Downbeat Nystagmus with Phenytoin

JOSEPH R. BERGER, M.D.
ANDREW G. KOVACS, M.D.

Abstract

Downbeat nystagmus is generally the result of a structural lesion at the craniocervical junction. It has rarely been reported as a manifestation of metabolic disease or drug intoxication. We observed two patients with downbeat nystagmus secondary to phenytoin (Dilantin®) intoxication. Both individuals had other features of phenytoin-induced central nervous system dysfunction with toxic blood levels of the drug (> 20 μg/ml). Complete resolution of the downbeat nystagmus followed the return of phenytoin levels to the therapeutic range.

Since its introduction as an anticonvulsant by Merritt and Putnam in 1938, phenytoin (Dilantin®) has been recognized to effect ocular motility. Gaze-evoked horizontal nystagmus and impaired smooth pursuit eye movements are frequently observed with phenytoin. On rare occasions, transient abduction paresis, divergent strabismus, oculogyria, periodic alternating nystagmus, and abnormalities of optokinetic nystagmus have been attributed to phenytoin administration. Additionally, total external ophthalmoplegia to command and pursuit, as well as doll’s head maneuver and caloric stimulation, may occur with toxic blood levels.

In three individuals, primary position downbeat nystagmus has been noted as a complication of anticonvulsant therapy; however, in all reported instances the patients were receiving multiple anticonvulsants. In one individual, the nystagmus was attributed to carbamazepine (Tegretol®). In two others, phenytoin was believed causative, although both patients were receiving carbamazepine, and in neither were serum phenytoin levels documented to be in the toxic range at any time. We describe two patients with primary position downbeat nystagmus complicating phenytoin intoxication. In one patient, phenytoin was the sole anticonvulsant and in both, the downbeat nystagmus resolved when serum phenytoin levels returned to the therapeutic range.

Case Reports

Case 1

A 51-year-old man was admitted to the hospital for evaluation of gait ataxia. His pertinent history dated to 1943, when he suffered a gunshot wound of the head resulting in a left hemiparesis and post-traumatic seizures that were partial with secondary generalization. On phenytoin 400 mg daily, he averaged one to three seizures per month. His gait ataxia developed approximately 1 week prior to admission and was accompanied by vertigo and frequent falling. He denied visual disturbance including oscillopsia.

General examination revealed multiple recent bruises and lacerations as well as a healed right fronto-temporo-parietal cranioplasty. His mental status was normal. Pupils were 4 mm and briskly reactive to light. Fundoscopy was normal and visual fields were full to confrontation testing. Primary position downbeat nystagmus with a symmetric, superimposed horizontal component on lateral gaze was apparent. Extraocular movements were full. A mild central facial paresis and left spastic hemiparesis were evident with pathologically brisk left-sided muscle stretch reflexes and extensor plantar response. There was dysmetria of all extremities and his walking required assistance because of a wide-based, ataxic gait.

His initial serum phenytoin levels was 38 μg/ml (therapeutic level 10-20 μg/ml). Computed tomography (CT) of the brain revealed a hypodense lesion in the right frontoparietal region with scattered metallic densities in a similar distribution. There was no evidence of brain stem or cervico-medullary abnormality on CT scan. An electroencephalogram (EEG) revealed a rare right anterior temporal spike. Chest roentgenogram and routine laboratory studies including complete blood count, blood chemistries, and serology were normal. Phenytoin administration was withheld and his primary position downbeat nystagmus, as well as dysmetria, vertigo, and ataxia resolved within 2 days of admission when his phenytoin level measured 18 μg/ml.
Case 2

A 54-year-old woman was hospitalized because of gait and limb ataxia that followed the administration of 1000 mg of phenytoin. Her pertinent medical history dated to age 24 when she was diagnosed as having a static encephalopathy of unknown etiology and primary generalized motor seizures. Prior to the alteration of her drug regimen, she was receiving phenytoin 200 mg twice daily, phenobarbital 60 mg twice daily, and primidone 125 mg twice daily. Other medications included perphenazine 4 mg 3 times daily and thioridazine 100 mg twice daily. Review of systems was unremarkable and she denied any visual symptomatology including oscillopsia.

Her general physical examination revealed coarse facial features, gingival hyperplasia, and hirsutism secondary to long-term phenytoin therapy. She was alert, but intellectually impaired, being oriented to person only and displaying poor memory and calculatory ability and an inability to perform complex motor tasks. Her speech was mildly dysarthric. Her pupils were 3 mm and briskly reactive to light. Fundoscopy was normal. Visual fields were full to confrontation testing. Primary position downbeat nystagmus with a symmetric, superimposed, coarse, horizontal component on lateral gaze was apparent. Extraocular motility was intact. Occasional buccolingual dyskinesias were noted. Limb dysmetria and a broad-based, ataxic gait were striking. She was not able to stand with eyes open on a narrow base nor tandem walk.

A CT scan of the brain revealed a moderate degree of widening of cortical sulci and cerebellar subarachnoid cisterns with mild enlargement of the fourth ventricle. No brain stem or cervicomedullary pathology was appreciated. The serum phenytoin level was 27 μg/ml while phenobarbital was 24 μg/ml and primidone 6.3 μg/ml. Complete blood count, blood chemistries, serology, and chest roentgenogram were normal. An EEG revealed excessive slowing of the background walking rhythms with an occasional isolated spike and slow wave burst over the right temporal region.

Twenty-four hours after discontinuing the phenytoin her downbeat nystagmus resolved. The serum phenytoin level at that time was 14 μg/ml. Phenobarbital and primidone dosages were unchanged and serum levels approximated those on initial evaluation. Her ataxia improved dramatically, though coarse, horizontal gaze-evoked nystagmus persisted.

Discussion

Downbeat nystagmus is defined as nystagmus in the primary position with the fast phase directed downward. Its presence generally implies structural disease at the cranio cervical junction as may be seen with the Arnold-Chiari malformation, platybasia, basilar invagination, arachnoidal adhesions, and neck injury. On rare occasion, the downbeat nystagmus in Arnold-Chiari malformation may be paroxysmal; this may occur with the other features of this disorder as well. It has also been noted with structural brain stem and cerebellar disorders (Table 1), such as strokes, tumor, syphilis, and multiple sclerosis. Hereditary cerebellar degeneration and that secondary to alcohol abuse may also result in downbeat nystagmus. While nystagmus frequently accompanies intoxication by certain drugs, downbeat nystagmus is an unusual manifestation of drug intoxication or metabolic abnormality. Saul and Selhorst reported a patient who developed downbeat nystagmus secondary to magnesium deficiency. Exceptionally, it may result from anticonvulsant administration. Wheeler et al. described a patient with downbeat nystagmus attributed to carbamazepine. Their patient was receiving phenytoin and phenobarbital in addition to carbamazepine, and resolution of the nystagmus correlated with a decreasing carbamazepine-free fraction despite an increasing total serum carbamazepine. The phenytoin level in their patient was 22.2 μg/ml, though no comment was made by the authors of its possible contributory role. While Alpert attributed the downbeat nystagmus he had observed in two epileptic patients to phenytoin, both were on multiple anticonvulsants, including carbamazepine, and in neither was the phenytoin in the toxic range. In contrast, both our patients had toxic levels of phenytoin, 38 μg/ml and 27 μg/ml, and symptoms of phenytoin intoxication at the time downbeat nystagmus developed. One patient was solely on phenytoin and neither was taking

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### Table 1. Differential Diagnosis of Downbeat Nystagmus

<table>
<thead>
<tr>
<th>Category</th>
<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td>A. Structural lesions at cranio cervical junction</td>
<td>1. Arnold-Chiari malformation, platybasia, basilar invagination, arachnoidal adhesions, neck injury</td>
</tr>
<tr>
<td>B. Diseases of cerebellum or lower brain stem</td>
<td>1. Hereditary spinocerebellar degeneration, metabolic disorders</td>
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<tr>
<td>C. Metabolic disorders</td>
<td>1. Hypomagnesemia, drug intoxication</td>
</tr>
<tr>
<td>D. Hereditary cerebellar degeneration</td>
<td>1. Hereditary spinocerebellar degeneration</td>
</tr>
<tr>
<td>E. Alcohol cerebellar degeneration</td>
<td>1. Hereditary spinocerebellar degeneration</td>
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Journal of Clinical Neuro-ophthalmology
carbamazepine. Resolution of the downbeat nystagmus and symptoms of phenytoin intoxication occurred simultaneously with a decrease in serum phenytoin levels to the therapeutic range. In one of our patients, cerebellar atrophy was noted by CT scan. This cerebellar abnormality may have predisposed the individual to the development of downbeat nystagmus with toxic phenytoin levels. Similarly, Campbell reported on the development of transient periodic alternating nystagmus with phenytoin intoxication in an individual with alcoholic cerebellar degeneration. While the mechanism for the development of periodic alternating nystagmus and downbeat nystagmus is undoubtedly different, both frequently reflect disease at the cranio cervical junction and both may coexist in the same patient.

Baloh and Spooner propose that downbeat nystagmus is a central vestibular type of nystagmus. Using a computer model, Zee et al. suggest that it is the result of a pursuit system defect secondary to pathology of the archicerebellum or lower brain stem. Despite the fact that metabolic disorders rarely result in downbeat nystagmus, our two patients clearly demonstrate that it may be a manifestation of phenytoin intoxication. In all patients presenting with downbeat nystagmus, anticonvulsant, particularly phenytoin, intoxication should be considered in the differential diagnosis.

References


Write for reprints to: Joseph R. Berger, M.D., Department of Neurology (D 4-5), University of Miami School of Medicine, P.O. Box 016960, Miami, Florida 33101.