pyridoxine challenge, and the recent identification of the genetic basis of the disorder, as well as the description of a reliable biomarker, now allow for an accurate diagnostic evaluation.[12,13]

Most individuals with pyridoxine-dependent epilepsy have deficient enzyme activity of α-aminoadipic semialdehyde (α-AASA) dehydrogenase associated with two pathogenic mutations in the *ALDH7A1 (antiquitin)* gene.[12,13] The enzyme substrate α-AASA is increased in blood, urine, and CSF.[12–14] The enzyme functions in the brain-specific pathway of lysine catabolism via pipecolic acid (Fig 1). α-AASA is in equilibrium with the cyclic compound $\Delta^1$-piperideine 6-carboxylate, which forms an adduct with pyridoxal-5-phosphate, the active vitamer of vitamin B6, via a Knoevenagel reaction.[12] It is hypothesized that seizures are due to functional depletion of pyridoxal-5-phosphate in the brain, with an effect on metabolism of neurotransmitters such as glutamate and GABA.[12,15,16] Treatment with pyridoxine is presumed to overcome the depletion.

Evaluation for both pyridoxine-dependent epilepsy and folinic acid–responsive seizures is considered important for an infant with intractable seizures. These have been believed to be two distinct disorders, each responsive to a different vitamin cofactor.[1] In this report, we describe two patients with early infantile epileptic encephalopathy who exhibited the characteristic peak pattern of folinic acid–responsive seizures on CSF monoamine metabolite analysis, but who were responsive to pyridoxine. Investigation for pyridoxine-dependent epilepsy identified increased α-AASA in CSF and two known or likely pathogenic mutations in the *ALDH7A1 (antiquitin)* gene, confirming a diagnosis of α-AASA dehydrogenase deficiency, and indicating that folinic acid–responsive seizures are identical to

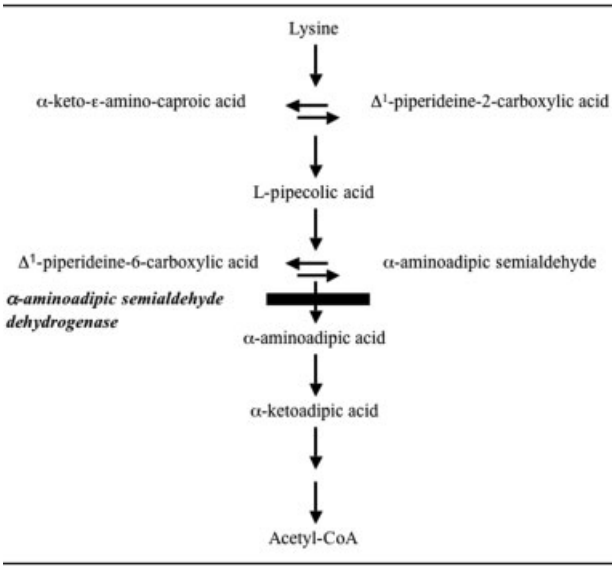


*Fig 1. Pathway of presumed brain lysine metabolism. CoA = coenzyme A. Solid bar = site of block in 2-AASA dehydrogenase deficiency.*

pyridoxine-dependent epilepsy. Results from additional patients further support this conclusion.

## Patients and Methods

### *Case Reports*

PATIENT 1.

Patient 1, the first child of nonconsanguineous parents, was born by uncomplicated vaginal delivery at term. He had jitteriness, poor sleep, and myoclonic jerking movements in the first 2 days of life. An EEG showed an immature discontinuous pattern. Brain imaging by computed tomography and magnetic resonance imaging showed small hemorrhages and a large cisterna magna. A sepsis evaluation and metabolic screening tests were nondiagnostic. He was treated with phenobarbital. At discharge on day 11, he had hypertonia of the lower extremities and sun-setting of the eyes. After 2 days, jitteriness returned, he had increased alertness, decreased oral intake, and was not sleeping. On readmission on day 14, he had cortical thumbs, bilateral ankle clonus, multiple episodes of myoclonus not associated with epileptiform discharges, and a burst suppression background on EEG. He had electrical seizures indicated by paroxysmal fast activity on EEG that was associated with lip smacking. His presentation was consistent with a severe early infantile epileptic encephalopathy. After obtaining blood and CSF samples, a dose of 100mg pyridoxine was administered intravenously under EEG monitoring with no clinical or EEG changes. He continued to receive phenobarbital, topiramate therapy was added, and an oral trial of folinic acid 5mg/day (1.5mg/kg/day) and pyridoxine 50mg/day (15mg/kg/day) was given. After several days, no more seizures or myoclonus were noted, and he was more alert. The EEG was improved though still moderately abnormal because of periods of relative discontinuity during wakefulness and sleep, and multifocal spikes suggesting a global abnormality. A stepwise withdrawal of vitamin cofactors was performed. One week after stopping pyridoxine, and 5 days after stopping folinic acid, he again exhibited decreased sleep, increased jitteriness, and myoclonus. The peaks characteristic of folinic acid–responsive seizures were reported to have been identified in CSF monoamine metabolite analysis. Folinic acid was restarted at 5mg/day and was increased to 20mg/day (5mg/kg/day) with no change in clinical symptoms. He also received additional phenobarbital. After 5 days without response to folinic acid therapy, a single 50mg oral dose of pyridoxine had a dramatic effect. Within 30 minutes there was marked decrease in tone, decrease in startle, and absence of myoclonus. As a result of this clinical response, further laboratory investigations for pyridoxine-dependent epilepsy were initiated. Plasma pipecolic acid, obtained before pyridoxine therapy, was increased at 14.0μmol/L (reference value, <3.9). In CSF, the α-AASA level was 14μmol/L (reference value, <0.1) and pipecolic acid was 9.5μmol/L (reference value, <0.12). Two mutations were identified in *ALDH7A1* (Table 2). These results confirmed a diagnosis of α-AASA dehydrogenase deficiency, or pyridoxine-dependent epilepsy. He remains on folinic acid therapy at 20mg/day (1.6mg/kg/day) and pyridoxine at 15mg/kg/day. He is no longer receiving anticonvulsants. He has no seizures, myoclonus, or sleep disturbance. Three months after restarting pyridoxine and folinic acid the EEG was normal. At 18 months, he had global developmental delay and hypotonia. A lysine-restricted diet, proposed for the potential benefit of decreasing the formation of the presumed toxic α-AASA, was declined by the parents.

PATIENT 2.

Patient 2 was born to nonconsanguineous parents after an uncomplicated pregnancy and delivery. His mother reported shaking movements of his legs and twitching eye movements since 1 month of age. At 2 months of age, he was admitted to the local hospital because of clusters of twitching eye deviation to the left, and jerking of arms and legs lasting from 30 seconds up to 10 minutes, accompanied by irritability and prolonged crying. An infectious workup had negative results. A cranial computed tomographic scan was unremarkable apart from an enlarged cisterna magna. The infant received antibiotics, acyclovir, and a loading dose of phenytoin. He had persistent clonic movements of his legs and was transferred to a tertiary care center. He was given a loading dose of phenobarbital 10mg/kg followed by a maintenance dose of 5mg/kg/day. A sleep EEG performed after phenytoin and phenobarbital loading showed no epileptiform or electrical seizure activity. He continued to have jerking movements, and he was still encephalopathic. Oral pyridoxine, 100mg twice daily, was added to his treatment. With this therapy the jerking movements improved gradually, though this could not clearly be attributed to the pyridoxine treatment. Phenytoin was discontinued at discharge; he remained on phenobarbital and pyridoxine therapy. He remained hypotonic, and further diagnostic evaluation was initiated.

A CSF sample collected at age 4 1/2 months showed the two peaks on monoamine metabolite analysis characteristic of folinic acid–responsive seizures, and folinic acid, 10mg twice daily (3mg/kg/day), was added to his treatment. At age

***Table 2.*** **Concentrations of α-Aminoadipic Semialdehyde and Pipecolic Acid in Cerebrospinal Fluid Samples from Patients Previously Classified with Folinic Acid–Responsive Seizures, and Mutations Detected in the *ALDH7A1 (Antiquitin)* Gene**

| Subjects | α-AASA (μmol/L) | Pipecolic Acid (μmol/L) | Mutations | Deduced Effect |
|---|---|---|---|---|
| Patient 1[a] | 14.0 | 9.5 | c.248G>A[b]/c.1208C>T | p.Gly83Glu[b]/p.Pro403Leu |
| Patient 2[a] | 8.2 | 3.0 | c.750G>A[c]/c.1195G>C | r.748_787del[c]/p.Glu399Gln |
| Anonymous 1 | 11.7 | 6.9 | c.1208C>T/c.1208C>T | p.Pro403Leu/p.Pro403Leu |
| Anonymous 2 | 12.6 | 4.8 | c.890C>G[b]/c.1405+5G>A[c] | p.Thr297Arg[b]/splice error[c] |
| Anonymous 3 | 5.5 | 1.4 | c.1195G>C/c.1195G>C | p.Glu399Gln/p.Glu399Gln |
| Anonymous 4 | 4.1 | 1.4 | c.248G>A[b]/c.410G>T[b] | p.Gly83Glu[b]/p.Gly137Val[b] |
| Anonymous 5 | 4.9 | 5.2 | c.107delA[b]/c.1274A>G[b] | p.Glu36GlyfsX14[b]/ p.Gln425Arg[b] |
| Anonymous 6 | 2.3 | 2.1 | c.1263T>A[b]/[d] | p.Asn421Lys[b]/[d] |
| Anonymous 7 | 1.9 | 1.3 | c.419_422delTCTT[b]/ c.1197G>T[b] | p.Ile140SerfsX10[b]/ p.Glu399Asp[b] |
| Control subjects | <0.1 | <0.12 | | |

[a]DNA analysis of the parents showed that each parent was a carrier of one of the mutations, confirming compound heterozygosity of their child.
[b]Novel mutation.
[c]These mutations have been reported to result in erroneous splicing.[18,26]
[d]Second allele not identified because of lack of sufficient recovery of DNA.
AASA = aminoadipic semialdehyde.

12 months, laboratory testing for pyridoxine-dependent epilepsy was initiated because two episodes of breakthrough seizures had each occurred after he had run out of pyridoxine 2 days prior. Urine contained increased α-AASA of 32.7mmol/mol creatinine (reference value, <1.0), and a stored CSF sample showed increased α-AASA of 8.2μmol/L (see Table 2). Plasma pipecolic acid was 7.9μmol/L (reference value, <4.2), and pipecolic acid in CSF was 3.0μmol/L (see Table 2). DNA sequencing identified two pathogenic mutations in the *ALDH7A1* gene (see Table 2). At 13 months, an EEG showed normal background activity but some frontal sharp wave activity during sleep. Magnetic resonance imaging and magnetic resonance spectroscopy of the parietal white matter and basal ganglia were normal. Phenobarbital was tapered off without seizure recurrence. At 19 months, he had mild-to-moderate developmental delay with lack of active speech. He remains on pyridoxine 24mg/kg/day and folinic acid 2.4mg/kg/day.

### *Methods*

Patient samples were examined after obtaining informed consent. The study was approved by the institutional review board.

#### BIOCHEMICAL METHODS.

CSF was analyzed for monoamine metabolites by high-performance liquid chromatography with electrochemical detection.[3] CSF samples from Patients 1 and 2, and from seven other anonymized patients previously diagnosed with folinic acid–responsive seizures, were analyzed for the presence of α-AASA using liquid chromatography tandem mass spectrometry.[12]

#### *Mutation Analysis*

DNA was isolated using standard techniques from blood or CSF of Patients 1 and 2 and their parents, and from anonymized CSF samples of the seven others diagnosed with folinic acid–responsive seizures. The 18 exons of *ALDH7A1,* including the intron-exon junctions, were amplified by polymerase chain reaction as previously described using the listed primers extended with M13 tails.[19] Purified polymerase chain reaction products were directly sequenced using an ABI PRISM 3130XL or 3730 Genetic Analyzer (Applied Biosystems, CA, USA) and analyzed using Mutation Surveyor (Softgenetics, PA) or CodonCode Aligner software (CodonCode Corporation Dedham, MA).

## Results

Analysis of CSF of Patients 1 and 2 and of seven further patients previously identified with folinic acid–responsive seizures showed increased α-AASA and pipecolic acid in all cases (see Table 2). DNA sequencing demonstrated that Patient 1 is a compound heterozygote for the known pathogenic mutation[17] c.1208C>T, p.Pro403Leu (paternal allele) in exon 14 and a novel DNA sequence alteration: c.248G>A, and p.Gly83Glu (maternal allele) in exon 4 of the *ALDH7A1* gene. Patient 2 is a compound heterozygote for the common mutation[13] c.1195G>C: p.Glu399Gln (paternal allele)

in exon 14 and the c.750G>A mutation[18] (maternal allele), which has been proved to result in erroneous splicing (r.748_787del; p.Val250GlyfsX23). Sequencing of DNA of the seven anonymized patients with folinic acid–responsive seizures identified two DNA sequence alterations that are likely to be pathogenic mutations in the *ALDH7A1* gene in all but one of seven patients (see Table 2). Insufficient DNA was retrieved from CSF of Patient 6 to complete the sequence analysis (only half of the exons were fully sequenced), and only one DNA sequence alteration was identified. The c.248G>A, c.410G>T, c.890C>G, c.1197G>T, c.1263T>A, and c.1274A>G missense alterations were not encountered in 210 control alleles. All involve amino acids that are highly conserved in evolution.[18]

As a result of the recognition that folinic acid–responsive seizures is allelic with α-AASA dehydrogenase deficiency, a relation between α-AASA and the peaks characteristic of folinic acid–responsive seizures was investigated. A highly significant correlation was found between the CSF concentrations of α-AASA and the larger of the unknown peaks ($p < 0.0005$; $R = 0.95$; Fig 2).

## Discussion

We report two patients with severe neonatal epileptic encephalopathy, diagnosed with folinic acid–responsive seizures by CSF monoamine metabolite analysis, who responded to pyridoxine according to clinical diagnostic criteria. Patient 1 did not respond to folinic acid or to a single dose of intravenous pyridoxine, but did respond to pyridoxine in two cofactor trials. Patient 2 apparently responded to pyridoxine and had recurrence of seizures with discontinuation of pyridoxine. The interpretation of a clinical response to pyridoxine may be difficult to assess because the initiation of pyridoxine may be concurrent with a change in dose of an antiepileptic medication, the initiation of a new antiepileptic medication, or the use of other vitamin cofactors. Conversely, pyridoxine may have an antiepileptic effect in individuals without α-AASA dehydrogenase deficiency.[8] In the two patients reported here, α-AASA dehydrogenase deficiency was confirmed by the identification of increased α-AASA in CSF and two mutations in the *ALDH7A1* gene. Three of the four mutations identified in these two individuals have been reported in patients with pyridoxine-dependent epilepsy caused by α-AASA dehydrogenase deficiency,[12,18] the fourth mutation (p.Glu83Gln), which is novel, was also detected in one of the anonymous patients and involves a highly conserved amino acid, suggesting that it is pathogenic. These results indicated that folinic acid–responsive seizures are identical to pyridoxine-dependent epilepsy.

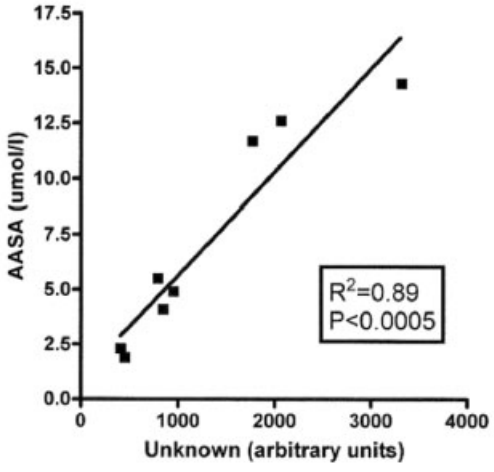


*Fig 2. Association between aminoadipic semialdehyde (AASA) and one of the unknown folinic acid–responsive peaks seen in cerebrospinal fluid. The concentrations of AASA were determined by tandem mass spectrometry (MS/MS), and the relative amounts of the unknown were determined by comparing integrated areas after high-performance liquid chromatography separation and electrochemical detection.* $R^2 = 0.89$; $p < 0.0005$.

To confirm this, we analyzed additional anonymous CSF samples from seven other patients who had been diagnosed biochemically with folinic acid–responsive seizures. In these samples, α-AASA level was increased, and DNA sequencing showed mutations in *ALDH7A1* that were not detected in 210 control alleles (see Table 2). Two additional individuals were homozygous for known pathogenic mutations in *ALDH7A1* that have been described previously in pyridoxine-dependent epilepsy (see Table 2: Anonymous 1 and 3). In five of the anonymous individuals, nine DNA sequence alterations were identified, eight of which are novel. One mutation (p.Glu399Asp) involves a highly conserved amino acid that is altered in the common p.Glu399Gln mutation,[12,18] and one (p.Glu83Gln) was also identified in Patient 1. Two mutations can be presumed to be pathogenic because they are frameshifts leading to stop codons. The other four novel mutations cause substitutions of amino acids that are highly conserved in evolution, suggesting that these mutations also are pathogenic; confirmation of the pathogenicity of the six novel missense mutations reported here will depend on their identification in additional affected individuals, and/or expression of the mutant allele and enzyme assay. The results in these seven additional patients confirmed the initial findings of increased CSF α-AASA and known or likely pathogenic mutations in *ALDH7A1* in patients diagnosed with folinic acid–responsive seizures. Our conclusion that folinic acid–responsive seizures and pyridoxine-dependent epilepsy are identical rests on the identification of three individuals (see Table 2: Patient 2, Anonymous 1, and Anonymous 3) with the CSF findings of folinic acid–

responsive seizures who also have increased CSF α-AASA and two *ALDH7A1* mutations that have been described previously in pyridoxine-dependent epilepsy.

These results demonstrate that folinic acid–responsive seizures and pyridoxine-dependent epilepsy are allelic; indeed, the molecular genetic basis of the two conditions is identical in at least some cases. In addition, analysis of CSF from four patients with pyridoxine-dependent epilepsy on the basis of confirmed α-AASA dehydrogenase deficiency demonstrated the presence of the unknown peaks characteristic of folinic acid–responsive seizures in CSF monoamine metabolite analysis, indicating that the disorders are also identical biochemically (C. Jakobs, K. Hyland, unpublished observations). The high degree of correlation between the concentration of one of these unknown peaks and that of α-AASA (see Fig 2) is further evidence that they reflect the same pathogenic process. Despite this insight, the chemical nature of the compounds associated with these peaks remains unresolved. Results indicate that they do not correspond to α-AASA, $\Delta^1$-piperideine 6-carboxylate, or its pyridoxal-5-phosphate adduct. There is no evidence of a Knoevenagel reaction between $\Delta^1$-piperideine 6-carboxylate and formyltetrahydrofolate (folinic acid) or 5-methyltetrahydrofolate (E. A. Struys, C. Jakobs; unpublished results). CSF methyltetrahydrofolate was normal in Patient 2 (162nmol; reference range, 40–240nmol). Pyridoxine and folate are both involved in homocysteine metabolism, but plasma homocysteine was normal in Patient 1 (5.4μmol/L; reference value, <11μmol/L). Thus, the biochemical relation with folinic acid is not yet evident, and we can advance no hypothesis for the response to folinic acid, alone or in conjunction with pyridoxine, observed in some patients with α-AASA dehydrogenase deficiency. It has not yet been determined whether the peaks characteristic of folinic acid–responsive seizures decrease with pyridoxine therapy alone; a decrease in these peaks has been reported in response to folinic acid therapy.[2]

Recognition that folinic acid–responsive seizures and pyridoxine-dependent epilepsy are identical has several important clinical implications.

First, patients previously diagnosed with folinic acid–responsive seizures should be treated with pyridoxine, because the basis of this therapy is understood and pyridoxine therapy has been shown to be efficacious. As there has been high mortality in individuals with folinic acid–responsive seizures, the addition of pyridoxine therapy may be life-saving for some. Only three of the seven fully reported individuals with folinic acid–responsive seizures received oral pyridoxine (see Table 1). One was successfully treated with pyridoxine monotherapy (Case 3), which is now explained by our results.

Second, the absence of a clinical response in Patient 1 (this report) and in Case 4 (see Table 1) to a single dose of intravenous pyridoxine indicates that an oral pyridoxine trial should be performed with a sufficient dose (30mg/kg/day) over at least 3 consecutive days to assess pyridoxine responsiveness, because some affected individuals have no clinical or EEG response to an intravenous pyridoxine dose.

Third, two individuals reported to have folinic acid–responsive seizures had some response to pyridoxine (see Table 1: Cases 1 and 7), but when seizures recurred, they were controlled with the addition of folinic acid, leading to the designation folinic acid–responsive seizures. This indicates that folinic acid therapy may be of added benefit in at least some patients with α-AASA dehydrogenase deficiency, though the biochemical basis for this is unclear. The presence of the abnormal peaks associated with clinical response to folinic acid, the reduction of this biochemical abnormality with folinic acid therapy,[2] and the clinical response of some patients to folinic acid treatment all argue for the addition of folinic acid. Therefore, we recommend consideration of treatment with both pyridoxine and folinic acid in patients with α-AASA dehydrogenase deficiency. Current therapy with pyridoxine alone provides seizure control but is insufficient for optimal developmental outcome in many patients, even with extremely high doses and prenatal treatment.[19-23] Despite combined cofactor therapy, Patients 1 and 2 have developmental delay, and the impact of combined treatment must be determined. In addition, rather than separate, sequential testing with pyridoxine and folinic acid,[1] we recommend an intravenous dose of 100mg pyridoxine, followed by pyridoxine 30mg/kg/day for 3 to 7 days, optionally combined with folinic acid, 3 to 5mg/kg/day, to assess clinical responsiveness. It is also important that the evaluation of neonates and infants with epileptic encephalopathy include the measurement of α-AASA in urine, a reliable laboratory test for α-AASA dehydrogenase deficiency.[24]

Finally, we also suggest that a lysine-restricted diet be considered, to reduce the accumulation of the presumed neurotoxin α-AASA. Ideally, optimal treatment would be determined by long-term, controlled trials of affected individuals treated with pyridoxine alone, pyridoxine plus folinic acid, and these therapies with or without a lysine-restricted diet.

In conclusion, folinic acid–responsive seizures are caused by α-AASA dehydrogenase deficiency, as is the most common form of pyridoxine-dependent epilepsy. These two forms of treatable seizures appear to be genetically and biochemically identical. This new understanding must lead to reevaluation of optimal strategies for diagnosis, treatment, and patient monitoring of infants with α-AASA dehydrogenase deficiency. We recommend consideration of treatment with both pyridoxine and folinic acid for patients with this condition,

as well as consideration of limitation of lysine in the diet to reduce α-AASA levels.

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