Atypical Presentations of Pyridoxine-Dependent Seizures: A Treatable Cause of Intractable Epilepsy in Infants

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We report on 3 patients with atypical pyridoxine-dependent seizures. Each had either late onset of convulsions (2 cases) or seizure-free intervals of up to several months' duration in the absence of pyridoxine supplementation. The findings, taken together with those in 9 previously reported cases, indicate that a trial of pyridoxine should be performed in all seizure disorders with onset before 18 months of age, regardless of type.

Goutières F, Aicardi J: Atypical presentations of pyridoxine-dependent seizures: a treatable cause of intractable epilepsy in infants. Ann Neurol 17:117–120, 1985

Pyridoxine dependency is a rare cause of convulsions. According to classic descriptions [3–5, 7–17, 20–22], pyridoxine-dependent convulsions occur during the neonatal period and respond well to the administration of vitamin B_6. If pyridoxine supplementation is interrupted, seizures recur within 2 to 23 days [8, 15, 20, 22]. The spectrum of pyridoxine-dependent seizures, however, may be broader than these limits. Recently, several articles have drawn attention to atypical cases with onset after the neonatal period or with seizure-free intervals of several months in the absence of pyridoxine supplementation [1, 2, 13]. We report 3 such atypical cases.

Case Reports

Patient 1

A female infant, aged 30 months at the time of this report, is the sixth child of consanguineous parents. An elder brother died at 8 months of age of unexplained status epilepticus. The patient developed normally up to 7 weeks of age, when she briefly developed clonic jerks of the left hand and foot. She then remained seizure free for 5 weeks, at which time she had a generalized clonic seizure lasting 45 minutes. Results of neurological examination, electroencephalogram (EEG), and computed tomographic scan following the seizure were normal. She was given phenobarbital (45 mg a day), but a convulsion occurred 1 month later and, at age 6 months, she had a 6-hour attack of status epilepticus with a right-sided onset that stopped only following high intravenous doses of diazepam, phenytoin, and barbiturates. At 7½ months clonic seizures appeared every 15 to 30 minutes for 10 days despite high intravenous doses of anticonvulsants. On admission she was unresponsive and febrile (temperature, 40°C) and exhibited continuous asynchronous, erratic jerks of the face and limbs. Fifteen hours later she was given 25 mg of pyridoxine intravenously, with immediate cessation of the jerks. She then received pyridoxine orally, 20 mg daily, while other anticonvulsant drugs were withdrawn. Ten days later she became fretful and sleepless, and the dose of pyridoxine was increased to 40 mg per day. At age 1 year pyridoxine treatment was discontinued. Ten days later she became agitated and restless and suffered a brief, generalized clonic seizure. The jerks disappeared 5 minutes after 80 mg of pyridoxine was given intravenously. Subsequently, on a regimen of 25 mg of pyridoxine daily, she has been seizure free but is microcephalic and mentally retarded.

Patient 2

A male infant born normally after an uneventful 38-week gestation weighed 2,950 gm at birth. The cord was wrapped around his neck, and he was mildly cyanotic. On day 5 he experienced a brief seizure, which stopped spontaneously. At age 3 weeks he developed excessive crying, restlessness, and loss of appetite. At that time he had an episode of clonic status epilepticus, which lasted for 24 hours despite treatment with barbiturates, diazepam, and phenytoin given intravenously. Thereafter he received 15 mg per day of phenobarbital and developed normally until 5 months of age, when he again had a brief left-sided clonic seizure. Five weeks later generalized or unilateral seizures recurred, stopping only after 5 days of high doses of diazepam, phenytoin, and barbiturates. From 7 to 11 months of age, while receiving 50 mg of phenobarbital and 1 mg of clonazepam per day, he had

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Received Mar 5, 1984, and in revised form May 29. Accepted for publication June 2, 1984.

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several clonic seizures, which lasted for 5 minutes to 6 hours and were frequently preceded by vomiting and irritable behavior. At age 11 months, pyridoxine dependency was suspected, and pyridoxine (50 mg a day) was added to the regimen. On this regimen he remained seizure free for the next 6 months. Pyridoxine treatment was then discontinued. Twenty days later the infant became agitated and irritable. The previously normal EEG showed diffuse paroxysmal activity. A few minutes later a right-sided, secondarily generalized clonic seizure developed; it stopped 10 minutes after intravenous injection of 40 mg of pyridoxine (Figure). Thereafter phenobarbital and clonazepam were withdrawn and the child received only 50 mg per day of pyridoxine. He remained seizure free for the next 15 months but was mentally retarded. At age 29 months, he was given isoniazid because of an alleged contact with an adult with tuberculosis. A brief tonic seizure at 32 months spontaneously stopped in a few minutes. Pyridoxine dosage was increased to 100 mg per day. One month later the boy had another brief seizure, and isoniazid treatment was discontinued.

Patient 3

A male infant had developed normally until 4 months of age, when 3 days following the first dose of diphtheria-pertussis-tetanus vaccine he underwent a generalized clonic seizure lasting 25 minutes. Generalized or predominantly right-sided, long-lasting seizures with partial preservation of consciousness recurred several times over subsequent days despite high doses of several anticonvulsant drugs. An episode of status epilepticus at 5½ months necessitated intravenous administration of barbiturates. The child then appeared mentally retarded, and a computed tomographic scan showed mild bilateral ventricular enlargement. He remained seizure free for 3 months on a daily regimen of 50 mg of phenobarbital, 100 mg of phenytoin, and 2 mg of clonazepam, but at 8½ months he had another episode of status epilepticus. At age 9 months, phenytoin and clonazepam treatment was discontinued. One week later he became fretful and irritable and had a clonic seizure involving the eyelids, tongue, and left hand. On the EEG bilateral spike waves predominated over the right frontocentral area. The seizure was arrested within 2 minutes by 40 mg of pyridoxine given intravenously, and the paroxysmal EEG activity cleared. A similar attack 8 days later stopped within 3 minutes following administration of the same dose of pyridoxine. On a daily oral regime of 50 mg of pyridoxine, the infant remained seizure free for the next 6 months. An attempt to withdraw pyridoxine was followed after 6 days by a generalized clonic seizure, which ceased only after three intravenous doses of 40 mg of pyridoxine. A 50 mg daily dose of pyridoxine was then reinstituted. Plasma pyridoxal levels measured at age 9 months were 20.6 nmol/L before treatment, 50.5 nmol/L at the time of a seizure immediately before pyridoxine injection, and 2,400 nmol/L during four days of intravenous administration of 40 mg of pyridoxine followed by a daily administration of 50 mg; levels were 1,100 nmol/L 6 months later with pyridoxine supplementation, and 109 nmol/L during an attack that occurred 6 days after withdrawal of pyridoxine. The normal value for this laboratory is 20 to 60 nmol/L.

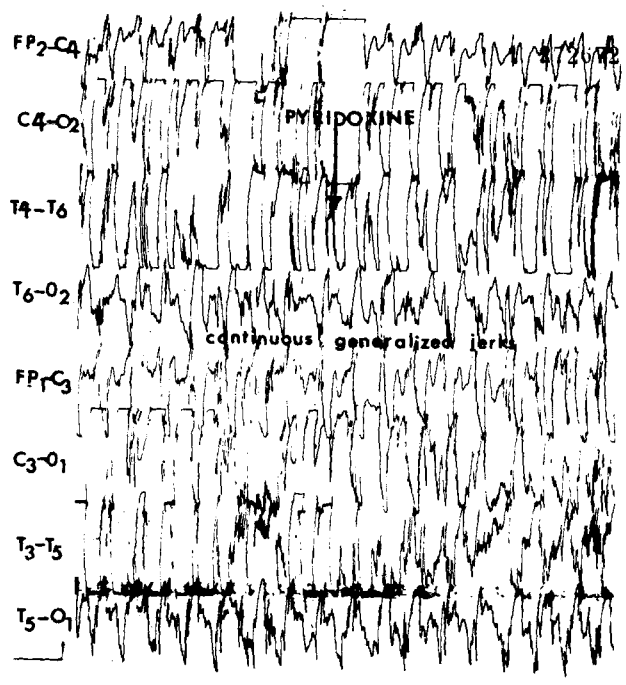
Discussion

These 3 patients had a severe convulsive disorder beginning in the first year of life. The diagnosis of pyridoxine-dependent seizures was demonstrated by (1) the immediate effect of the intravenous injection of pyridoxine, which arrested long-lasting seizures within a few minutes, and (2) the absence of seizures while the children were receiving pyridoxine orally after withdrawal of all anticonvulsant drugs. The occurrence of two seizures in Patient 2 after a 15-month seizure-free period is probably related to isoniazid therapy [6]. The supranormal levels of pyridoxine apparently necessary to prevent recurrences in Patient 3 are further evidence supporting the diagnosis of pyridoxine dependency.

In contrast to the classic descriptions of pyridoxine-dependent seizures, our patients showed late onset of their attacks (Patients 1 and 3), prolonged seizure-free periods while not receiving pyridoxine (up to 4 months and 1 week in Patient 2), or both. Moreover, some of their long-lasting seizures were controlled by conventional anticonvulsants. Onset between 3 and 14 months [1, 13, 18, 19] and seizure-free intervals without pyridoxine as long as 5 months [2] have been observed. Postneonatal pyridoxine deficiency seizures may be more common than early ones. The 3 patients reported here were observed over an 18-month period, whereas we have discovered no neonatal cases over a 15-year period despite routine screening for pyridoxine dependency.

The diagnosis of pyridoxine dependency should be systematically suspected in every infant with convulsions in the first 18 months of life. Certain clinical features may be especially suggestive. These include (1) cryptogenic seizures in a previously normal infant without abnormal gestational or perinatal history; (2) a history of a severe convulsive disorder, often leading to death during status epilepticus, in a previous sibling or consanguineous parents; (3) the occurrence of long-lasting focal or unilateral seizures, often with partial preservation of consciousness; and (4) irritability, restlessness, crying, and vomiting preceding the actual seizures.

Even though long-lasting seizures and, above all, repeated occurrences of status epilepticus are highly suggestive of pyridoxine dependency, all types of seizures can be observed. Brief seizures (generalized or partial), myoatonic seizures [13], and infantile spasms [2, 7] have been reported. As a consequence, pyridoxine should be administered as a diagnostic test in all cases of convulsive disorders of infancy in which no other diagnosis is evident. Because no biological test exists, this is the only available method of confirming the diagnosis. In emergency situations (e.g., long-lasting seizures), we advise intravenous injection of 100 to



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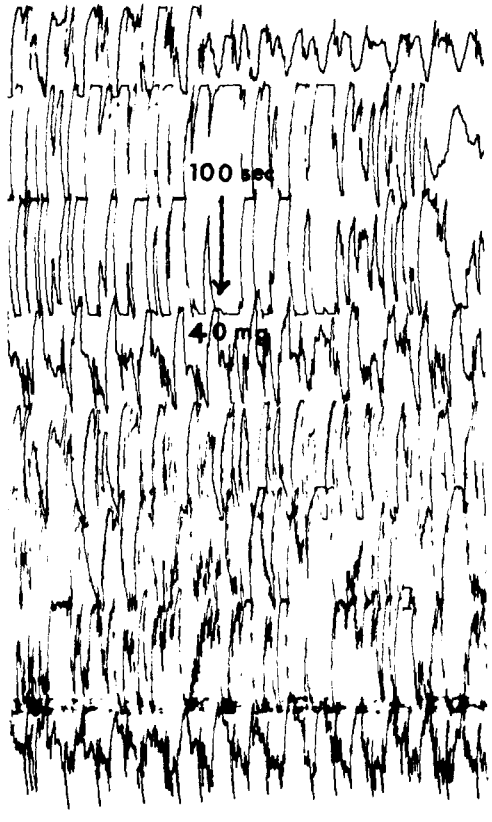

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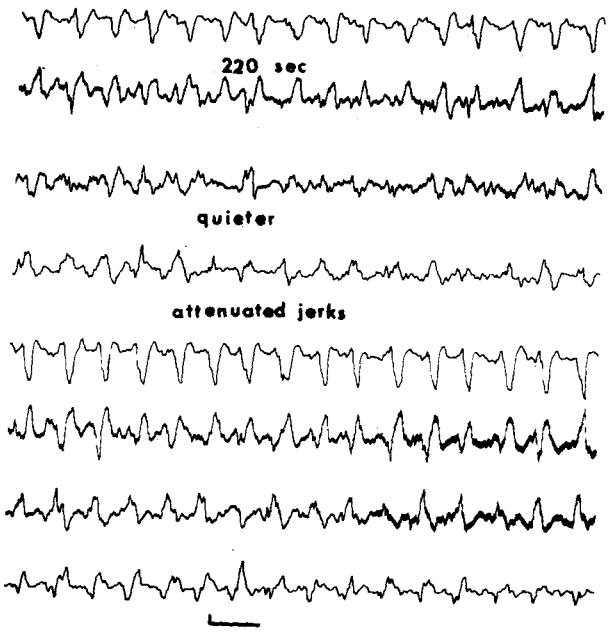

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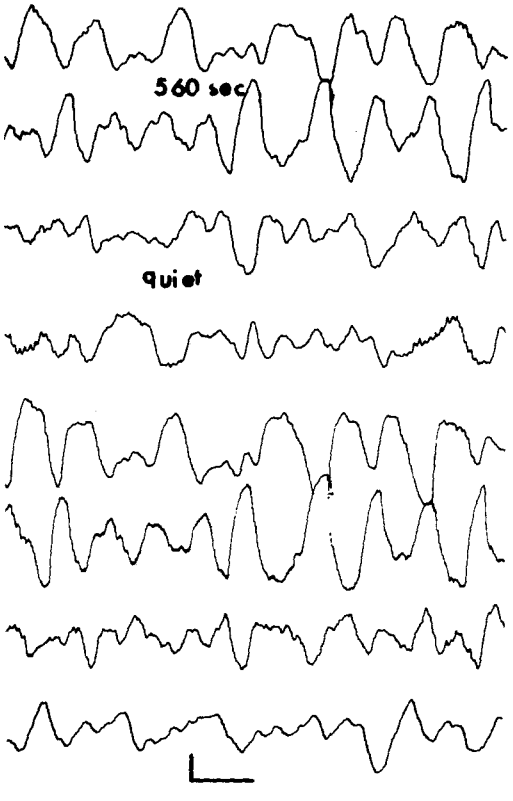

D

Electroencephalographic (EEG) monitoring of Patient 2. (A, B) Before intravenous injection of 40 mg of pyridoxine, the EEG shows generalized spikes, polyspikes, and high-voltage slow waves while the patient has a generalized clonic seizure. (C) At 220 seconds after the beginning of the injection, the jerks are attenuated and the paroxysmal EEG activity has decreased. (D) At 560 seconds after the beginning of injection, the seizure has stopped and the EEG shows generalized slow waves.

200 mg of pyridoxine prior to administration of long-half-life anticonvulsant drugs, and after the failure of short-acting drugs. The chance to identify specificity is lost if pyridoxine is given together with, or after, many anticonvulsant drugs. Doses of 40 to 50 mg are too small, as shown by our experience with Patients 1 and 3. With a large dose the effect should occur within minutes, and rapid restoration of full consciousness is additional evidence for the diagnosis. In long-term situations (e.g., in patients with brief recurrent seizures), oral administration of 50 mg per day is advised. Only immediate control of the seizures that is sustained after discontinuation of treatment with other anticonvulsant drugs is adequate evidence of pyridoxine dependency. In both circumstances we believe an attempt to withdraw pyridoxine is desirable. In our patients seizures recurred 6 to 20 days after pyridoxine withdrawal. Long delays (up to 5 months) have been reported, however [2, 19]. Once the diagnosis is confirmed, maintenance therapy should be continued indefinitely and the doses increased with age or intercurrent illnesses. In the absence of early appropriate treatment, the prognosis is poor, all survivors being severely mentally retarded. Of the 7 children reported to have developed normally, 6 [2, 5, 14, 16, 17, 22] were diagnosed and treated during the first month of life. The seventh patient [1], who had late-onset pyridoxine-dependent convulsions, was given pyridoxine immediately after the first attack of status epilepticus at 8 months of age.

Dr A. Hamfelt, Department of Clinical Chemistry, Central Hospital of Sundsvall, Sweden, kindly determined pyridoxal phosphate plasma levels.

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