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ORIGINAL PAPER

Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry

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Abstract To facilitate clinical research on pyridoxine-dependent seizures (PDS), a rare disease registry was established for affected patients in the United States and Canada. From 1999 to 2007, 63 cases, ranging in age from 11 months to 40 years, were registered. All registered cases were diagnosed with PDS by their physicians using clinical criteria. Seventy percent of the cases presented with neonatal seizures, and the mean lag time between presentation and diagnosis was 313 days. Pyridoxine treatment regimens were varied, ranging from 50 to 2,500 mg per day (1.4 to 67.8 mg/kg/day). While 47 of the cases were seizure-free on pyridoxine monotherapy, over time, eight other cases also required the concomitant use of anticonvulsants for effective seizure control, while the remainder continued to have recurrent seizures, despite the use of pyridoxine and multiple anticonvulsants. Our review of this collection of cases suggests that, for some registered individuals, either pyridoxine may be acting as an adjunctive anticonvulsant or the patient may have developed a secondary etiology for seizures. In addition, some of these cases may have pyridoxine-responsive seizures (PRS) rather than pyridoxine-dependency. Four adult and seven school-aged cases were described as developmentally normal, while the other cases had a variety of neurodevelopmental

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handicaps. Twenty-five percent of the cases required the pharmacologic treatment of behavioral symptoms. Clinicians caring for neonates and other young patients with intractable seizures do not necessarily consider PDS as an etiology; therefore, certain cases may be undiagnosed or diagnosed late in the course of their evaluation and treatment. As the diagnosis of PDS can now be confirmed by genetic and biochemical testing, formal screening protocols for this disorder should be developed. Patients previously diagnosed with PDS by clinical criteria should also receive confirmatory testing.

Keywords Pyridoxine-dependent seizures · Pyridoxine-responsive seizures · *ALDH7A1* · Antiquitin · Pipecolic acid · α-aminoadipic semialdehyde

Abbreviations

PDS	Pyridoxine-dependent seizures
PRS	Pyridoxine-responsive seizures
PA	Pipecolic acid
AASA	α-aminoadipic semialdehyde
P5P	Pyridoxal-5-phosphate
OCD	Obsessive compulsive disorder
AD	Autistic disorder
PDD	Pervasive developmental disorder, not otherwise specified
BPSU	British Paediatric Surveillance Unit

Introduction

Pyridoxine-dependent seizures (PDS) are a rare autosomal recessive inborn error of metabolism (MIM226100) that result in intractable neonatal or early infantile seizures, which are controlled only after treatment with daily pharmacologic doses of pyridoxine (vitamin B_6). Since the initial description of this disorder in 1954 [20], over 100 cases have been reported, with many cases having been described over the past 15 years [4, 14, 18]. These more recent reports have stressed a variety of later onset (i.e., after 28 days of age) and other atypical clinical presentations of PDS [2, 10, 11, 16, 17, 39], along with imaging [1, 5, 15, 36] and neurophysiology findings [24, 27] and epidemiological aspects [3, 5, 7, 12] of the condition.

While the relatively recent description of elevations in plasma pipecolic acid (PA) [30, 31] and α-aminoadipic semialdehyde (AASA) [9, 32, 37] in PDS patients, together with the subsequent discovery of causal mutations in the *ALDH7A1* (antiquitin) gene [22, 26, 34], will eventually change how this condition is diagnosed, PDS has traditionally been suspected and confirmed entirely on clinical grounds. PDS is clinically diagnosed by demonstrating that a newborn or young child with previously intractable seizures achieves complete seizure control once high doses of pyridoxine are added to the daily treatment regimen and then maintains this seizure control following the withdrawal of all anticonvulsants. The diagnosis of PDS is not considered to be confirmed until the pyridoxine is subsequently withdrawn, followed by a reoccurrence of clinical seizures that are, again, successfully treated with pyridoxine. In very uncommon circumstances, some patients felt to have PDS do not have a return of clinical seizures after the withdrawal of pyridoxine, suggesting that their epileptic disorder is not dependent upon the vitamin. Baxter has proposed that this represents a different clinical entity and that patients who demonstrate these clinical features should be designated as having pyridoxine-responsive seizures (PRS) [3].

Baxter has suggested that only patients who fit the strict set of clinical criteria noted above should be designated as having definite PDS. He defined possible cases as those where no trial of pyridoxine withdrawal was performed, and, therefore, some of these may represent true cases of PRS. A third category, probable cases, has been defined as individuals who either have seizures that are controlled by pyridoxine and a similarly affected sibling who presented at the same age or who have a history of neonatal seizures that responded to a single dose of pyridoxine, followed by a later recurrence of seizures that, again, were controlled with pyridoxine, which was then continued. As with the definition of possible instances of PDS, a formal trial of pyridoxine withdrawal was not attempted for these probable PDS cases [3].

To facilitate clinical research on PDS, a registry was established for patients in the United States and Canada diagnosed with the disorder. This registry was designed to obtain information about the presentation, natural history, and treatment of these patients, and to serve as a clearing house for other investigators seeking cases of this rare disorder for inclusion in new studies. This paper describes an analysis of the clinical information that has been provided to the registry since its inception in 1999.

Methods

The PDS patient registry was established at the University of California, Davis, CA, in 1999 and then moved to the Children's Hospital and Regional Medical Center in Seattle, WA, in 2000; the human subjects committees of both institutions have approved the protocol of the registry. The establishment of the registry was initially disseminated via announcements in journals that focused on child neurology, the newsletter of the Child Neurology Society, various list serves, and via a dedicated web site. The registry was

notified about potential cases either by physicians caring for PDS patients or by the parents of individual patients. For a case to be considered for the registry, either the referring physician indicated that the patient carried a diagnosis of PDS or the parent stated that the child had been given the diagnosis and that the condition was being specifically managed by a physician. Once the registry was notified of a case, the parent was then sent information about the registry together with an informed consent document and a medical information release form. After the signed forms were returned to the registry, the parent was then contacted by telephone so that the registry project could be discussed in detail, and informed consent could be also documented verbally. Subsequently, specific questionnaires were sent to the parents and the medical provider designated by the parent. While both questionnaires contained some similar queries regarding the natural history and treatment of the cases, the parent questionnaire requested information regarding family history, development, and school progress, while the physician questionnaire focused on the medical aspects of the case. The provider was given the option of returning relevant medical records to the registry in place of (or in addition to) the questionnaire. For instances in which informed consent was obtained, but in which one or both questionnaires were not returned, the parents and/or physicians were contacted on a regular basis to remind them of the program and to encourage their participation. Finally, in order to acquire the most current clinical information, a brief follow-up questionnaire was sent to the parents of cases who were registered more than two years before the analysis for this report was conducted.

Results

Demographics of registry cases

Between August 1999 and July 2007, the registry was contacted about 85 cases, 64 from parental referral and the remainder from physician referral. The registry was also informed about several cases from non-English-speaking regions of the Western Hemisphere, as well as from other parts of the world. However, participation in the registry required the use of English for the completion of the questionnaires, along with electronic correspondence and telephonic conversations (originating primarily during Pacific Coast business hours) with the parents and providers. Therefore, only cases residing in the United States and Canada were registered. Of these 85 individuals, the parents of 70 completed the informed consent process. A case was considered to be registered if one or both of the parent and physician questionnaires were subsequently returned; as such, 65 cases were registered. Of the five consented but unregistered cases, three cases were withdrawn either due to the inability of the registry personnel to contact the parents and physicians after consent had been obtained or because the parents were no longer interested in participating. The other two consented but unregistered cases were withdrawn because the parents indicated that the diagnosis of PDS was no longer correct. In addition, two registered cases were subsequently withdrawn for the same reason. Therefore, the clinical information for a total of 63 cases (37 males and 26 females) was available for review, with 60 consented cases having the parent questionnaire returned, 56 cases having the physician questionnaire or medical records submitted, and both questionnaires having been returned for 51 cases. Follow-up parent questionnaires were obtained for 47 of the cases. At the time of this analysis, these 63 cases ranged in age from 11 months to 40 years (12.8±9.2 years, mean ± S.D.) and resided in 23 states and three Canadian provinces.

Clinical features of cases

As the clinical aspects of the various cases came from our reviews of a mixture of parent questionnaires, physician questionnaires, and medical records, we were not able to use Baxter's classification scheme for the entire set of cases. Therefore, after reviewing the presentation, management, and clinical course of each of the registered individuals, four specific groups of cases were initially defined as follows: group 1 consisted of 19 cases who achieved complete seizure control on pyridoxine monotherapy and displayed seizure recurrence after the withdrawal of pyridoxine, i.e., definite cases by Baxter's criteria [3]; group 2 consisted of 28 cases who had complete control of seizures on pyridoxine monotherapy but who had never had a trial of pyridoxine withdrawal; group 3 included eight cases who initially achieved complete seizure control on pyridoxine but who subsequently developed a seizure relapse that only became under control with pyridoxine in conjunction with the use of one or more anticonvulsants; group 4 included eight individuals who initially achieved complete seizure control on pyridoxine but who subsequently developed a seizure relapse and continued to have clinical seizures, despite the use of pyridoxine and one or more anticonvulsants. Elevated plasma PA levels were documented for two cases within group 1, as well as for four cases within group 2 and one case within group 4; therefore, these five individuals in groups 2 and 4 were considered to have definite PDS and were added to group 1, increasing its total to 24 cases.

As PDS is a familial disorder, it was not surprising that some of the registered cases had one or more affected siblings. The registry included ten families with multiple

cases; one family had three affected children, which included a pair of male dizygotic twins. At least two other families registered their older PDS child but did not register their younger affected children. An additional five registered cases had a sibling with a history of epilepsy who had expired and, thus, were not registered. Four of these deceased individuals were older than their registered sibling but only one of them had been diagnosed with PDS, while the fifth deceased sibling was younger than the registered case and had also been diagnosed with PDS.

The age of presentation, age at the time of diagnosis (i.e., when successful treatment with pyridoxine was initiated), and the length of time between clinical presentation and the initiation of pyridoxine therapy (the delay before treatment) for the four groups are listed in Table 1. Seizure onset was principally within the neonatal age range (less than four weeks of age), with 19 neonatal cases (68%) in group 1, 14 neonatal cases (46%) in group 2, six neonatal cases (75%) in group 3, and five neonatal cases (71%) in group 4. Of the 19 cases that presented with seizures beyond the neonatal period, eight presented at between one and two months of age, and 11 presented later. In particular, two cases in group 1 did not present with seizures until nine months of age and two years of age. A delay in diagnosis and pyridoxine treatment was not uncommon, with the lag in the diagnosis for the entire group averaging 311 days (range 0 days to 8.5 years). This delay was substantially reduced to 39 days (range 0 to 145 days) for the ten kindreds where an older registered child had been previously diagnosed with PDS. For the four additional registered cases who had an older unregistered sibling who had previously expired, the lag in the diagnosis of PDS was also prolonged at 320 days (range 14 days to 2.9 years). Only one of these deceased older siblings had been formally diagnosed with PDS, and in that family, the diagnosis was confirmed in the younger sibling 146 days after presentation. As the clinical recognition of PDS has increased over the past 50 years, we examined the relationship between the decade in which the patient presented with seizures and the length of time needed to make a diagnosis; a significant correlation was not demonstrated.

Information regarding the clinical semiology of seizures was available for 53 cases. Of these, 16 presented with partial seizures, ten with generalized seizures, three with myoclonic seizures, 17 with mixed seizures, and seven with infantile spasms. Six of the cases were believed to have experienced intrauterine fetal seizures. Sixteen of the cases experienced recurrent episodes of status epilepticus, while ten cases were noted to have recurrent bouts of encephalopathy. Thirteen of the cases had an evolution of the seizure semiology prior to the diagnosis of PDS, with two of these cases eventually developing infantile spasms. All seven cases who presented with infantile spasms as the initial seizure type were between three and six and a half months of age; this represents 64% of the late-presenting cases. The two cases where infantile spasms emerged as a secondary type of seizure had the clinical presentation of epilepsy at a younger age, specifically 36 h, and two months. The initial control of clinical seizures with anticonvulsants was noted in 16 of the cases before the seizures became intractable and pyridoxine treatment was considered. While four of the six cases of intrauterine fetal seizures were in group 1 (i.e., definite PDS cases) and nine of the ten cases noted to have recurrent episodes of encephalopathy were in groups 1 and 2, none of the other particular clinical features tended to cluster within any of the four specific groups that we defined.

Management of cases

The total daily dose of pyridoxine and the daily dose by weight of pyridoxine for the four groups are shown in Table 2. For the entire set of cases, pyridoxine doses ranged from 50 mg to 2,500 mg per day, with an average of 354 mg, while the daily dose by weight ranged from 1.0 to 67.8 mg/kg, with an average of 13.1 mg/kg. The amount of pyridoxine used was higher and more variable in group 4, the cases where seizures remain poorly controlled, despite the use of pyridoxine and one or more anticonvulsants. Of note is that one case each in groups 2 and 4 received pyridoxal-5-phosphate (P5P) instead of pyridoxine, while

Table 1 Mean age at presentation, age at diagnosis, lag time to diagnosis, and current age for 63 cases submitted to the pyridoxine-dependent seizures (PDS) registry

Group*	Number of cases	Age at presentation in days (range)	Age at diagnosis in days (range)	Lag time to diagnosis in days (range)	Current age in years (range)
1	24	54 (1 day–2 years)	404 (1 day–7.5 years)	351 (0 days–7.5 years)	14.8 (4–40)
2	24	50 (1–195 days)	282 (7 days–9 years)	232 (0 days–8.5 years)	11.3 (0.9–32)
3	8	19 (1–42 days)	418 (10 days–6 years)	399 (15 days–6 years)	14 (2.3–34)
4	7	29 (1–90 days)	390 (30 days–3.2 years)	361 (27 days–2.9 years)	10 (3–21)

*Grouping of cases as defined in the text

Table 2 Mean daily total dose and dose by weight of pyridoxine for 63 cases submitted to the PDS registry

Group*	Dose in mg/day (range)	Dose by weight in mg/kg/day (range)
1	248 (50–1,000)	10.7 (1.4–21.2)
2	365 (50–1,250)	12.5 (1.0–34.3)
3	329 (100–600)	9.3 (1.1–18.3)
4	855 (75–2,500)	31.8 (2.1–67.8)

*Grouping of cases as defined in the text

one case each in groups 1 and 4 received P5P in addition to pyridoxine.

A number of the cases were treated with anticonvulsants and other medications, along with their pyridoxine supplements. In particular, one case in group 1 with PDS clinically confirmed in infancy, and subsequently noted to have an elevated plasma PA level, eventually experienced frequent breakthrough seizures. In addition to his pyridoxine therapy, he was treated for several years with the ketogenic diet and now with oxcarbazepine. In other cases, anxiety, tics, attention deficit, mood disturbances, and other psychiatric symptoms required pharmacotherapy. Two of the other cases in group 1 received anticonvulsants, specifically carbamazepine, clonazepam, and lamotrigine, for the treatment of behavioral symptoms. Other psychotropic medications prescribed for four individuals in group 1 include risperidone, escitalopram, fluvoxamine, sertraline, alprazolam, buspirone, and hydroxyzine. While none of the cases in group 2 were receiving anticonvulsants for psychotropic purposes, seven cases were being treated for behavioral or sleep disturbances with medications including guanfacine, clonidine, dextroamphetamine, fluvoxamine, sertraline, risperidone, and chloral hydrate. All eight cases in group 3 and all seven cases in group 4 were treated with one or more anticonvulsants for the management of seizures; their regimens include the use of phenobarbital, primidone, carbamazepine, topiramate, levetiracetam, clonazepam, and vigabatrin. Psychotropic medications including risperidone, clonidine, fluoxetine, and sertraline were prescribed for two cases within group 3 and one case in group 4. Of note is that one case in group 3 and two cases in group 4 also received daily supplements of folinic acid.

Outcomes

The vast majority of the registered cases (55 of the 56 cases within groups 1, 2, and 3) had excellent seizure control. With the exception of one case in group 1 (see above), for these 55 cases, rare seizures were reported only during periods of either acute illness or temporary noncompliance with pyridoxine. The individuals in group 4 continued to have seizures, in one case more than ten times a week. The developmental and behavioral characteristics of 47 cases were provided to the registry by their parents and/or physicians. While a few of the cases were described as having normal development (four in group 1, three in group 2, and one in group 3), including one community college graduate (see below) and two competitive teenage athletes, a wide variety of neurodevelopmental handicaps were described in the other individuals. Twenty-seven of 34 school-aged cases required special education and combinations of physical therapy, occupational therapy, and speech therapy services. Severe neurodevelopmental problems were described more frequently in cases within groups 3 and 4. Four of five cases in group 3 and two of three cases in group 4 were described as having severe developmental delay, with one child noted to have associated obsessive compulsive disorder (OCD) and one with autistic disorder (AD). In groups 1 and 2, only ten of 39 cases were described as having a constellation of severe neurodevelopmental handicaps, with two individuals diagnosed with OCD and five other cases diagnosed with either pervasive developmental disorder, not otherwise specified (PDD) or AD. Eight of the 42 cases had reached adulthood (18–40 years of age). Four of these individuals (all in group 1) lived independently, with three of them working in service industry positions and one also having a driver's license and a two-year community college degree. Another adult in group 1 worked in a sheltered workshop. Of the two adults in group 2, one took life skills courses and read at the third grade level, while another who was previously employed is now disabled due to complications of PDS-associated hydrocephalus. The one adult in group 4 had profound mental retardation and was blind.

As the developmental and behavioral outcome information for the cases was primarily qualitative, and the age range was quite broad, for the most part, it was not possible to accurately evaluate the relationship between developmental outcome and seizure type, the age of seizure onset, and lag time until a diagnosis of PDS was reached. A few observations from the review of this information should be mentioned. Of the six cases with PDD or AD, four had early-onset seizures, two of which evolved into infantile spasms, and the other two presented with late-onset infantile spasms. Unexpectedly, all four of the independent adults in group 1 presented with neonatal seizures, and the lag time until diagnosis was 0, 10, 146, and 363 days, respectively. Of the seven school-aged cases considered to be normal by their parents, three presented with neonatal seizures, with the time to diagnosis ranging from nine to 70 days, while the other four had seizure onset between five and nine months of age, and a lag time to diagnosis ranging from zero to 120 days. While the lag time to a PDS diagnosis in younger siblings was generally (but, surprisingly, not always) much shorter than the time that was required to reach a diagnosis in the older affected sibling,

adequate developmental outcome information was not provided to the registry and it was not possible to determine if an earlier diagnosis resulted in a better outcome in each specific kindred.

Discussion

Prior to the development of this rare disease registry, reports of small case series of PDS patients and various review papers had been published [4, 5, 14, 18], and a few studies of the epidemiology of PDS had been performed [3, 7, 12]. For example, a study conducted throughout the United Kingdom and the Republic of Ireland via the British Paediatric Surveillance Unit (BPSU) noted a point prevalence of definite and probable cases of approximately 1:600,000 [3], while a survey from the Netherlands noted a birth incidence of 1:396,000 [7]. Since clinicians caring for neonates and other young patients with intractable seizures do not necessarily consider PDS as a potential cause of the epileptic encephalopathy in their patients, certain cases may be undiagnosed or diagnosed late in the course of their evaluation and treatment. As such, a study from a German facility, where pyridoxine treatment was part of a protocol for the treatment of neonatal seizures, reported a birth incidence of probable cases of 1:20,000 [12].

To our knowledge, the registry study described herein, which acquired cases from across North America through voluntary reports of both parents and physicians caring for patients with PDS, is the largest set of PDS cases collected by one group of investigators to be reported. As the cases submitted to our registry received their health care from a variety of public and private providers over a large geographic area, the structure of this study does not permit the development of formal epidemiologic findings. However, several general clinical features of the registered cases can be described and compared with those reported previously. Twenty-four of the 63 cases (38%) can be considered as definite examples of PDS, similar to the finding in the BPSU study, where definite cases made up 42% of the 33 reported cases. In his 2001 comprehensive review of previously published PDS cases [4], Baxter noted that fewer than half fulfilled the strict clinical criteria necessary for diagnosing definite PDS. An additional 38% of our cases (the 24 cases within group 2) need to be classified as either probable or possible cases of PDS, as they have complete seizure control with pyridoxine monotherapy, but either the vitamin supplementation has never been withdrawn for the clinical confirmation of a definite diagnosis or the registry was not notified of either the biochemical or genetic confirmation of the diagnosis. As such, some of these cases could represent examples of PRS, and, as suggested by Baxter [3, 4], a variety of explanations for seizure etiology could be suggested, such as transient pyridoxine deficiency due to low maternal intake, a transient neonatal or infantile seizure disorder that coincidentally ceased around the time that pyridoxine treatment was initiated, or forms of infantile spasms that dramatically respond to pyridoxine, some with favorable developmental outcomes such as those which have been reported in the Japanese literature [28]. Indeed, of the eight school-aged children in the registry who were felt by their parents to have appropriate development, three of them presented with infantile spasms and never had a trial of pyridoxine withdrawal; hence, they were placed in group 2 and are either examples of possible PDS or PRS.

As in previous reports, the majority of our cases were of neonatal onset, and a variety of clinical seizure types were described. Intrauterine fetal seizures and episodes of either recurrent status epilepticus or recurrent encephalopathy were noted in many cases. These particular clinical features, while not distinctive, should alert clinicians caring for infants with intractable seizures to initiate a trial of treatment with pyridoxine and, if successful, subsequent biochemical and genetic confirmatory testing. Atypical presentations of PDS were not uncommon, with 19 cases presenting beyond the neonatal age range and 16 cases initially responding to anticonvulsants before seizures became intractable. The BPSU study demonstrated that atypical presentations accounted for just over a third of the cases, similar to the present study [3].

Under accepted clinical criteria, it would be difficult to conclude that the cases in groups 3 and 4 represent examples of PDS. The eight cases in group 3 eventually required the use of one or more anticonvulsants in order to remain seizure-free, and the seven cases in group 4, over time, developed intractable epilepsy, despite the use of pyridoxine and one or more anticonvulsants. In these cases, it is tempting to conclude that these individuals do not have PDS, but that pyridoxine is acting as an adjunctive anticonvulsant. However, one case in group 1, where PDS was confirmed both early in life on clinical grounds and subsequently by demonstrating an elevation of plasma PA, also continues to have frequent seizures, despite the use of pyridoxine and anticonvulsant therapy. Therefore, this individual, along with some of the cases in groups 3 and 4, may have an additional cause of epilepsy, such as hydrocephalus, cortical dysplasia, other forms of brain dysgenesis, or secondary mesial temporal sclerosis, all of which have been described in cases of PDS [4]. The measurement of plasma PA and AASA or testing for mutations in the *ALDH7A1* gene would help determine if these cases in groups 3 and 4 (as well as the cases in group 2) have definite PDS.

A small number of cases received P5P as either the sole source of vitamin B_6 supplementation or in addition to pyridoxine, while a few others also received folinic acid supplementation. In Asia, vitamin B_6 is commonly supplied as P5P, and there has been a recent report of several children with intractable seizures who had a better clinical response to P5P as compared to pyridoxine [38]. In addition, a rare P5P-dependent severe neonatal epileptic encephalopathy (unresponsive to pyridoxine) due to a deficiency of pyridox(am)ine 5′-phosphate oxidase has been described [19, 25, 29], as has a rare condition of folinic acid responsive seizures [13, 21]. As the majority of the patients receiving P5P and/or folinic acid were in group 4 and, therefore, continued to have recurrent seizures, it is unlikely that they have either of these rare conditions, unless secondary causes of epilepsy are also present.

A somewhat broad range of doses of pyridoxine were used to treat the cases and it was not surprising that the seven cases in group 4, on average, were treated with both a higher total daily dose as well as a higher daily dose on a weight basis. Prolonged exposure to high doses of pyridoxine (megavitamin therapy) is well known to lead to a sensory neuropathy that may be profound [35]. In adults, daily pyridoxine doses of 1 g have been shown to lead to both clinical and electrophysiologic evidence of sensory neuropathy after one year of treatment, with a dose–response effect being noted with higher daily doses [8]. The neurotoxic dose of pyridoxine in children has not been established, but clinical and electrophysiologic evidence of sensory neuropathy has been reported in patients with PDS, with one patient receiving 2 g per day [23, 33]. None of the registered patients were reported to have neuropathy by their physicians, but electrophysiologic studies were not reported to the registry.

Presumably, all of the cases reported to the registry have had one or more formal psychoeducational assessments conducted, either through a local school district or a medical or mental health provider. The formal results of such evaluations were not submitted to the registry and, therefore, the developmental outcomes of our cases were qualitative and based primarily on parental descriptions or physician reports. Certainly, the cases described as having normal development could have some deficits in learning that would be demonstrated on psychometric evaluation. A spectrum of neurodevelopmental handicaps associated with PDS, including the delayed acquisition of motor, cognitive, and language milestones, delayed maturation of visual function, varying degrees of learning disabilities, and in some older cases, chronic motor deficits, have been reported previously[4, 6, 18]. Similar constellations of developmental disabilities, as well as OCD, PDD, and AD, along with their psychopharmacologic treatment, were described in many of our cases. It is felt that developmental outcome depends on several factors, including the age at seizure onset, the extent of the delay in diagnosis and the initiation of effective treatment, the use of prenatal pyridoxine supplements in pregnant women who have older children with PDS, and the dose of pyridoxine supplementation administered, with late-onset cases who had a relatively prompt diagnosis and initiation of pyridoxine treatment having a better outcome [4, 18]. Running counter to these reported observations would be our case with the most favorable outcome, a 31-year-old community college graduate who presented with neonatal seizures but was not diagnosed with and treated for PDS until 12 months of age. In addition, a recent report described a kindred with three affected children with neonatal onset PDS and confirmed *ALDH7A1* mutations, and noted moderate to severe learning disabilities in all three, despite prenatal maternal treatment and the immediate postnatal treatment of the two younger siblings, as well as relatively high dose pyridoxine supplementation of between 17 to 22 mg/kg/day for all three children [33]. Taken together, these cases suggest that developmental outcome in PDS may be due more to phenotypic variability than to the timing of diagnosis and the initiation of pyridoxine treatment. As more cases of PDS are genetically confirmed with the mutation testing of *ALDH7A1*, genotype–phenotype correlation studies may enhance our understanding of the natural history of PDS and its treatment.

In summary, the analysis of the 63 cases in this rare disease registry emphasizes the variation in the presentation, natural history, associated behavioral symptoms, and the treatment of this disorder, as well as the amount of time that is generally required for clinicians caring for these patients to consider the diagnosis and initiate treatment. PDS is a rare but highly treatable cause of intractable seizures in infants and young children. A trial of pyridoxine supplementation should be provided to young patients with anticonvulsant resistant seizures, as well as to those with epileptic encephalopathies, such as West and Ohtahara syndromes, early during the course of therapy. The diagnosis of PDS can now be confirmed with genetic testing of the *ALDH7A1* gene, and screening protocols for the disorder by measuring the plasma levels of PA or AASA should be developed.

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