# Neuroleptic Malignant Syndrome Without Neuroleptics

**K C Ong, E L Chew, Y Y Ong**


## ABSTRACT

**Neuroleptic malignant syndrome is an uncommon condition characterised by hyperthermia, rigidity, altered mentation and autonomic instability. Recognition of this condition is essential because its complications are potentially lethal, leading to death in 20% of patients. Not all cases of this syndrome are associated with the use of neuroleptics and there is an increasing number of reports of this condition occurring after withdrawal of therapy with dopaminergic drugs, typically in patients with Parkinsonism. In this setting, there is tremendous potential for misdiagnosis and delay in institution of treatment because of the traditional and common association of the syndrome with the use of neuroleptics only. We report a case of neuroleptic malignant syndrome in a patient with Parkinsonism subsequent to the withdrawal of levodopa and bromocriptine.**


**Keywords: Parkinsonism, hyperthermia, levodopa, bromocriptine, dopaminergic agents**

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## INTRODUCTION

Since its original description in 1968, neuroleptic malignant syndrome (NMS) has received increasing recognition as a potentially lethal condition. NMS was so named because the initial reported cases were all associated with the use of neuroleptic drugs. Subsequently, it became established that other dopamine-blocking agents eg metoclopramide hydrochloride or dopamine-depleting agents eg reserpine may also cause this syndrome[1]. Tricyclic antidepressant drugs and monoamine oxidase inhibitors have also been implicated[1]. Less well appreciated, however, is that withdrawal of dopaminergic agents can also produce the same syndrome. We report a case of NMS developing in a patient with Parkinsonism after the withdrawal of dopaminergic therapy.

## CASE REPORT

A 63-year-old Chinese woman was hospitalised for the complaints of fever and cough with yellow sputum for 3 days, and epigastric discomfort for one week. She was diagnosed to have Parkinson's disease 11 years ago and had been on levodopa/benseraside and benzhexol since the diagnosis was made. Bromocriptine was subsequently added 3 years ago. For at least 9 months before her hospitalisation she had been taking levodopa l00mg/benserazide 25mg (Madopar 125mg) three times a day, levodopa l00mg/benserazide 25mg Hydrodynamically Balanced System (Madopar HBS 125mg) twice a day as well as bromocriptine 5mg twice a day. She had remained compliant with these medications despite having a very poor appetite and occasional vomiting for one week prior to her hospitalisation. She did not take any other medication during the period she had been unwell. Although previously ambulant with a walking frame, she had become bed-ridden and totally dependent on her activities of daily living for two weeks prior to her admission.

Clinical examination on admission revealed an alert and rational woman with a temperature of 40°C, a blood pressure of 140/88 mmHg and a pulse rate of 110/min. She had a mask-like facies and there were resting coarse tremors of the hands with cogwheel rigidity of both wrists. There was generalised rigidity. Chest and abdominal examination were normal and there were no obvious sources of sepsis clinically.

Her investigations on admission to hospital were as follows: chest X-ray - normal; total white cell count (TW) 10,960/$mm^3$ with 74% of polymorphs; serum urea 19.5mmol/L and creatinine 180μmol/L. Urine and blood cultures were negative. She was empirically started on intravenous Ceftriaxone but her fever remained.

On the third day of hospitalisation, she was noted to be perspiring profusely, tachypnoeic and extremely stiff during the morning ward round, but she was otherwise alert. She became drowsy and hypotensive with a systolic blood pressure of 60mmHg in the afternoon. There was sinus tachycardia of 130 beats per minute. Fluid resuscitation and intravenous dopamine were started immediately. Intravenous

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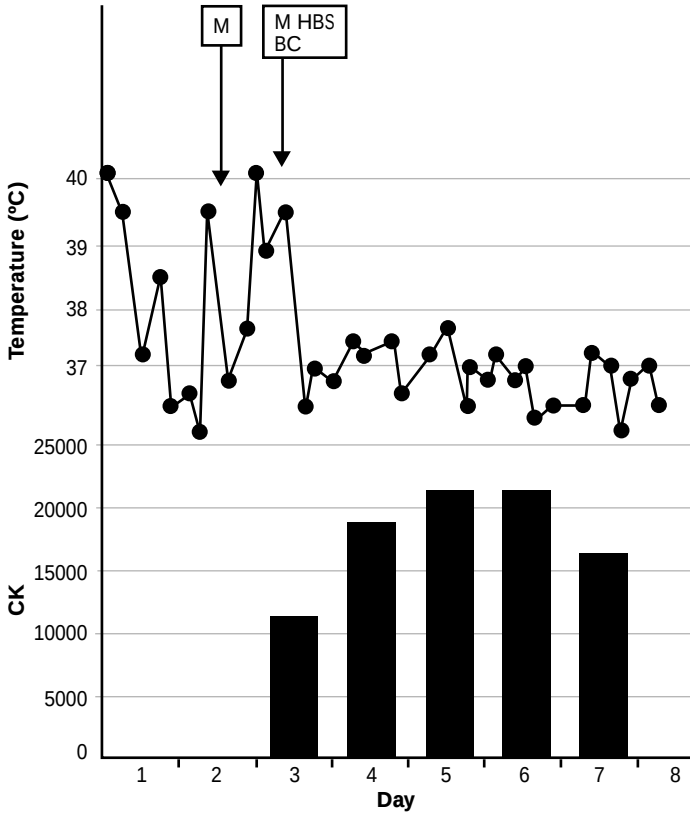
**Fig. 1** Clinical course showing elevated serum creatine kinase in this patient with NMS caused by withdrawal of dopaminergic therapy as well as the temporal relationship between restarting dopaminergic therapy and the decline in body temperature.




*M = levodopa/benserazide; M HBS = levodopa/benserazide HBS; BC = bromocriptine; CK = serum creatine kinase in U/L

Metronidazole was added to Ceftriaxone to cover for suspected aspiration pneumonia. She was transferred to the medical intensive care unit (MICU) for further management.

The results of blood investigations performed in the MICU were as follows: Haemoglobin 14.8 g/dL, TW 11,690/mm$^3$, platelets 98,000/mm$^3$, blood urea 30.5mmol/L, creatinine 392µmol/L, creatine kinase (CK) 12,120 U/L with a CKMB level of 16.9 U/L, aldolase 43.1 U/L. Aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH) levels were 336 U/L, 151 U/L and 1816 U/L respectively. An electrocardiogram was normal. Although her urine was noted to be dark red upon catherisation, urine myoglobin was not detected.

Septic work-up was repeated and the cultures of blood, urine and sputum were negative. A repeat chest X-ray again showed clear lung fields with no evidence of pneumonia An ultrasound examination of the abdomen was normal. Serum D-dimers were raised, but fibrinogen level was normal and soluble fibrin monomers were absent. Leptospiral, legionella, mycoplasma serologies and dengue IgM were all negative. Convalescence levels of leptospiral, legionella and dengue antibodies done 2 weeks later were also negative. Thyroid function tests and CT scan of the brain were normal.

It was noted that she was not served Madopar for one day and was also not given Bromocriptine for 2 days after her admission to hospital although these medications had been prescribed. Upon restarting these medications at the previous dosages, her fever settled (see Fig. 1) and she became alert and rational. The generalised hypertonia also gradually subsided and she became more mobile over the next few days. A diagnosis of NMS secondary to the withdrawal of dopaminergic drugs was made on the fourth day after hospitalisation.

The serum CK level rose to a maximum of 21,863 U/L on the fifth day of hospitalisation. It declined gradually after that with normalisation of levels 20 days later. Serum creatinine level normalised on the fourth day of hospitalisation.

Her subsequent hospitalisation period was complicated. A gastroscopy performed to investigate an acute decline in haemoglobin level showed antral gastritis with chronic duodenal ulcer and she was treated with Famotidine for 6 weeks. She also developed acute urinary retention due to detrussor weakness and required prolonged catheterisation. In addition, she developed dope dyskinesia with on-off phenomenon which required several adjustments of her anti-parkinsonian medication. She was eventually discharged after several weeks of intensive physiotherapy.

## DISCUSSION

NMS is thought to occur as a result of sudden reduction of central dopaminergic drive in the striatum and hypothalamus[2]. The relative hypothalamic dopamine deficiency can result from either dopamine receptor blockade (eg by neuroleptics) or dopamine withdrawal. NMS occurs in approximately 0.5-1% of all patients receiving neuroleptic drugs[1]. Although there have been several reports that this syndrome can also occur after withdrawal or reduction of dopaminergic agents eg amantadine[3,4], bromocriptine[5] and levodopa[5-12], this association is still not well recognised.

The cardinal clinical features of NMS are hyperthermia, extrapyramidal signs, altered mentation and autonomic instability. Our patient had all these features, thus enabling the diagnosis to be made with confidence. In a large series of cases, Kurlan et al[13] tabulated the frequency of various signs of NMS and the most common signs of autonomic dysfunction were fever (100%), tachycardia (79%), diaphoresis (60%), labile blood pressure (54%). The most common extrapyramidal symptoms were rigidity (92%) and tremors (92%) while coma (27%) or stupor (27%) were the most frequent forms of mental status alteration.

Other associated findings include sialorrhoea, urinary incontinence or retention of urine, neurological dysfunction eg dysphagia, aphonia, dysarthria and prolonged convulsions. The most common laboratory abnormality is an elevated CK level (usually >l0,000 U/L) resulting from rhabdomyolysis due to sustained muscle contraction associated with rigidity[1,12]. Myogloginuria may occur leading to acute renal failure. Other muscle derived enzymes like AST, ALT, LDH may also be raised[2] as in the present case. Leukocytosis (10,000-25,000 cells/$mm^3$) is common[2].

Differential diagnoses of NMS include infections especially viral or bacterial meningitis and encephalitis, pneumonia and urinary tract infection, heatstroke; movement disorders eg acute dystonias, Parkinsonism, tetany, acute catatonia; malignant hyperthermia and allergic reactions, Especially relevant in this case is that the early signs of NMS eg rigidity, tremors and confusion in a patient with Parkinsonism may be mistakenly attributed to worsening of the Parkinsonian state. Nonetheless, hyperthermia, severe axial rigidity and rapidly changing mentation should suggest a diagnosis of NMS rather than uncomplicated Parkinsonism. Other pitfalls in diagnosis include the lack of familiarity with withdrawal of dopamine therapy as a cause of NMS. Inclusion of the term "neuroleptic" in NMS may inhibit consideration of the diagnosis when the offending pharmacological manipulation does not involve neuroleptic drugs. Several cases had previously demonstrated increased mortality and morbidity as a result of delay in recognising this syndrome and restarting dopaminergic therapy[1]. Furthermore, failure to recognise this condition may result in inappropriate attempts to treat the confusion with neuroleptic drugs[1].

There is a wide spectrum of clinical circumstances associated with withdrawal of dopaminergic agents leading to the development of NMS[1]. In the present case, poor absorption of the drugs as a result of the patient's gastro-intestinal complaints may have led to the development of NMS. The syndrome subsequently became full-blown with the inadvertent omission of these medications for the first 2 days of hospitalisation. Other reports have described the development of NMS secondary to abrupt cessation of dopaminergic therapy as a result of patients misunderstanding instructions[1], non-compliance[12], presumed side effects[11], planned levodopa drug holiday[1,8] and attempts to replace one dopaminergic agent with another[1]. The remarkable sensitivity of some patients with Parkinsonism to withdrawal of dopaminergic therapy is illustrated by the reported case of a patient suffering from response fluctuations to carbidopa/levodopa (the "on-off" phennomena) who developed recurrent hyperthermia several times daily in phase with the "off" episodes and ultimately died of NMS[14]. There is also variability of onset of NMS among cases secondary to withdrawal of dopaminergic drugs but there are, to our knowledge, no reports that the syndrome developed more than a few weeks after discontinuation of anti-Parkinsonism medication. The syndrome usually evolves over a 72-hour period[12].

When NMS is due to acute withdrawal of dopaminergic therapy, the first step in treatment is to reinstate therapy with these agents. Supportive therapy is essential and includes the use of cooling blankets and antipyretics for hyperthermia, correction of electrolyte abnormalities and fluid imbalances, blood pressure monitoring, nutritional support if the syndrome is protracted and hemodialysis for renal failure. Therapy with dantrolene is an established treatment of NMS of any cause Recently, carbidopa/levodopa has been used effectively as an adjunct to or in place of dantrolene in management of NMS caused by neuroleptics[15,16].

Finally, even though NMS is potentially a life-threatening condition, not all cases of NMS result in serious consequences. A "benign" type of malignant syndrome consisting of moderate elevation of serial CK and worsening of motor symptoms in Parkinsonian patients with mild upper respiratory tract infections have been described[17].

## CONCLUSION

The timely diagnosis and appropriate treatment of NMS can be life-saving. Therefore, it is critical that the entire spectrum of causes of this syndrome be appreciated, including withdrawal, reduction, or alteration of dopaminergic therapy. In this regard, the term "neuroleptic malignant syndrome" must be considered inaccurate and misleading. "Acute dopamine depletion syndrome" has been suggested as a more appropriate term[1], However, as it is likely that the original terminology for the syndrome will remain, it is perhaps simpler to always remember to refer to NMS, with qualification, as the neuroleptic (not always) malignant (sometimes) syndrome.

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