

## Malignant Syndrome of Two Parkinson Patients due to Withdrawal of Drugs

Dear Editor,

Neuroleptic malignant syndrome (NMS) is characterised by the impairment of consciousness, high fever, rigidity and autonomic instability. Although originally described in patients taking neuroleptic drugs, this syndrome may also occur in patients with Parkinson's disease (PD) during withdrawal or reduction of levodopa therapy or other dopaminergic drug therapy and is called malignant syndrome (MS) or neuroleptic-like syndrome.<sup>1,2</sup> Dehydration, antiparkinsonian drug withdrawal, infections and hot weather are considered to trigger this syndrome. Diagnostic criteria were originally proposed by Levenson.<sup>3</sup> Two patients with PD who developed MS, one of whom suffered from severe cerebral degeneration, are presented.

### Case 1

The patient was a 68-year-old man with 10 years of rigid-akinetic PD with UPDRS (unified Parkinson's disease rating scale) 72. His medication was 1 gr/d levodopa-benserazid and 15 mg/d selegiline. He was living with his son and doing his daily activities by himself. His son stopped his medication and tried to use alternative therapeutic methods. After 24 hours of stopping medication he was admitted to the emergency room. Increased salivation, diaphoresis and depressed turgor were observed on physical examination. Neurological examination revealed that he was stuporous. There was no toxic material in the alternative therapy. His axillary temperature was 38°C. Table 1 shows the laboratory findings at initial presentation and a week later. There were no abnormalities in the cerebrospinal fluid (CSF) tests. CSF, blood and urine cultures were sterile. Electrocardiography showed a normal sinus rhythm and a cardiology consultation did not indicate any abnormality. Electroencephalogram revealed abnormally slow waves on background activity. Cranial magnetic resonance (MR) was normal. Plasmapheresis was administered in the intensive care unit (ICU). Bromocriptine and levodopa were administered. A week later, the neurological examination revealed akinetic-mutism, rigidity with low grade fever (37.5°C to 38°C) and the UPDRS was 102. Blood transfusion was performed because of anaemia. A month later cranial MR and SPECT (Fig. 1) imaging demonstrated severe degeneration on both the centrum semiovale and the hypoperfusion on grey matter. After 10 months, the patient remains in the same state.

### Case 2

A 72-year-old man, with a history of 8 years tremor

dominant PD while at Hoehn & Yahr stage 3, was evaluated by a family doctor. His medication (625 mg/d levodopa, 0.75 mg/d pergolide) was discontinued and substituted by 20 mg/d propranolol. Rigidity developed 48 hours later, and he was almost unable to walk. After another 48 hours, he fell into somnolence. After admission to the ICU, his axillary temperature was 38.5°C. Table 1 shows the initial and 10-days laboratory findings of the case. CSF analysis were within normal limits. No changes were noticed in repeated blood, CSF and urine cultures. Intravenous fluid infusion and bromocriptine and levodopa through a nasogastric tube were administered. After 15 hours he was alert, but rigidity continued for 2 more days. Five days later upon discharge he had obviously not returned to his earlier state but Hoehn & Yahr stage was 3.

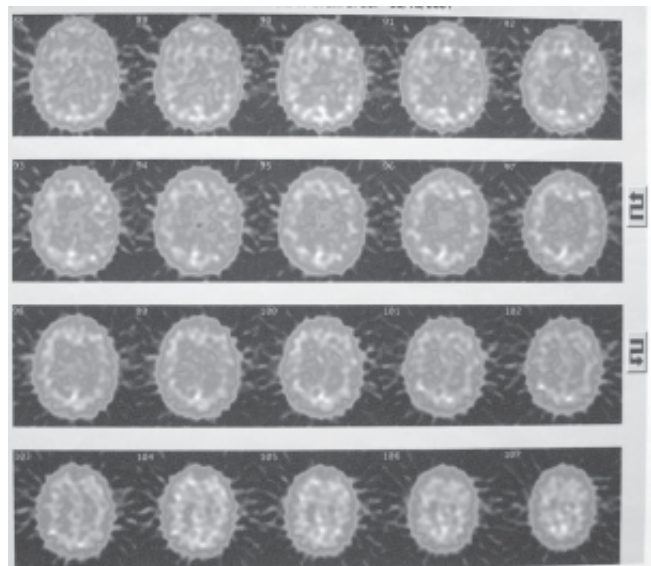


Fig. 1. Brain SPECT: Done with Tc-99-M-HMPAO showing heterogenous and general hypoperfusion in grey matter of Case 1.

### Discussion

Many theories have been presented on MS and there are no consensus. In pathogenesis, the long latency period between levodopa withdrawal and the appearance of MS features has been explained by the increased D-2 receptors as a result of chronic levodopa therapy.<sup>4</sup> But the mechanism of the disturbance of consciousness in MS is explained by the hypofunction of the meso-cortical dopaminergic system, especially the inhibition of the ventral tegmental area by somatodendritic D-2 receptors.<sup>5</sup> In the first patient, dehydration may be another cause of the MS in addition to the withdrawal of levodopa, if he could not take enough

Table 1. Laboratory Findings of Patients During Malignant Syndrome

		Glucose (mg/dl)	ALT (IU/l)	ALT (IU/l)	BUN (mg/dL)	Creatinin (mg/dL)	CK (IU/l)	Na (mEq/l)	Hb (g/dL)	WBC (cmm)
Case 1	Initial	121	133	226	14	0.59	800	132	12.5	13,300
	7 days later	110	68	134	12	0.50	210	130	8.52	9500
Case 2	Initial	98	56	67	22	1.0	920	130	13.2	10,800
	7 days later	100	45	33	18	0.7	180	135	11.4	11,000

ALT: alanine aminotransferase; BUN: blood urea nitrogen; CK: creatine kinase; Na: sodium; Hb:haemoglobin; WBC: white blood count

fluid as in Kuno et al's description of a patient with MS in hot weather, while taking the medication regularly.<sup>4</sup> It was very hot in Adana-Turkey (nearly 42°C in shadow) at the time of the event. The none response to a levodopa supplement and the subsequent degeneration of the basal ganglia indicate that there was something more than withdrawal of levodopa that worsen the clinical state. No such cases have been reported in literature except 2 reporting on a patient with severe high fever that was thought to be the cause of the cerebellar degeneration, and another patient who died of MS showing focal necrosis in the anterior and lateral hypothalamus.<sup>2,6</sup> Fever and an ischaemic process due to anaemia may be the cause of the degeneration on both sides of the centrum semiovale. This deterioration may be accepted as an indirect sequel of the NMS. Our second case is similar to the previously published cases. A central nervous system infection was excluded by CSF analysis. Serum CK elevation was present in both patients, but neither had rhabdomyolysis. Older age, higher Hoehn & Yahr scale, higher akinesia score, and the absence of a wearing off phenomenon prior to developing MS were associated with poor prognosis. The main treatments are intravenous fluid, levodopa, dantrolene sodium, bromocriptine, propranolol and amantadine. To our knowledge, the first patient is the only reported case of MS with bilateral centrum semiovale degeneration. Most of the cases improve within 1 to 4 weeks, as described in the second case. There is no study about cerebral imaging changes of these patients.

In conclusion, in spite of the fact that many patients reported on earlier had returned to pre-MS scores, the physicians evaluating MS patients with unfavourable

outcomes should check these patients' brain imaging for cerebral degeneration and take into consideration that the deterioration may be caused by the indirect affects on the NMS by anaemia, fever and ischaemia. The withdrawal of antiparkinson drugs is advised to be done under hospital conditions.

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