

Pyridoxine dependent seizures—a wider clinical spectrum

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SUMMARY We report 4 infants with pyridoxine dependent seizures who had clinical features that led to diagnostic uncertainty. Their clinical course was unusual in 1 or more of the following: later onset of initial seizures; a seizure free period after taking of anticonvulsants, but before taking of pyridoxine; a long remission after withdrawal of pyridoxine; and atypical seizure type. This report illustrates a broader range of clinical features and highlights the need to consider the diagnosis of pyridoxine dependent seizures in any infant with intractable epilepsy, regardless of the pattern of seizures and the response to anticonvulsant medications. In such a case, 100 mg intravenous pyridoxine should be given and, if a definite clinical response is established, oral pyridoxine should be continued indefinitely.

Pyridoxine dependent seizures were first described by Hurst *et al.*¹ in 1954 and more than 50 cases have been reported since that time. The inheritance pattern is autosomal recessive. It is believed that these fits are caused by defective binding of pyridoxine to its apoenzyme, glutamate decarboxylase, which catalyses the conversion of glutamic acid to gamma-aminobutyric acid, an inhibitory neurotransmitter in the central nervous system. The reduced concentrations of gamma-aminobutyric acid result in a lower seizure threshold.² The typical natural history of pyridoxine dependent seizures is fits beginning within hours of birth which are difficult to control with anticonvulsant drugs but 'turn off' within minutes of the administration of parenteral pyridoxine, after which the baby is often floppy and unresponsive for a period. There may be a history of intrauterine convulsive movements. Fetal distress in labour and meconium stained liquor are common, and the baby may appear asphyxiated at birth. Pyridoxine in pharmacological dosage controls the seizures, but they usually recur within days of stopping pyridoxine and recurrence is often preceded by irritability. Mental development is usually impaired. We report on 4 babies with pyridoxine dependent seizures in whom the clinical presentation and subsequent course have been atypical, suggesting that the manifestations of this disorder may present a broader range than is generally thought. This has important implications for diagnosis.

Case reports

Case 1. A girl, the first child of unrelated parents, was delivered at term by breech extraction after a normal pregnancy. Her Apgar scores were 8 at 1 minute and 10 at 5 minutes, her birthweight was 3410 g, and she had a normal neonatal course and was discharged on day 6. Multifocal motor seizures began on day 8 and were treated with phenytoin. The fits stopped for 5 days but then recurred, and she was admitted to hospital on day 19. A combination of phenytoin and phenobarbitone controlled the fits briefly, but recurrence of seizures necessitated repeated admissions. Anticonvulsant drugs and steroids failed to control her seizures, and at 2 months of age she was treated with thiopentone, assisted ventilation, and intravenous megavitamin treatment, which consisted of pyridoxine 50 mg, thiamine 50 mg, riboflavin 50 mg, pantothenic acid 50 mg, biotin 50 mg (oral), nicotinamide 600 mg, folate 15 mg, ascorbic acid 2000 mg, and vitamin B₁₂ 1 mg. The seizures were controlled and did not recur after the withdrawal of thiopentone. At 3 months of age all vitamins were stopped. Prednisolone was withdrawn over one week, while phenobarbitone, phenytoin, and sodium valproate were continued. On this regimen and a normal diet with no added vitamins she had no fits for 5½ months; she became more alert and responsive to visual and auditory stimuli and her head control improved. At 8 months, however, she

was not rolling over and was unable to sit without support.

The recurrence of multifocal motor seizures occurred at 9½ months. Anticonvulsants failed to control the fits, but they stopped approximately 3 minutes after pyridoxine, 100 mg was given intravenously. They recurred 10 days later and again stopped within 1 minute after 50 mg of intravenous pyridoxine. Maintenance dosage of pyridoxine, 75 mg a day orally, began and other anticonvulsants were stopped. When the child was last seen at one year of age, no further seizures had occurred but her development was delayed—she was now sitting without support, but was unable to crawl or pull herself to standing position.

An electroencephalogram (EEG) at 3 weeks of age showed well defined paroxysmal activity and a periodic pattern of burst suppression type during light sleep, but two weeks later it was normal. At 7 weeks of age no paroxysmal activity was present but some abnormal slow and sharp wave components were noted. One week after pyridoxine treatment was started (in the form of megavitamins) the EEG was unchanged. At 9½ months of age frank epileptiform discharges were again seen. Within two days of giving 100 mg of intravenous pyridoxine there was marked improvement, with no epileptiform discharges, but some slow components and sharp wave forms persisted.

Case 2. A boy, the second child of healthy unrelated parents, was born by vaginal delivery at 37 weeks' gestation after a normal pregnancy. His birthweight was 2480 g and his Apgar scores were 5 at 1 minute and 8 at 5 minutes. Thick meconium stained liquor was noted during labour. At 1½ hours he developed respiratory distress with episodes of apnoea. Seizures were first seen at 4 hours of age, and they continued intermittently throughout the first week. At 1 week of age, after treatment with phenobarbitone and phenytoin, no further seizures were evident, but assisted ventilation was required for 11 days because of a pulmonary haemorrhage. He was discharged at 3 weeks of age, but phenobarbitone and phenytoin were prescribed. Occasional seizures recurred in the next 2 weeks, but from 5 to 9 weeks of age there were no further fits. During this time, on a normal diet with no added vitamins, his developmental progress was normal.

When seizures recurred at 9 weeks of age he was admitted to hospital. Typical infantile spasms of the flexor type, occurring in clusters, were frequently observed and the EEG showed continuous generalised discharges with a burst suppression pattern. Over the next 5 days phenobarbitone, phenytoin, and injections of diazepam, clonazepam,

and paraldehyde failed to control these seizures, but after 50 mg of pyridoxine by intramuscular injection they stopped within 2 minutes and he became hypotonic and unresponsive. His conscious state improved over the next 24 hours, but he became jittery and frank seizures were again observed 31 hours after the first dose, Pyridoxine, 50 mg, given intravenously under EEG control, stopped the seizures within one minute. There was no immediate improvement in the EEG, but an improvement was noted over 2 days, and after 4 days the EEG showed no paroxysmal activity and only a moderate excess of background slow activity.

The child was discharged on oral pyridoxine, 75 mg a day but when reviewed at 6 months of age he had made no developmental progress, his head control was poor, and he was unable to roll or sit without support. No further seizures had occurred.

Case 3. A girl, the third child of first cousin Lebanese parents, was born at term by normal vaginal delivery. She was well until 6 weeks of age, when she suffered generalised and continuous seizures and was admitted to hospital. The seizures stopped after 2½ hours with the administration of paraldehyde, diazepam, and phenobarbitone. Lumbar puncture on admission showed 24 white cells per ml, of which 16 were polymorphs and 8 monocytes, and there were 51 red cells with a protein of 30 mg/100 ml. She was treated first with ampicillin and gentamicin, but no organisms were cultured from the cerebrospinal fluid. It was considered that an encephalitic illness was the most likely cause of the seizures and pleocytosis. She was discharged on phenobarbitone 9 days after admission, but seizures recurred 4 weeks later during an upper respiratory tract infection and phenytoin was added to her maintenance treatment of phenobarbitone. No further seizures occurred for 7 weeks.

She was readmitted to hospital at 4 months of age with seizures, which were initially right sided and then became generalised and continuous. Phenobarbitone, phenytoin, paraldehyde, diazepam, and a xylocaine infusion failed to control the fits, but after 100 mg of intravenous pyridoxine they stopped within 15 minutes. On a maintenance dosage of phenobarbitone and phenytoin seizures recurred 5 days later. On pyridoxine, 50 mg given intravenously under EEG control the seizures stopped within a few minutes. Multifocal spike activity had largely disappeared within a few minutes, but background high voltage slow activity persisted. She was started on a maintenance regimen of oral pyridoxine, 75 mg a day and had no further seizures.

At 11 months of age she was admitted because of increasing weakness and hypotonia and for a trial of

pyridoxine withdrawal—seizures recurred within 8 days. It was thought that her conscious state improved after a total of 300 mg of pyridoxine had been given intravenously, but there was no obvious change on the EEG. On a maintenance dosage of pyridoxine, 75 mg a day she had no further seizures. The results of investigations for weakness and hypotonia were consistent with spinal muscular atrophy, which had been diagnosed earlier in her older brother who did not suffer from seizures. An older sister is normal.

Case 4. A girl, the second child of unrelated parents, was born at term. The liquor was meconium stained, her Apgar score at 1 minute was 6, and her birthweight was 3120 g. She developed respiratory distress and, at 4 hours of age, evidence of a pulmonary haemorrhage requiring ventilation for 4 days. Generalised seizures began at 5 hours of age and were difficult to control with a combination of phenobarbitone, phenytoin, diazepam, and paraldehyde. As her respiratory state improved the seizures gradually decreased in frequency and she was discharged at 3 weeks of age on phenytoin. No further seizures occurred for 3 months, but at 4 months of age she was readmitted with right focal and then generalised seizures, which were easily controlled by a combination of phenytoin and nitrazepam. Her development was severely delayed—primitive reflexes persisted and she was not fixing or following. No seizures occurred for a further 4 weeks. At 5 months of age she presented with intractable epilepsy and died. Permission for necropsy was refused.

Case 5. A retrospective presumptive diagnosis of pyridoxine dependent seizures was made in case 4, when the next infant born to the family was found to be pyridoxine dependent. This girl was born at 38 weeks' gestation by vaginal delivery after a normal pregnancy. The liquor was meconium stained, the Apgar scores were 6 at 1 minute and 7 at 5 minutes, and birthweight was 3300 g. Seizures began at 4 hours of age. Pyridoxine dependency was established when 100 mg of intravenous pyridoxine was given under EEG monitoring and seizures stopped within 15 minutes, followed by normalisation of EEG burst suppression activity and spike wave discharges. She was treated with oral pyridoxine, 75 mg a day. Seizures recurred on two occasions, precipitated by a fever and an intercurrent illness, but were controlled with additional oral pyridoxine, 100 mg a day. At 5 years of age her intelligence quotient was in the low/normal range.

Discussion

The diagnosis of pyridoxine dependency in 4 of these

patients was made when seizures were controlled after the administration of pyridoxine, with no other change in treatment. The presumptive diagnosis in the fifth baby (case 4) is based on pyridoxine dependent seizures in a sibling. In all cases diagnosis was delayed because of the atypical features of the history.

Although the classic picture of pyridoxine dependency described in the introduction is imprinted in the minds of doctors, the clinical picture, even in the published reports, is much broader. A review of 36 cases¹⁻¹⁸ gives the following symptoms. The average age of onset of seizures was 4 hours, but it varied from onset at birth to onset at 3 months of age.³ Unusual fetal movements, suggesting intrauterine seizures, have been described. A seizure free period on anticonvulsant drugs without pyridoxine was unusual, but there were isolated reports of such periods lasting up to three weeks.^{4,5} Seizures normally stopped quickly after pyridoxine had been given, after an average interval of 10 minutes, but this has taken up to an hour.⁶ Seizures have been described as generalised, or focal becoming generalised.⁶⁻⁹ The interval between giving intravenous pyridoxine and normalisation of the EEG has varied from minutes^{1,8} to several weeks.⁶ Recurrence of seizures while on pyridoxine may be caused by intercurrent illnesses or growth of the child. After stopping pyridoxine, seizures recurred sooner in the neonate (1½ to 7 days) than in the older child (2 to 14 days). In one presumptive case treated incidentally with vitamins, including 5 mg pyridoxine, from day 4 for 6 days, seizures did not occur until 23 days after withdrawal of pyridoxine.⁹ The minimum daily requirement of pyridoxine has ranged from 2 to 200 mg. Most of the children have been mentally retarded. Children reported to be mentally normal have responded rapidly to the dose of parenteral pyridoxine—in less than 5 minutes.^{4-6,8} Small doses of pyridoxine taken by the mother in late pregnancy did not influence the outcome favourably in two cases,^{7,12} but in the third⁴ the infant was not mentally retarded. In one report, large doses of 110 mg a day of pyridoxine stopped the fetal movements which suggested intrauterine convulsions,⁷ but that child, although treated from birth, was mildly mentally retarded.

The patients described illustrate a broader range of clinical features than is commonly appreciated. The unusual features that led to diagnostic uncertainty include:

- (1) Late onset of seizures (day 8 in case 1; 6 weeks in case 3).
- (2) Prolonged seizure free period with anticonvulsant drugs before administration of pyridoxine

(4 weeks in case 2; 3 months in case 3; 3 months in case 4).

(3) Prolonged remission after stopping pyridoxine (5½ months in case 1).

(4) Presentation with types of seizures commonly associated with structural brain pathology (focal seizures in case 1; infantile spasms in case 2). Only one case of infantile spasm has been reported in association with pyridoxine dependent seizures¹³ and this has not been discussed in recent reports. Response to pyridoxine was described in the treatment of infantile spasm in the 1950s and pyridoxine deficiency was suspected in these cases because of increased xanthanuric acid excretion after tryptophan loading.

(5) The history of fetal distress in labour (cases 2 and 4) has led at times to seizures being attributed incorrectly to intrauterine hypoxia.

Pyridoxine dependent seizure should be considered in any infant with intractable epilepsy regardless of previous pattern of fitting, type of seizure, and response to conventional treatment. The diagnostic use of pyridoxine has been advocated for more than 20 years, but the infrequent occurrence of the condition makes it easy to forget, especially when presentation differs from the classic picture. Pyridoxine dependency is still one of the few treatable causes of intractable seizures in infancy, and the need for vigilance cannot be overemphasised.

A neonate with seizures, even with documented birth asphyxia, should be given 100 mg of intravenous pyridoxine and, unless severe seizures continue, be observed for 30 minutes before the administration of anticonvulsant drugs. If the infant is already receiving anticonvulsant treatment, 100 mg of intravenous pyridoxine should be given without changing the anticonvulsant treatment and the child should be observed carefully. The response may take up to an hour, and fitting may recur as soon as 36 hours or as long as several weeks after giving pyridoxine. When possible, pyridoxine should be given with EEG monitoring. An immediate response may be seen on the EEG, but this may take several days. Assessment may be particularly difficult in children with intermittent seizures. In such doubtful cases pyridoxine in doses of 100 mg orally may need to be given on several occasions, or given daily for several days then stopped abruptly, and the infant observed for recurrence of seizures. Once a definite clinical response has been established, pyridoxine treatment should be continued indefinitely, and an increase in dosage may be required as the child grows and when there is an intercurrent illness.

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