

# Phenytoin-induced parkinsonism

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## ABSTRACT

**This report presents a 30-year-old man who developed subacute phenytoin-induced cerebellar ataxia and parkinsonism that resolved after discontinuation of the phenytoin treatment. Phenytoin was started for seizure prophylaxis in another health institution where he was referred for bilateral intracerebral orbitofrontal haemorrhage due to a head trauma. To our knowledge, there has been only one other case report describing phenytoin-induced parkinsonism, which was also reversible. The issue of the development of parkinsonism due to the phenytoin toxicity in the case of bilateral orbitofrontal lesion is addressed.**

**Keywords:** diphenylhydantoin toxicity, movement disorder, parkinsonism, phenytoin toxicity, traumatic brain injury

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## INTRODUCTION

Movement disorders induced by antiepileptic drugs are frequently of the hyperkinetic variety, and parkinsonism is encountered rarely<sup>(1,2)</sup>. There has been only one case report of parkinsonism, which was attributed to diphenylhydantoin (DPH)<sup>(1)</sup>, and a clinical study in which parkinsonian symptoms of the patients were reversed by the administration of DPH<sup>(3)</sup>. We report a patient who developed cerebellar ataxia and parkinsonism during the first month after he started to take phenytoin 300 mg/day. The temporal relationship of the development of cerebellar ataxia which was shown to be due to DPH intoxication and parkinsonism, and the gradual disappearance of the symptoms after discontinuation of DPH, led us to attribute the clinical picture to DPH intoxication.

## CASE REPORT

A 30-year-old man was admitted to our neurology department with complaints of diplopia, gait

disturbance, slowness of his movements, and slurred speech. His physical examination was normal, except for the neurological examination that revealed gaze-evoked nystagmus, bilateral slight intentional tremor of the hands, and gait disturbance due to cerebellar ataxia. He had parkinsonism manifesting as bilateral rigidity, bradykinesia, bradykinesia, and loss of arm swing during walking, slightly stooped posture, and a hypophonic, slurred and monotonous speech that developed subacutely within two weeks. He had a history of head trauma one month before his admission to our inpatient clinic.

Magnetic resonance (MR) imaging on the day of the trauma showed intracerebral haemorrhage localised on both gyrus recti (Fig. 1). The patient was hospitalised in the neurosurgical department of a state hospital, and prophylactic antiepileptic treatment with DPH 300 mg/day was started which was continued until his admittance to our department. After two weeks following the initiation of the DPH treatment, he experienced an intentional tremor of his hands and bradykinesia with stiffness of his arms and legs. Subsequently, gait ataxia, diplopia, and bradykinesia were added to the clinical picture. There was nothing remarkable in his past medical history and family history.

Laboratory findings, including routine blood and urine analysis, were normal. The electroencephalography examination was unremarkable. Repeat MR imaging of the brain showed a partially-resolved haematoma in both gyrus recti, when compared with the first MR images performed after the head trauma (Fig. 2). The most significant finding was a high level of DPH (40 µg/dL) in the blood (normal range, 10-20 µg/dL), and the patient was duly diagnosed to have DPH intoxication. After replacement of DPH with carbamazepine, the symptoms slowly disappeared, beginning with the cerebellar symptoms and diplopia. Within two weeks, plasma DPH concentration returned to the normal therapeutic range, and subsequently approached zero. Parkinsonism also decreased dramatically but more slowly than

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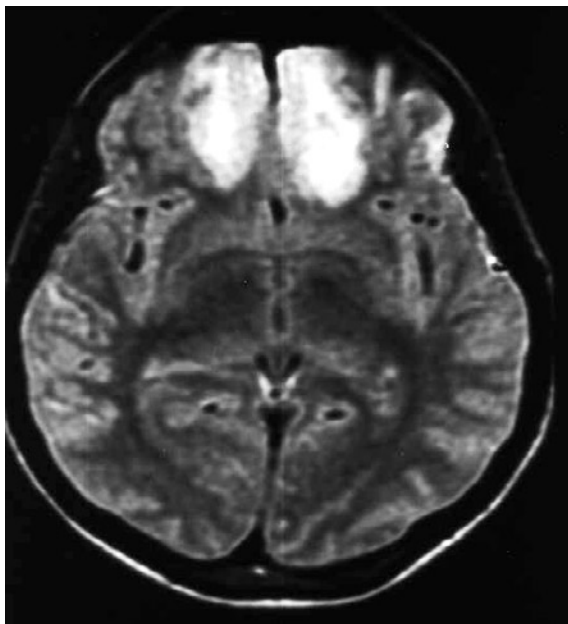
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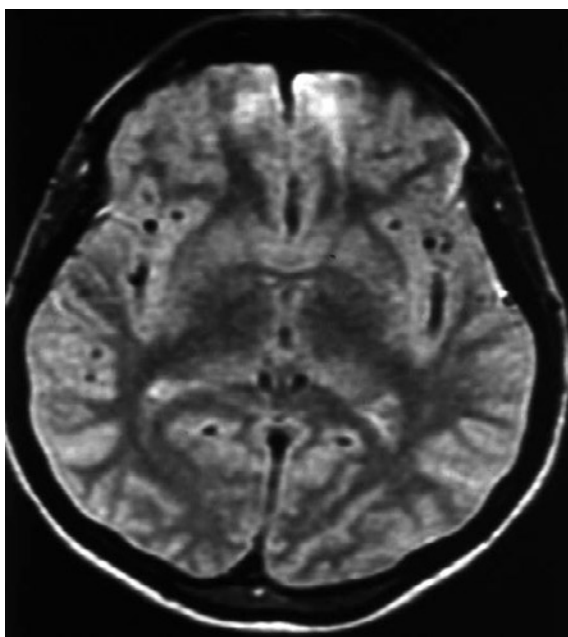
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**Fig. 1** Proton-weighted MR image of the patient on the day of trauma shows haematomas in the gyrus recti bilaterally.



**Fig. 2** Proton-weighted MR image taken one month after trauma shows noteworthy regression of the haematoma in both gyrus recti.

the cerebellar symptoms in the two weeks following cessation of DPH intake. Improvement of the parkinsonian symptoms and signs continued. All of the symptoms detected on admission had disappeared after six months of the follow-up period.

## DISCUSSION

The temporal relationship between the initiation of the prophylactic DPH treatment, and the occurrence of either cerebellar and parkinsonian symptoms in

this case led us to attribute the clinical picture to DPH intoxication. However, considering the experience with DPH and the fact that there is to date only one case report of parkinsonism due to the treatment with this drug<sup>(1)</sup>, our patient might have a distinctive feature that rendered him prone to the development of this side effect. The presence of bilateral orbitofrontal cortex lesion is the most important feature in this case, which may contribute to the development of parkinsonism when combined with DPH toxicity.

Nystagmus, ataxia, and drowsiness, which are the most frequently-encountered dose-related side effects and signs of DPH toxicity, are correlated with its plasma levels. It was revealed that in the majority of the patients, nystagmus, ataxia, and drowsiness appear when plasma levels reach 20, 30, and 40  $\mu\text{l/dL}$ , respectively, but dose-related side effects may show a great diversity among patients<sup>(4)</sup>. Choreaethosis, ballismus, myoclonus, dystonia, and oro-facial dyskinesias have also been reported to be related to DPH use, although rare<sup>(5,6)</sup>.

Involvement of the extrapyramidal system is rather rare in DPH intoxication. Studies in the literature have stated that the antiepileptic effect of this agent is mainly due to the inactivation of sodium channels<sup>(4,7)</sup>. Experimental studies using ganglion root cells<sup>(8,9)</sup>, hippocampal pyramidal neurons in rats<sup>(10,11)</sup>, neocortical neurons in humans<sup>(12)</sup>, tumour cell cultures in hamsters<sup>(13)</sup>, and pituitary cells<sup>(14)</sup> revealed that DPH may also block voltage-gated calcium channels. Moreover, rat embryos exposed to teratogenic doses of this agent showed significant down-regulation of the gene expression of voltage-gated calcium channels<sup>(15)</sup>. DPH also inhibits the binding of the calcium antagonist nitrendipine to voltage-dependent calcium channels in brain membranes, and can be regarded as a calcium channel-blocking effect<sup>(16)</sup>. This effect is not the principal antiepileptic mechanism of DPH action, but is accepted merely as a contributory anticonvulsant mechanism, and may be important in the adverse effects of the drug.

The orbitofrontal cortex is mainly involved in the maintenance of normal behavioural features and related to the ventral striatum and dopaminergic system. There is no information in the medical literature that relates orbitofrontal lesions to any clinically-evident movement disorder, including parkinsonism. The orbitofrontal cortex, along with mesial frontal cortices, is suggested to participate in the neural processes involved in self-initiation of movement<sup>(17)</sup>. The cerebellum, which is known to be the principal structure involved in the DPH intoxication, is also suggested to participate in the

initiation of sensory-triggered movements<sup>(18)</sup>. In our patient, the underlying mechanism of akinesia, which is among the major symptoms of parkinsonism, is expected to be due to the combined effect of the orbitofrontal cortex lesions, cerebellar dysfunction and calcium channel blockade due to toxic levels of DPH, since parkinsonism appears rarely as one of the features of DPH intoxication, in spite of its widespread use in clinical practice.

There are also changes reported to occur in the dopamine content of the orbitofrontal cortex in Parkinson's disease. A positron emission tomography study, which investigates changes in dopamine transporter availability, showed that dopamine release is significantly increased in the orbitofrontal cortex, and decreased in the putamen during gait in patients with Parkinson's disease, when compared with that in normal subjects<sup>(19)</sup>. Orbitofrontal cortex, as a component of the mesocortical dopaminergic system, is implied to participate in sustaining execution of independent gait with the aid of external stimuli in Parkinson's disease. The increased dopaminergic activity of the mesocortical system that involves the orbitofrontal cortex may be a consequence of the compensatory changes aimed to overcome the motor deficit due to the dysfunction of the nigrostriatal system.

This patient developed parkinsonism as a part of the whole clinical picture of the DPH intoxication, together with cerebellar signs and with its maximum expression in parallel with toxic blood levels of DPH, in spite of the partial resolution of the pre-existing haematoma on both gyrus recti at the same time. The radiological findings persisted, while the clinical features of parkinsonism resolved slowly following the discontinuation of DPH. Although speculative, involvement of one of the terminals of this mesocortical system, the cerebellum, and the effect of the calcium channel-blocking effect of the toxic levels of DPH on the basal ganglia, may lead to the development of parkinsonism, as a symptom of DPH toxicity in the patient presented in this report.

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