Phenytoin-Induced Choreoathetosis in Infancy: Case Reports and a Review

K. S. Krishnamoorthy, MD, E. L. Zalneraitis, MD, R. S. K. Young, MD, and P. G. Bernad, MD

From the Departments of Neurology and Pediatrics, Harvard Medical School, Massachusetts General Hospital, Boston

ABSTRACT. Three cases of choreoathetosis which developed during phenytoin therapy in children less than 2 years of age are described. The most striking clinical manifestations included the sudden onset of restlessness and agitation with superimposed choreoathetosis. None of these children had toxic levels of phenytoin in the blood. Discontinuation of phenytoin resulted in prompt cessation of the symptoms. Phenytoin-induced choreoathetosis should be a diagnostic consideration in children with a preexisting CNS insult who manifest violent choreoathetosis during therapy for seizure control. This consideration is especially pertinent in the pediatric intensive care unit, where other more common causes of agitation could be misdiagnosed. *Pediatrics* 1983;72:831–834; *phenytoin, anticonvulsants, choreoathetosis, pediatric intensive care unit.*

Although phenytoin is an extensively used and safe anticonvulsant, a rare and ill-understood complication is the induction of movement disorders, including choreoathetosis. In most reported cases in adults, this complication has been observed during long-term phenytoin therapy associated with the usual symptoms of phenytoin intoxication (eg, nystagmus, ataxia).[1–3] The clinical presentation of this complication in children appears to be somewhat different.[4–6] Of the 11 cases reported thus far in children less than 18 years old (Table),[2,4–10] only one child was less than age 3 years. We describe three additional cases in children less than 3 years of age; all three were seen in the intensive care unit of the Massachusetts General Hospital (MGH) within a 6-month period.

Received for publication Dec 20, 1983; accepted March 16, 1983.
Reprint requests to (K.S.K.) Pediatric Neurology Unit, Massachusetts General Hospital, Boston, MA 02114.

CASE REPORTS

Case 1

This 2-year-old boy was admitted to the pediatric intensive care unit at MGH because of multiple congenital anomalies, psychomotor retardation, a history of seizures, and intermittent upper airway obstruction. The child was born at term after an uncomplicated vaginal delivery to a 32-year-old woman with polyhydramnios. Multiple anomalies included clubbed feet, abnormal hands, and bilateral inguinal hernias. "Blue spells," developing shortly after birth, were positional, occurring when the head was flexed and sometimes during sleep, and they were associated with clonic movements. An EEG performed at an outside hospital showed scattered sharp and slow brain waves. The child was given a trial of phenytoin (3 to 6 mg/kg) but continued to have spells of obstructive apnea and seizures.

Physical examination upon admission to the MGH revealed a head circumference of 47.5 cm (tenth percentile) and height and weight below the third percentile. Visual attention was poor. Highly arched palate, ulnar deviation of the fingers, clasped thumbs, and clubbed feet were noted. The neurologic examination was characterized by marked hypotonia, decreased symmetrical tendon reflexes, and severe developmental delay. Routine laboratory tests were normal. No paroxysmal activity was seen on the EEG. An electromyogram and a computed tomographic (CT) brain scan were normal.

The 19th day of hospitalization marked the commencement of multiple respiratory arrests associated with seizures confirmed by an EEG showing spike and wave patterns. The child was given several boluses of intravenous phenytoin (up to 25 mg/kg), and the seizures stopped. Multiple phenytoin levels registered only 4 μg/mL. Phenobarbital was added to the regimen but had to be discontinued in a short time due to lethargy and apneic spells. The lethargy was alternated with periods of restlessness and thrashing during the second week of phenytoin treatment. Characteristics of the abnormal movements included side-to-side body and head contortions, violent internal rotation of the arms and forearms, and slow writhing movements of the fingers. Intermittent

TABLE. Reported Cases of Phenytoin-Induced Choreoathetosis in Children

Reference	Age of Patients (yr)	Phenytoin Blood Levels (μg/mL)	Preexisting Neurologic Disorder
Bellman and Hass,[10] 1974	11	42	+
Rosenblum et al,[4] 1974	9	100	+
McLellan and Swash,[7] 1974	15	50	+
Shuttleworth et al,[9] 1974	18	43	+
Chalub et al,[5] 1976	8	<11.2	+
Zinsmeister and Marks,[6] 1976	3¼	<26.8	+
Luhdorf and Lund,[2] 1977	18	26	+
Buchanan et al,[8] 1977	1 10/12	11.5	+

pursing of the lips and tongue protrusions accompanied the violent movements. Because of the intermittency and severity of the movements, causes such as airway obstruction, undisclosed pain, and seizure activity were considered initially in the differential diagnosis. These movements could not be controlled by atarax or thorazine. The serum phenytoin level was, at this point, still only 2.0 μg/mL. Phenytoin was discontinued and the involuntary movements disappeared promptly within 48 hours. The seizures were controlled with phenobarbital and the infant was discharged to a chronic care facility.

Case 2

This 2-year-old boy was in an unresponsive state when seen at an outlying hospital. His birth history was unremarkable. He had, until this time, enjoyed good health with normal growth and development.

On the day of admission, his parents noted the following unusual behaviors: repetitive rolling of his eyes, twisting of the neck, and a forward jerking accompanied by a whooping noise. Two brief generalized tonic-clonic seizures followed, and the child was brought to a local hospital. His temperature was 38.9°C (102°F) and he reacted only to noxious stimuli. Two additional brief and generalized seizures occurred. Lumbar punctures were traumatic. Diffuse, high voltage, delta slow activity noted on EEG was unchanged by a 5-mg intravenous injection of diazepam. The patient was transferred to the Pediatric Intensive Care Unit at the MGH.

On arrival at the MGH, the child was unconscious but able to respond appropriately to noxious stimuli. His head circumference (75th percentile) was large for height and weight (25th percentile). Three small café-au-lait spots were noted, and there was mild neck stiffness. Tone was decreased, associated with diminished tendon reflexes and a positive Babinski sign bilaterally.

CT scan on admission was normal. Complete blood count, metabolic studies, and a toxic screen were unrevealing. The lumbar puncture was consistent with a prior traumatic tap. Three days later, a final lumbar puncture was entirely normal. Viral and bacterial cultures were negative. EEGs on three occasions showed abnormalities characterized by generalized, high voltage slowing, without paroxysmal activity. Phenobarbital (25 mg/kg) and phenytoin (15 mg/kg) were administered intravenously to control the seizures.

With prompt seizure control, the patient showed improved alertness. An increasing restlessness, however, soon became evident. Over the next few days, this restlessness became more pronounced with extended periods of agitation, hyperkinesis, and decreased sleep. By the eighth hospital day, the hyperactivity was almost constantly accompanied by purposeless strong contortions of the head, body, and extremities and slow writhing movements of the fingers. Sleep-wake cycles were interrupted; the child slept only two to four hours per day. Feeding was voracious, but there was no spontaneous interest in eating.

By the 11th day of hospitalization, the abnormal movements dominated the child's overall activity. Phenobarbital was discontinued because it was felt that it may have been contributing to the hyperactivity; yet no change was noted. A diagnosis of partial complex seizures was ruled out on the basis of the EEG which remained unchanged during the movements. Thyroid studies and antistreptolysin-O titers, obtained in considering the differential diagnoses of hyperthyroidism and Sydenham's chorea, were unremarkable.

By the 13th day, the movement disorder remained severe and unremitting. The blood phenytoin level was 6 μg/mL. A trial of 25 mg of intravenous diphenhydramine (Benadryl) produced no significant change. On the 14th day we decided to discontinue the phenytoin. Within 24 hours, the patient was less irritable. After 48 hours, there was a dramatic decrease in both the involuntary movements and the hyperactivity. Sleep and feeding had resumed with appropriate periodicity. Within three days, the child was smiling, playing, and able to sit.

Case 3

This 15-month-old boy was entirely well until the evening of Dec 14, 1978, when he fell from his crib. He initially sat up and cried, but moments later he became limp and apneic. His mother began mouth-to-mouth resuscitation. The child was transported by ambulance to an outlying hospital. On arrival there, he had no pulse and only gasping respirations. The pupils were fixed and dilated, and he made no response to painful stimuli. Initial blood gases showed pH 6.8, P_{CO_2} 70 mm Hg, and P_{O_2} 30 mm Hg. He was intubated and transferred to the MGH. Examination in the Pediatric Intensive Care Unit 3 hours after the injury revealed a pale child who responded to his name and cried when disturbed. His limbs were flaccid and avoided painful stimuli. His pupils were equal and reactive and extraocular movements were full. Because of periodic stiffening and clonic movements of

the extremities, the boy was treated with phenytoin (6 mg/kg/d). When he was examined three days later, he had fair strength in his legs and his arms lay flaccidly by his side. Cortical blindness was present.

As the infant improved gradually over the following days, he developed a peculiar state of agitation, which consisted of thrashing movements of the head and contortions of the shoulders, arms, and fingers. Sleep was interrupted and he displayed no spontaneous interest in food, despite a voracious eating behavior. Hyperkinesis and violent movements occurred intermittently, unresponsive to chloralhydrate, diphenhydramine (Benadryl), and thioridazine (Mellaril). The blood phenytoin level was 9.5 μg/mL. On the basis of our previous experiences, we considered the possibility of phenytoin-induced choreoathetosis and terminated the phenytoin therapy. Within 48 hours the uncontrolled agitation and involuntary movements had decreased considerably. The child was able to sit on his mother's lap for the first time since his accident. Thereafter, the movement disorder gradually subsided. Over the next several weeks his vision improved, and he was able to walk with assistance.

COMMENT

The data presented here suggest that the acute development of choreoathetosis in these three cases was related to phenytoin treatment. The onset of the movement disorders soon after initiating phenytoin, the failure to respond to various sedatives, and the prompt disappearance of the abnormal movements once phenytoin was withdrawn strongly support this diagnosis. Other causes of choreoathetosis were excluded after careful consideration. The children were not rechallenged with phenytoin.

Previous reports of phenytoin-induced movement disorders include hemichorea,[2,9] orofacial dyskinesia,[5,10] hemiballismus,[11] and choreoathetosis.[3,5,6,8,12] Generalized choreoathetosis was observed in all three of our patients. Orobuccal dyskinesia occurred in one (case 1).

It is important to emphasize that the diagnosis of phenytoin-induced choreoathetosis may be easily overlooked. One important clinical manifestation observed in all three infants was an intermittent restlessness and agitation, superimposed on violent attacks of choreoathetosis, lasting for several minutes to hours and leading to exhaustion. With careful scrutiny one can distinguish this hyperkinetic behavior (related to choreoathetosis) from other abnormal behaviors commonly encountered in the intensive care unit, such as agitation arising from airway obstruction, seizures, or undisclosed pain. EEG performed in two infants during an attack failed to demonstrate paroxysmal activity. It would seem that discontinuation of phenytoin is the most useful diagnostic test.

As noted above, a preexisting structural (anatomic) or organic CNS disorder appears to be a necessary prerequisite for the precipitation of phenytoin-induced choreoathetosis.[2,3,5,9,13] This finding would suggest a pathophysiologic similarity to movement disorders induced by dopamine agonists in persons at risk for Huntington's disease[14] or patients with prior Sydenham's chorea, in whom an asymptomatic movement disorder is unmasked.[15] Studies in experimental animals have also suggested that susceptibility to drug-induced movement disorders may be related to preexisting brain damage.[9]

In our patients, as well as in a few others reported in the literature,[2,5,8] toxic blood levels of phenytoin (>20 μg/mL)[16] were not always present. Even though adults frequently have had toxic blood levels,[1,5,9] therapeutic blood concentrations of phenytoin should not exclude the diagnosis of this complication.[5,15] Other anticonvulsants, such as ethosuximide[17] and carbamazepine[14] have also been associated with the induction of movement disorders, when used alone or in conjunction with phenytoin. It is possible that these major anticonvulsants may share a common underlying mechanism of action that is responsible for the development of dyskinesia.

The mechanism of this movement disorder remains speculative. A direct effect on brain serotonin or alteration of acetylcholine-dopamine metabolism, by enhancing both serotonergic and dopaminergic striatal activity, may be a possible mechanism.[5,8,18] Certain clinical manifestations in our patients supported this concept. Two of our patients (cases 2 and 3) had an abnormally short duration of sleep. Behavior involving appetite, satiety, and food preference was markedly altered. There was no spontaneous desire for food and yet when food was presented, the children ate voraciously. These behaviors occurred as temporal concomitants of phenytoin administration and disappeared once the drug was withdrawn. Therefore, disordered serotonergic or dopaminergic function, affecting sleep and appetite,[19] might be involved in these unusual behaviors associated with choreoathetosis.

Our experience suggests that phenytoin-induced choreoathetosis should be considered in a child with a preexisting CNS insult who manifests sudden episodes of violent choreoathetosis and hyperkinetic behavior during phenytoin therapy. Prompt withdrawal of the drug will not only alleviate the symptoms, but will obviate the need for unnecessary investigations.

REFERENCES

1. Kooiker JC, Sumi SM: Movement disorder as a manifestation of diphenylhydantoin intoxication. *Neurology*

2. Luhdorf K, Lund M: Phenytoin-induced hyperkinesia. *Epilepsia* 1977;18:409–415
3. Mauguiere F, Dalery J, de Villard R, et al: Transient hyperkinesia after a single intravenous perfusion of diphenylhydantoin. *Eur Neurol* 1979;18:116–122
4. Rosenblum E, Rodochok L, Hanson P: Movement disorder as a manifestation of diphenylhydantoin toxicity. *Pediatrics* 1974;54:364–366
5. Chalub EG, Devivo DC, Volpe JJ: Phenytoin-induced dystonia and choreoathetosis in two retarded epileptic children. *Neurology* 1976;26:494–498
6. Zinsmeister S, Marks RE: Acute athetosis as a result of phenytoin toxicity in a child. *Am J Dis Child* 1976;130:75–76
7. McLellan DL, Swash M: Choreo-athetosis and encephalopathy induced by phenytoin. *Br Med J* 1974;2:204–205
8. Buchanan N, Rosen E, Rabinowitz L: Athetosis and phenytoin toxicity, letter. *Am J Dis Child* 1977;131:105
9. Shuttleworth E, Wise G, Paulson G: Choreo-athetosis and diphenylhydantoin intoxication. *JAMA* 1974;230:1170–1171
10. Bellman MH, Hass I: Toxic reaction to phenytoin. *Br Med J* 1974;2:256–257
11. Chadwick D, Reynolds EH, Marsden CD: Anticonvulsant induced dyskinesias: A comparison of dyskinesias induced by neuroleptics. *J Neurol Neurosurg Psychiatry* 1976;39:1210–1218
12. Rasmussen S, Kristensen M: Choreo-athetosis during phenytoin treatment. *Acta Med Scand* 1977;201:239–241
13. Klawans HL Jr, Paulson GW, Ringel SP, et al: Use of L-dopa in the detection of presymptomatic Huntington's chorea. *N Engl J Med* 1972;286:1332–1334
14. Nausieda PA, Koller WC, Klawans HL, et al: Phenytoin and choreic movements, correspondence. *N Engl J Med* 1978;298:1093
15. Kutt H, Penry JK: Usefulness of blood levels of antiepileptic drugs. *Arch Neurol* 1974;31:283–288
16. Kirschberg GJ: Dyskinesia: An unusual reaction to ethosuximide. *Arch Neurol* 1975;32:137–138
17. Klawans HL: The pharmacology of tardive dyskinesias. *Am J Psychiatry* 1973;130:82–86
18. McGeer PL, Eccles JC, McGeer EG: *Molecular Neurology of the Mammalian Brain*. New York, Plenum Press, 1978, pp 256, 309–310