

Phenytoin and Dyskinesias: A Report of Two Cases and Review of the Literature

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Summary: Dyskinesia is a recognized but uncommon side-effect of treatment with phenytoin. Two additional cases of dyskinesia during treatment with phenytoin are described; both had radiographically documented thalamic infarctions. The reported experience to date with movement disorders induced by phenytoin is reviewed and the clinical features summarized. The available experimental evidence addressing the mechanism underlying this side effect is discussed. **Key Words:** Phenytoin—Anticonvulsants—Drugs, side effects—Choreoathetosis—Dyskinesia.

Since its introduction in 1938 both the therapeutic efficacy and side-effects of phenytoin have been well established. The reported neurologic toxicity includes both acute and chronic effects (1-3). The cerebellar syndrome of acute toxicity is well recognized and there are reports of irreversible cerebellar degeneration as well. Encephalopathy, both acute and chronic, exacerbation of seizures, focal neurologic deficits, ophthalmoplegia (4), and peripheral neuropathy have all been described. Involuntary movements are a less familiar complication of treatment with phenytoin and include tremor, asterixis, myoclonus and dyskinesias. We describe here two cases of dyskinesia exacerbated by phenytoin, both of whom had radiographically demonstrable thalamic lesions. The clinical features are discussed in the context of a review of the other cases reported in the English language literature.

CASE REPORTS

Case 1

The first patient is a 71-year-old, right-handed man with a history of hypertension and a right lat-

eral thalamic infarction 1 year prior to this admission, who presented to the emergency room at the University of Virginia Hospital following a generalized seizure beginning with clonic activity in the right arm. At the time of presentation he was being treated for depression on the psychiatric service. Following his thalamic infarction he had residual deficits which included a left hemisensory loss, mild hemiataxia, transient chorea of the left arm and a chronic pain syndrome. His previous neurologic evaluation included an angiogram, which revealed small vessel disease, a 60% left internal carotid artery stenosis and a small right middle cerebral artery aneurysm. Laboratory evaluation included an extensive rheumatologic workup, which was negative with the exception of an elevated erythrocyte sedimentation rate of 60 mm/h. There was no prior history of treatment with neuroleptic medications. At the time of evaluation he was taking amitriptyline and aspirin for his vascular disease. In addition, there was a remote history of alcohol abuse with documented abstinence for over 3 years. There was no family history of neurologic disease.

On physical examination immediately following the seizure he was confused and agitated. He was afebrile and blood pressure was 130/60. General physical examination was unremarkable. On mental status exam he was oriented only to person and did not follow commands. There were no abnormalities

A videotape segment accompanies this article.

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on cranial nerve examination. On motor examination there was no evidence of focal weakness. Sensory exam was intact to deep pain. Deep tendon reflexes showed a left-sided predominance with an extensor plantar response on the left. Laboratory evaluations included normal chemistries and CBC, and negative screen of urine for toxins. Cerebrospinal fluid had a protein of 42 and a glucose of 65. There were two white cells and no red cells.

After the initial examination in the emergency room, he had a second seizure and was loaded with 1 g of intravenous phenytoin. The next morning he was noted to have prominent dyskinesias. These included marked orofacial dyskinesias consisting of eyebrow elevation, occasional blepharospasm, tongue protrusion, and facial grimacing. He also demonstrated both axial and limb dyskinesia with frequent side-to-side head movement and occasional truncal rocking, as well as repetitive shoulder elevation, abduction and extension of arms and legs, much more pronounced on the left. Distal choreic movements were less frequent. His phenytoin level was 14.3 mg/L. The dyskinesias resolved over 3 days coincident with a decrease in the phenytoin level to less than 2.5 mg/L. His mental status returned to baseline within 24 h of admission. An MRI (Fig. 1) showed the old right thalamic infarction and was unchanged. An EEG revealed left temporal spikes. Seizures were treated with valproate because of a prior history of allergy to carbamazepine, used to treat his thalamic pain syndrome, and development of a rash in hospital while treated with phenobarbital. On follow-up evaluation he has remained stable with no recurrence of choreic dyskinesias.

Case 2

The second patient is a 60-year-old, right-handed woman admitted 3 months prior to our evaluation with new onset dysarthria and right hemiparesis. On admission she was noted to be lethargic with dysarthria, right facial weakness and right hemiparesis involving both arm and leg. She had right-sided hyperreflexia but no sensory deficits. Past medical history was remarkable for hypertension, stage three adenocarcinoma of the ovaries resected in 1985 and two prior cerebral aneurysms clipped in 1963 and 1983 at another hospital.

Her hospital course was complicated by persistent lethargy, which cleared after several days. She continued to demonstrate mild weakness greater in

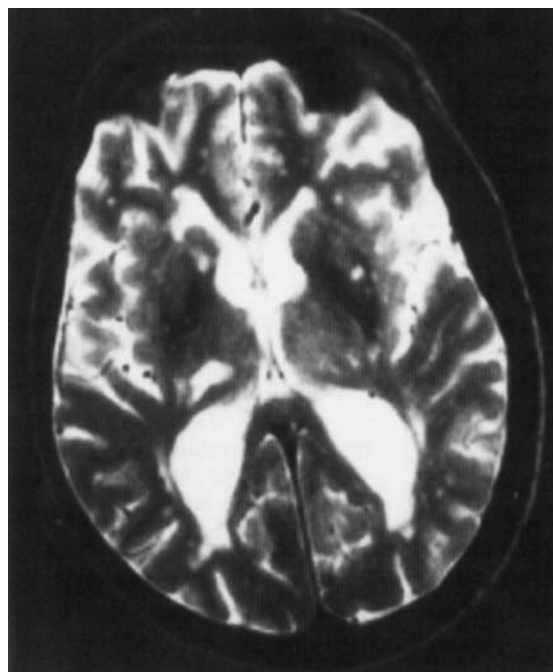


FIG. 1. *Case 1.* The MRI shows the previous infarction in the right thalamus, with probable involvement of the subthalamic nucleus or connections to it. Diffuse white matter disease and infarctions in the right internal capsule and caudate and left putamen are also present.

the arm than in the leg. Lumbar puncture was refused. Other evaluation included a CT scan (Fig. 2), which showed subacute infarction on the left involving the internal capsule and thalamus. An EEG showed suppression of background activity over the left hemisphere and independent bitemporal sharp waves. Phenytoin was begun with a level prior to discharge of 14.7 mg/L on a dose of 300 mg/day. Although not noted by the medical staff, the patient and her husband reported the onset of involuntary right hand movements before discharge.

Following discharge, because of dysphagia, she was changed to phenytoin elixir at the same dose. On medical follow-up she was found to have a phenytoin level of 36 mg/L. She was ataxic, but otherwise asymptomatic, and her phenytoin dose was reduced to 150 mg/day. When she returned for follow-up 2 months after her infarction, some adventitious movements were noted in her right hand. These were interpreted as possible seizure activity and her dosage was increased to 200 mg/day. She returned 1 month later complaining of more abnormal movements of the right hand interfering with

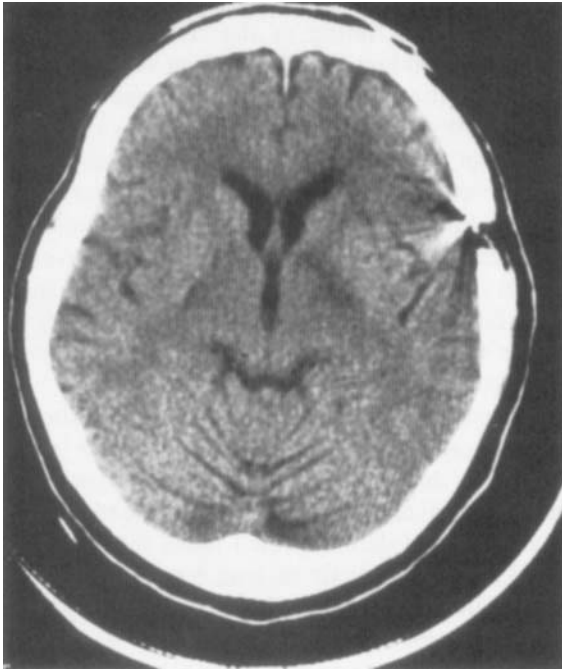


FIG. 2. *Case 2.* This CT scan shows a subacute infarction in the left thalamus.

use of the hand. At that time she was noted to have right-sided facial weakness and a high-pitched dysphonic voice without dysarthria. She had spasticity and mild weakness of the right arm. Deep tendon reflexes were increased in the right arm but were otherwise normal. The most prominent feature of her exam was repetitive, irregular, nonrhythmic flexion and extension movements at the right wrist and in the digits of her right hand. These were present at rest and with action and were increased with sustained posture. She was noted to have tapping of her right foot, which was asynchronous with the arm movements. Her gait was normal with the exception of accentuation of her dyskinesia; she developed more pronounced finger movements and proximal extension of dyskinesia to the shoulder. Her phenytoin level was 21.8 mg/L and her medication was held. Five days later, the phenytoin level was 5.1 mg/L and the movements were unchanged. One month subsequent to discontinuing the medication the movements had significantly improved although they had not completely resolved. When seen 3 months after phenytoin was stopped, the involuntary movements had decreased further, occurring only intermittently during her exam and no longer producing functional impairment.

DISCUSSION

Clinical Features

Dyskinesias induced by phenytoin represent an uncommon but recognized complication of phenytoin therapy. Seventy-seven cases have previously been reported in the English literature including four from German authors that have been described in review articles in sufficient detail to be included here. In 1950 there was a case report of acute toxicity secondary to phenytoin overdose in which "generalized tremors" were described (5), but the first case report in which choreoathetotic movements were clearly noted was in a 1962 (6) abstract with a full report published in 1966 (7). A 1963 article from the psychiatric literature described toxic psychosis, choreoathetosis, and truncal dystonia accompanying phenytoin toxicity (8). There have been multiple subsequent reports of dyskinesias during treatment with phenytoin (9–46). The cumulative experience with this entity and its clinical features are reviewed below, focusing on the dyskinesia/hyperkinesia syndrome. Tremor, asterixis, and myoclonus have been reported; these are less specific abnormalities, being seen in a wide range of metabolic and toxic disturbances.

The demographic distribution of the 77 cases is shown in Table 1. The age range is from 10 months to 81 years with the majority of cases occurring in younger individuals. Over 50% of the reported cases occurred in patients less than 20 years of age with only 20% in patients over 40. This age distribution may actually reflect epidemiologic features of epilepsy and/or phenytoin use. In addition, there

TABLE 1. *Demographic distribution*

	Age	N	
	Age (range: 10 mos–81 yrs)		
	0–10	27	(35%)
	11–20	13	(17%)
	21–30	12	(15%)
	31–40	9	(12%)
	41–50	1	(1%)
	51–60	6	(8%)
	61–70	3	(4%)
	>70	3	(4%)
	NS	3	(4%)
Sex	Male	43	(56%)
	Female	33	(43%)
	NS	1	(1%)

mos, months; yrs, years.

is a slight male preponderance with males representing 56% of the cases and females 43%. Our cases fall within the older end of the spectrum with only six previous cases (8%) reported in patients over the age of 60 (17,18,24,31,32,45).

Pharmacologic features of the previously reported cases are shown in Table 2. At the time the dyskinesias occurred, 32% of the patients were taking phenytoin alone while 68% were on two or more anticonvulsant drugs. Levels were measured in the majority of patients, and only 7% had levels of less than 10 mg/L. Four of these were children, one of whom was taking valproic acid concurrently (36,37). The other patient was an adult male with prior tardive dyskinesia that recurred on treatment with phenytoin and with quite low total levels (27). Twenty-three percent of the patients had total levels within the standard therapeutic range of 10–20 mg/L. In five of these patients the free levels were measured (36,45,46). It was at the expected fraction of 10% in one patient and elevated in four, three of whom were obstetrical patients with low serum albumin concentrations. In 57% of the previously reported cases the level was in the toxic range of greater than 21 mg/L. In 13%, drug level was not specified.

Use of more than one anticonvulsant may contribute to development of this side-effect by increasing free levels. Both phenobarbital and valproic acid, which were the most commonly combined medications, can increase the relative free fraction of phenytoin in the serum. It should also be noted that an identical clinical picture has occasionally been described during monotherapy with both carbamazepine (47–49) and phenobarbital (25,50,51). A case was also reported in which abnormal movements occurred after the addition of ethosuximide to phenytoin and subsided when the ethosuximide was withdrawn (52).

In prior case reports the determination of the

drug responsible has been made on the basis of an increased level, timing of the dyskinesias in response to introduction of the drug or increase in dosage and the response to withdrawal and/or rechallenge. With respect to our Case 1 it is of interest that 18% of the reported cases occurred after a single intravenous infusion. This may relate to the pharmacokinetics of the medication in which peak levels occur quite rapidly following an intravenous infusion (26). As the dyskinesia can persist in the face of falling drug levels, a single high peak in susceptible individuals may be sufficient to provoke the dyskinetic response.

The frequency of specific dyskinesias in the previously reported cases are shown in Table 3. The dyskinesias described represent a spectrum of hyperkinetic movement disorders. Frequently the patients described demonstrated more than one type of dyskinesia. Analysis of true frequency is hampered by the limited clinical data in many reports as well as inconsistency in the use of descriptive terms. Choreoathetosis was the most common manifestation, being present in 91% of the previously reported cases. Orofacial dyskinesia, which was quite prominent in our Case 1, has been seen in 67%, generally in connection with choreoathetosis. There are only three cases reported previously in which orofacial dyskinesias were seen in the absence of choreoathetosis and in one of those patients there was a concurrent neck dystonia (18,31). Dystonia has been reported in 23% of the patients, but in only three cases did the dystonia occur in the absence of another movement disorder (18,35,38). Ballism has been less commonly reported, being described in only 7% of the patients. In only one patient was it the sole manifestation. This was a 28-year-old man with a history of alcohol dependence in whom ballism was described as affecting only the lower extremities (29).

Another feature that has been considerably discussed in the literature is that of predisposing factors. These are shown in Table 4. The most commonly reported predisposing factor is static encephalopathy or mental retardation, described in 39% of the patients. Thirteen percent were reported to

TABLE 2. *Pharmacologic factors*

Treatment regimen			
Phenytoin alone	25		(32%)
≥Two AED's	52		(68%)
Phenytoin level (mg/L)			
<10	5		(7%)
10–20	18		(23%)
≥21	44		(57%)
NS	10		(13%)
Single IV infusion	14		(18%)

AED, antiepileptic drugs.

TABLE 3. *Type of dyskinesia*

Choreoathetosis	70	(91%)
Orofacial dyskinesia	49	(67%)
Dystonia	18	(23%)
Ballism	5	(7%)

TABLE 4. *Predisposing factors*

Static encephalopathy	30	(39%)
Prior dyskinesias	10	(13%)
Structural lesion	9	(12%)
Neuroleptic treatment	4	(5%)
Miscellaneous	5	(7%)

have had prior dyskinesias, two with a past history of Sydenham's chorea (31,38) one with tardive dyskinesia (27), and one who had previously received a diagnosis of senile chorea (31). Our clinical experience suggests that preexisting movement disorders may be underreported or undiagnosed and this figure may underestimate the true frequency of this predisposing factor. Neuroleptic treatment was a predisposing factor in only 5% of the cases. Three patients had been previously treated with neuroleptics and one, as mentioned, was already known to have tardive dyskinesia (13,27,32). In one patient the concurrent administration of phenytoin with a neuroleptic was the pharmacologic setting in which the dyskinesia occurred (32). There were miscellaneous causes identified as possible predisposing factors in five cases or 7%. One of these was a patient who had had a cardiopulmonary arrest (18), one was a patient with neurofibromatosis (25), one patient was documented to have abnormal metabolism of phenytoin (10), and one had abnormal copper metabolism (6). In the fifth case, both the seizures and abnormal movements occurred in the setting of meningoencephalitis (44).

In only 12% of the previously reported patients was a focal structural lesion identified. This was often not clearly related to the development of dyskinesia. One case description reports postmortem findings consistent with multiple lacunes in the striatum bilaterally (24). In another case, calcification in the globus pallidus was reported (36). The other structural lesions reported were left frontal abscess (18), residual shrapnel in the frontal lobe (23), a history of severe head trauma (37), a probable mass lesion with findings of midline shift on pneumoencephalography and angiography (17), a previously resected meningioma (32), parasagittal glioblastoma (41), and history of an old subdural hematoma (26). The two cases reported here represent the only two with radiographically documented thalamic lesions in spite of association of such lesions with both chorea (53) and oral dyskinesias (54). However, exacerbation of unilateral asterixis secondary to thalamic lesions by phenytoin treatment has been re-

ported (55). Our cases demonstrate recurrence (Case 1) and exacerbation (Case 2) of unilateral chorea secondary to thalamic infarction by the administration of phenytoin; in Case 1 the additional basal ganglia lesions may have contributed to the more generalized features.

Pathophysiology

In spite of the wealth of clinical observations regarding the potential of phenytoin to induce dyskinesias, there is little understanding of the mechanism of this effect. Phenytoin has been shown to accumulate in brain tissue. In experimental work in an overdose model in the cat, there was regional variability with higher levels in the cerebellum and basal ganglia than in the cortex (56). In human tissue examined after temporal lobe resection, levels in brain tissue were 4–10 times those in spinal fluid or serum (57). It has been established both in human tissue and animals, that phenytoin binding is not receptor mediated and appears to be nonspecifically bound to proteins and/or phospholipids (57,58).

An extensive literature exists on the pharmacologic effects of phenytoin on neurons in multiple preparations (59–62). At therapeutic concentrations, it has been shown to block sustained repetitive firing via an effect on sodium channels and this is believed to be the primary mechanism underlying its anticonvulsant effect. At supertherapeutic concentrations it has been shown to decrease both calcium influx into the neuron and transmitter release. This may be relevant even at therapeutic levels in view of the finding of a preferential concentration in neuronal tissue over and above the levels observed in the serum. It has also been shown to inhibit calcium and calmodulin regulated protein phosphorylation, which carries with it the potential for an impact on second messenger systems. The effects on chloride conductance have been variable in different studies. Both positive and negative effects on chloride conductance have been found. Under depolarizing conditions phenytoin also prevents increase of cyclic AMP. The interaction of phenytoin with various neurotransmitter systems in the brain has been examined as well. It has been shown to increase the concentration of gamma-amino-butyric acid (GABA). Variable effects have been reported on acetylcholine. While phenytoin has been shown to decrease the activity of acetylcholinesterase (63), there is a dose dependent effect on release with low doses stimulating and higher doses inhibiting acetylcholine release (62).

The pharmacologic system within the brain of greatest relevance to the dyskinetic side-effects is the dopaminergic system. Because of the clinical observations, the interactions of phenytoin with dopaminergic systems in the brain have been examined experimentally. The effects are summarized in Table 5. Because of the similarities of the clinical features to tardive dyskinesia, particularly the prominence of the orofacial dyskinesia, an initial hypothesis was that phenytoin produced this effect via a blockade of the D2 receptors, a mechanism similar to the action of neuroleptics. No studies have examined this directly by looking at inhibition of binding. However, effects on dopamine metabolism have been examined.

In the striatal slice preparation, phenytoin inhibits the uptake of tritiated dopamine, which is an active transport process occurring in the presynaptic dopaminergic terminals (64). Phenytoin has been found to have variable effects on dopamine metabolite levels. It has been shown to inhibit the monoamine oxidase system responsible for breakdown of dopamine in brain tissue (62). However, in the CSF of patients treated with phenytoin, an increased level of homovanillic acid (HVA), one of the degradation products of dopamine has been found (65). There was no change seen in the levels of either HVA or DOPAC (3,4-dihydroxyphenylacetic acid) in the rat brain after administration of phenytoin (66). The significance of the finding in humans is not clear. The possible mechanisms would include both increased turnover and decreased reuptake or decreased transport from the CSF.

Several studies have examined the effects of phenytoin administration on dopamine mediated behaviors. In the naive rat there was either no change or a decrease found in apomorphine-induced stereo-

typy (31,66,67). In animals pretreated with neuroleptics, behavioral supersensitivity to apomorphine was actually increased by phenytoin administration (31,68). However, after dopamine denervation in the 6-hydroxydopamine (6-OHDA) lesion model, phenytoin administration decreased the turning induced by apomorphine, which is another indicator of behavioral supersensitivity (66,69). In studies of the effects of acute administration, phenytoin produced catalepsy similar to that produced by administration of dopamine antagonists (67). In studies looking at chronic phenytoin administration and then withdrawal, motor activity increased after cessation of phenytoin treatment (67) and a delayed increase was seen in apomorphine-induced stereotypy (70).

To summarize, in models believed to represent supersensitivity, possibly at the level of the dopamine receptor, contradictory effects were found with a potentiation of supersensitivity after neuroleptic treatment but an inhibitory effect on apomorphine turning after a 6-OHDA lesion. It is interesting to consider these results in light of what is known about the effects of a 6-OHDA lesion on the interaction of the D1 and D2 subtypes of the dopamine receptor. In the normal rat, actions at the D1 and D2 receptor are synergistic and stimulation of both subtypes is required to produce dopamine-mediated behaviors. Conversely, treatment with either D1 or D2 antagonists can block these behaviors. In the 6-OHDA lesion model, dopamine denervation functionally uncouples the D1 and D2 receptor, so that stimulation at either receptor with a specific agonist can produce the full range of effects and treatment with one antagonist alone is not sufficient to block them. In the normal animal given a drug acting at both D1 and D2 receptors, there was little, if any, effect of phenytoin. In the setting of uniform dopamine depletion after a 6-OHDA lesion, an inhibitory effect on the expected increased response to a mixed dopamine agonist was seen, whereas in the setting of chronic blockade of one subset of the dopamine receptor, the D2 receptor, the dopamine agonist effects were potentiated. It may be that phenytoin's mechanism of action preferentially affects one subtype of the dopamine receptor or mimics its effects. This recalls the observation that phenytoin decreases the level of cyclic AMP in brain tissue, an effect which has also been reported through action at the D2 receptor.

The balance of the experimental evidence indicates that phenytoin can affect dopamine mediated

TABLE 5. *Interactions with the dopaminergic system*

Effects on dopamine metabolism:
Inhibits [³ H]-dopamine uptake in slices
Variable effects on dopamine metabolite levels
Effects on dopamine mediated behaviors:
No change or decrease in apomorphine induced stereotypy in naive rat
Increases behavioral supersensitivity to apomorphine after pretreatment with neuroleptics
Decreases turning induced by apomorphine after 6-OHDA lesion
Behavioral effects of phenytoin administration:
Acute: catalepsy
Chronic: after withdrawal, motor activity increases and there is a delayed increase in apomorphine induced stereotypy

behaviors although the mechanism remains unclear. This is supported by some clinical observations that are of interest in this context. There have been reports of decreased responsiveness to levodopa in patients with Parkinson's disease who received phenytoin therapy (69). In addition, there are two case reports in which a parkinsonian syndrome was induced after treatment with phenytoin, one in a child (71) and one in an adult (72). It has been known for some time that phenytoin can worsen the chorea in Huntington's disease (69). As we have seen in both of the cases presented here and those previously reported, it can either induce or worsen other hyperkinetic syndromes.

In summary, phenytoin-induced dyskinesias represent a well-documented complication of treatment. Though there is some clustering of occurrence at earlier ages, it can occur at any age during either chronic or initial treatment. It is more common in the face of an increased drug level and if it is suspected, free levels should be checked. This increase can be transient as in the setting of intravenous loading. It is more commonly seen with polytherapy with two or more anticonvulsants. The movement disorder is variable but usually consists of a generalized choreoathetosis with or without orofacial dyskinesias. A similar syndrome has been described less commonly with other anticonvulsants and should be suspected in that setting as well. Although the specific mechanism is unknown, we hypothesize that there is disturbance in the functional equilibrium of the basal ganglia output systems, perhaps due to a differential effect of phenytoin on dopamine receptor subtypes or their associated second messenger systems. There is evidence that vulnerability to this effect is increased in the abnormal CNS. The cases presented here represent the only two with radiographic evidence of a structural lesion of the thalamus and involvement of the connections to the subthalamic nuclei is most likely implicated as an underlying abnormality.

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LEGENDS TO VIDEOTAPE

Segment 1. This patient is a 71-year-old man with a previous right thalamic infarction (Case 1). He is shown the day after receiving 1,000 mg of phenytoin intravenously. Initially, he is at rest with

few adventitious movements; his dyskinesia is markedly activated when he begins to speak. He demonstrates axial dyskinesia involving neck and trunk and large amplitude proximal movements of the extremities, left more than right, resulting in limb displacement, as well as less frequent distal choreic movements. The prominent orofacial dyskinesias are demonstrated in the following portion. These include eyebrow elevation, occasional blepharospasm, tongue protrusion, and facial grimacing; the adventitious movements interfere with his attempt to sustain tongue protrusion. In the last two scenes, the patient is shown following discontinuation of phenytoin and resolution of the acute dyskinesia. Occasional movements of the left arm are seen as he describes his prior dyskinesia.

Segment 2. This patient is a 60-year-old woman with a previous left thalamic infarction (Case 2). She is shown at the time of initial evaluation 3 months after her infarction while receiving phenytoin. The abnormal movements shown are restricted to the right upper extremity and consist of repetitive irregular flexion and extension of the wrist and fingers. These are accentuated by use of the arm and by walking.

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