Transient hemiparesis: A rare manifestation of diphenylhydantoin toxicity

Report of two cases

GIDEON FINDLER, M.D., AND SYLVAN LAVY, M.D.

Department of Neurosurgery and Neurology, Hadassah University Medical Center, Ein-Kerem, Jerusalem, Israel

Among the common side effects of diphenylhydantoin (DPH) overdose, the most frequently encountered neurological signs are those of cerebellar dysfunction. Very rarely, the toxic neurological manifestations of this drug are of cerebral origin. Two patients are presented who suffered progressive hemiparesis due to DPH overdose. Both had brain surgery before DPH treatment. It is assumed that patients with some cerebral damage are liable to manifest DPH toxicity as focal neurological signs.

KEY WORDS □9 diphenylhydantoin toxicity □9 transient hemiparesis □9 brain damage □9 DPH

The common neurological manifestations of diphenylhydantoin (DPH) intoxication are nystagmus, ataxia, and dysarthria. Rarely, DPH toxicity may result in mental changes and focal signs, such as hemiparesis. These focal signs apparently occur more often in patients with previous brain damage. When such signs are encountered in patients following brain surgery, they may be misinterpreted and erroneously attributed to the surgical procedure. We present two such patients in whom the focal neurological signs completely resolved after cessation of the drug.

Case Reports

Case 1

This 40-year-old woman was admitted because of left-sided focal seizures. On examination, there was mild left hemiparesis, left central facial weakness, and increased deep tendon reflexes on the left side of the body. There was no papilledema. Computerized tomography (CT) of the brain demonstrated a large right frontal mass, compatible with a meningioma. The tumor was removed, and histological examination confirmed the diagnosis of a benign meningioma.

The postoperative course was uneventful. The patient was discharged 8 days after surgery, showing only minimal weakness on the left side of the body. She was started on DPH, 300 mg daily, as a prophylactic measure. Following a grand mal seizure several weeks later, phenobarbital (PB) was added, 100 mg daily, and DPH was increased to 400 mg. Two weeks later the patient was readmitted because of progressive weakness and gait disturbance.

On examination, she was disoriented, had coarse horizontal nystagmus, slurred speech, and ataxia. There also was dense left hemiparesis, left central facial weakness, and bilateral extensor plantar responses. There was no papilledema. The craniotomy bone flap was not under pressure, and there were no signs of infection. An electroencephalogram (EEG) demonstrated mild slowing in the anterior part of the brain, more marked on the right side. A repeat CT scan revealed an area of low density in the right frontal lobe, with no mass effect (Fig. 1). Routine blood examinations were normal; however, serum DPH level was 40 μg/cc (normal: 10 to 15 μg/cc). The drug was stopped. Phenobarbital was increased to 200 mg per day.

Over the following weeks the patient’s condition improved. The confusion cleared, the hemiparesis and
cerebellar signs receded. Three weeks after cessation of the drug, the blood DPH level was 1.5 \(\mu g/cc\), and the patient was virtually free of symptoms. She was discharged with no neurological deficits whatsoever, receiving PB 200 mg daily.

**Case 2**

This 50-year-old woman was hospitalized because of severe headache and visual disturbances. Examination revealed bilateral chronic papilledema as the only neurological sign. A CT scan demonstrated a right frontal tumor, compatible with a meningioma. The tumor was removed, and histological examination confirmed the diagnosis of benign meningioma. Recovery was uneventful. The patient was discharged with no neurological deficit. She was given DPH 300 mg daily, and PB 50 mg three times a day, prophylactically.

Six weeks later the patient was readmitted because of ataxia and confusion. Examination revealed coarse horizontal nystagmus, left hemiparesis, and left central facial weakness. Fundi were normal. The craniotomy site was not under pressure and there were no signs of infection. An EEG showed a severely disturbed record with a slowing of the electrical activity, especially over the anterior areas, with sharp-wave phase reversals in the right frontal region. A CT scan demonstrated a large porencephalic cyst in the frontoparietal area, with no mass effect (Fig. 2). Serum DPH levels were 34 \(\mu m/cc\). After cessation of the drug, there was a marked improvement in the patient's neurological condition, with a concomitant drop in blood DPH level. Five days later she was well oriented, with only residual hemiparesis, and the cerebellar signs resolved completely. One week after admission the patient was symptom-free; DPH in the blood was undetectable at that time. The patient was discharged, taking PB 100 mg daily.

**Discussion**

It is well established that prophylactic therapy with DPH is beneficial in patients who have undergone brain surgery. However, DPH is not without side effects. Besides the more common cerebellar signs, nausea, vomiting, blurring of vision, fever, and skin rash, DPH overdose may also be manifested by focal cerebral deficits such as unilateral choreoathetosis,\(^7\) hemihyperesthesia,\(^7\) and, rarely, progressive hemiparesis.\(^6\)

Our two patients who suffered DPH intoxication developed progressive hemiparesis, mental changes, and cerebellar signs, which resolved after cessation of the drug. Clinical improvement was concomitant with decrease of the high concentration of DPH in the blood.

Since the introduction of DPH as a major anticonvulsant in 1938,\(^4\) only two patients have been described with transient hemiparesis due to DPH toxicity.\(^4\) Their symptoms also resolved with cessation of DPH therapy. The toxic phenomena of DPH are more commonly observed in brain-damaged and mentally retarded patients.\(^7\) The patients described by Morris, \textit{et al.}\(^6\) as well as ours, suffered some brain damage before DPH therapy. Morris's patients were both mentally retarded and suffered from seizures, whereas our patients underwent brain surgery.

The pathophysiology of the transient focal motor deficit is obscure. Although DPH is known to prevent electrical spread at the synaptic level,\(^1\) it is not clear...
Diphenylhydantoin toxicity

why damaged areas of the brain are more susceptible to its suppressive effects. The simultaneous treatment of these patients with PB may increase the sensitivity of the brain to DPH.\(^2,3\)

The development of focal neurological signs in postoperative patients may pose diagnostic problems. Since these patients commonly receive DPH prophylactically, they are at risk to develop drug intoxication. We suggest that DPH should be stopped and its concentration in the blood determined before other more invasive procedures.

Acknowledgment

We are indebted to Dr. R. Silverberg for her most helpful cooperation.

References


Address reprint requests to: Gideon Findler, M.D., Department of Neurosurgery, Hadassah University Hospital, Ein-Kerem, Jerusalem, Israel.