

# Neurological Sequelae of Neuroleptic Malignant Syndrome

S Chakrabarti, D Sharma, G Singh

## Abstract

The case of a young man with bipolar disorder who recovered from neuroleptic malignant syndrome but subsequently developed extensive neurological sequelae is described.

**Key words:** Basal ganglia, drug effects, Cerebellum, neuroleptic malignant syndrome, complications

## Introduction

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic reaction, commonly associated with neuroleptic treatment. It is potentially fatal, with mortality rates of 10 to 20%. Most fatalities occur early — pneumonia and renal failure account for the majority of deaths during this stage.<sup>1</sup>

Patients who survive NMS usually completely recover.<sup>2</sup> Long-term neurological sequelae after an episode of NMS are rare, and their clinical manifestations diverse. However, there has been no systematic research on the subject. Thus, the incidence and prevalence of post-NMS neurological sequelae are unknown. Case reports indicate that presentations vary from subtle neuropsychological deficits such as transient or persistent cognitive impairment, including organic amnesic syndromes,<sup>3-5</sup> to widespread cerebellar damage.<sup>2,6,7</sup> Persistent abnormal involuntary movement disorders, such as dyskinesias, rigidity, hypertonia, dysarthria, and tremors following NMS have also been described.<sup>8-11</sup>

This report describes the case of a young man with bipolar disorder, who recovered from NMS, but subsequently developed extensive neurological sequelae.

## Case Report

A 20-year-old, previously healthy, computer student developed symptoms of elation, overactivity, grandiosity, disinhibition, overspending, disturbed sleep, and poor self

care over a period of 2 weeks without any apparent precipitant. A private psychiatrist diagnosed mania. Treatment commenced with a combination of oral and injectable haloperidol (total daily dose 10 to 40 mg/day) and lithium carbonate 600 mg/day. Carbamazepine 600 mg/day was added in a further effort to control symptoms. Manic symptoms subsided with this treatment, but after 3 weeks the patient developed a high-grade fever (39.4 to 40.5°C) and diffuse macular rashes. Carbamazepine was withdrawn. However, on the following day, the patient developed rigidity of the neck and back, rapidly extending to involve the whole body. All psychotropic medication was discontinued. The patient was treated with antibiotics and antipyretics, with little evident response. He was referred to the Department of Psychiatry at the Postgraduate Institute of Medical Education and Research for further management.

On admission, the patient was found to be febrile, and sweating profusely. He became progressively more rigid, mute, incontinent, unresponsive, and finally comatose. Investigations revealed leukocytosis, and a serum creatine phosphokinase isoenzyme MM (CPK-MM) level of 3730 IU/L (normal range, 30 to 140 IU/L). Other investigations, including cerebrospinal fluid (CSF) analysis, urine/blood cultures, viral serology for herpes simplex virus (HSV), and computed tomography (CT) and magnetic resonance imaging (MRI) studies of the brain were all normal. He was hypoxic ( $PO_2 = 45$ ) and required respiratory support for 3 days.

By the third day after admission, a diagnosis of NMS was made. Bromocriptine therapy 5 mg/day was initiated and gradually increased to 20 mg/day. This led to considerable improvement, with fever and rigidity subsiding over the following 3 to 4 weeks. Sensorium improved and the patient was able to recognise family members. He was able to comprehend language but, due to a severe dysarthria, was only able to communicate by gestures. The patient remained confined to bed and had minimal ability to move his limbs. Dyskinetic, choreoathetoid, and dystonic movements were noted for the first time during this period. The patient's recovery was further complicated by left lung collapse, secondary to an inspissated mucous plug, which was subsequently removed bronchoscopically. He also

---

*Dr S Chakrabarti, Assistant Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*

*Dr D Sharma, Registrar, Department of Psychiatry, Indira Gandhi Medical College, Shimla, India*

*Dr G Singh, Senior Resident, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

**Address for correspondence:** Dr S Chakrabarti, Assistant Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Tel.: (91 172) 747609 632 ext. 247

Fax: (91 172) 744401/745078/744503

E-mail: medinst@pgi.chd.nic.in

**Submitted:** 29 January 2001; **Accepted:** 11 July 2001

developed infected bedsores and a urinary tract infection (UTI) due to catheterisation. This resulted in high-grade fever and delirium that responded well to antibiotics and was thus of short duration.

During the following month, the patient's condition improved further, albeit gradually. His sensorium and comprehension returned to normal. He became continent and the catheter was removed. He started moving his limbs and could sit for brief periods. The CPK fell to 450 IU/L.

Neurological sequelae, however, became more marked at this stage and consisted of abnormal movements such as choreoathetosis, myoclonus, and dystonias of the neck, limbs and tongue. Speech output was minimal and scanning in character. Detailed neurological examination also revealed bilateral gaze evoked nystagmus, dysmetria, hypotonia, truncal ataxia, titubations, and pendular knee jerks. An electroencephalogram (EEG) recording was normal, but a repeat CT scan revealed midbrain atrophy, and MRI revealed more generalised brain atrophy, including severe cerebellar atrophy. Neurologists endorsed the diagnosis of post-NMS sequelae. Bromocriptine was discontinued, which led to some improvement in the abnormal movements.

For the following 5 months, the patient was treated with various drugs (anticholinergics, benzodiazepines, valproate), intensive physiotherapy, and regular speech therapy. Some improvements were seen but, at the time of discharge, the patient was only able to walk a few metres without support and speak a few words with great effort. Six months after discharge, all abnormal movements, except dystonias of the neck had ceased. The patient was able to walk without support, but still could only produce a few intelligible words.

## Discussion

This patient had a severe episode of mania, with marked agitation and excitement. He was treated with high doses of oral and injectable haloperidol, together with lithium and carbamazepine. It has been suggested that a psychiatric diagnosis of catatonia or mania, the presence of severe agitation/excitement, treatment with large doses of high potency antipsychotics such as haloperidol or lithium therapy, and parenteral drug use, are all potential risk factors for developing NMS.<sup>12</sup> The patient described in this report, having several of these risk factors, was therefore at high risk for developing NMS. However, it remains uncertain whether these same factors contributed to the post-NMS sequelae which developed in this patient.

The diagnosis of NMS was based on several parameters considered characteristic of this syndrome.<sup>12,13</sup> Firstly, he presented with pathognomonic clinical features, such as hyperthermia, generalised rigidity, altered sensorium, and evidence of autonomic dysfunction. A raised CPK level and leukocytosis were also detected at first presentation. These indices subsequently became normal. The patient's symptoms, developed following exposure to neuroleptics (in combination with mood stabilisers). Finally, every effort was made to exclude other pathology that could account for the

symptoms. In this regard, there was no evidence of any pre-existing physical illness to explain his symptoms, or the neurological sequelae which subsequently developed. Further, investigations, including CSF cytology and biochemistry to exclude encephalitis and meningitis, viral serology for HSV, blood and urine cultures to eliminate other possible sources of infection and septicaemia, and CT and MRI to identify any brain lesions, were all normal at the time of presentation.

There was some (possibly avoidable) delay in the diagnosis of NMS and institution of bromocriptine. The patient also developed respiratory distress, requiring respiratory support for the first few days, and later, left lung collapse, which resolved after bronchoscopic removal of an inspissated mucous plug. Still later, the patient developed fever and delirium secondary to UTI and infected bedsores. These complications were secondary to NMS. It has often been noted that renal and respiratory disorders are the most frequent complications during, and in the immediate aftermath of, an episode of NMS.<sup>1</sup>

Once the patient had survived the acute crisis, it became evident that he had sustained massive brain damage. Two distinct sets of neurological sequelae were discernible. One group of symptoms reflected cerebellar damage — nystagmus, ataxia, hypotonia, dysmetria, titubation, scanning speech, and pendular jerks. The other group of symptoms included abnormal involuntary movements such as choreoathetosis, dystonia, and myoclonus, suggestive of basal ganglia involvement. A MRI scan completed at this stage confirmed the presence of generalised brain atrophy, particularly of the cerebellum.

Hyperthermic injury of the cerebellum and consequent loss of Purkinje neurons is well-documented in heat stroke.<sup>2</sup> There are similar, although fewer, reports of heat-induced injury in NMS, resulting in post-NMS cerebellar sequelae.<sup>2,6,7</sup> In two of these reports, haloperidol used in combination with tetrabenazine or lithium carbonate was implicated as a causative factor.<sup>2,7</sup> NMS developed subsequent to lithium intoxication in the other instance.<sup>6</sup> The case reported by Lal et al concerned a 55-year-old woman with bipolar disorder who developed NMS when haloperidol was added to lithium for treatment of an acute manic episode.<sup>7</sup> After recovering from NMS this patient was initially mute, with ocular dysmetria, ataxia, and limb and trunk tremors, all suggestive of pancerebellar involvement. Four months later, her condition was largely unchanged, except that she now had minimal speech output, which was scanning in character. The authors ascribed the initial (transient) muteness to acute bilateral cerebellar injury, and the cerebellar symptoms to NMS-induced hyperthermic injury. The similarities in presentation with the current case are quite striking.

In a neuropathological study of post-NMS sequelae, Lee et al were able to demonstrate extensive Purkinje cell loss in the cerebellum at post mortem.<sup>2</sup> Similar findings of cerebellar degeneration and almost complete Purkinje cell loss at autopsy were also reported by Naramoto et al.<sup>6</sup> The patient was a 65-year-old female with bipolar disorder who developed NMS in association with lithium intoxication.

In both these reports, the selective vulnerability of the cerebellum to heat-induced injury was indicated by the sparing of the cerebral cortex, basal ganglia, and hippocampus, areas that are normally involved in hypoxic brain injury.

The patient described in this report also demonstrated abnormal involuntary movements suggestive of basal ganglia involvement. Such movements, as well as basal ganglia changes on single photon emission CT (SPECT) scans, have been reported during the acute stages of NMS.<sup>13,14</sup> However, no instances of basal ganglia damage secondary to NMS are evident in the literature. This leads to the speculation that basal ganglia involvement in this case could have been due to the hypoxia sustained during periods of respiratory compromise.

Finally, there is also the possibility that specific drugs could have contributed to the post-NMS sequelae seen in the patient described. There have been reports of organic brain syndromes and NMS in patients treated with a combination of high dose haloperidol and lithium.<sup>8,15</sup> Lithium in combination with neuroleptics may also increase the risk of a hypermetabolic crisis, possibly through serotonergic mechanisms.<sup>13</sup> Of note, lithium itself has been known to cause permanent cerebellar damage, although this usually follows an episode of acute intoxication.<sup>16</sup> The combination of lithium with carbamazepine is also known to be particularly neurotoxic in this regard.<sup>16</sup>

Whatever the mechanism, there can be no doubt that this patient sustained massive brain damage during, and as a result of, an episode of NMS. It has been suggested that mortality rates of NMS are declining because of improved detection and early treatment.<sup>12</sup> The case of this unfortunate young man serves to remind us that patients surviving NMS may have extensive, permanent, disabling neurological sequelae. Although this is an uncommon outcome of NMS, it highlights the need for early and accurate diagnosis, as well as adequate treatment for what is perhaps the most serious adverse effect of neuroleptic treatment.

## References

1. Addonizio G, Susman VL, Roth S. Neuroleptic malignant syndrome: review and analysis of 115 cases. *Biol Psychiatry* 1987;22:1004-1020.
2. Lee S, Merriam A, Kim TS, Liebling M, Dickson DW, Moore GR. Cerebellar degeneration in neuroleptic malignant syndrome: neuropathologic findings and review of the literature concerning heat-related nervous system injury. *J Neurol Neurosurg Psychiatry* 1989;52:387-391.
3. Kammerer T, Singer L, Patris M, Fiance MF, Tempe JD, Rey G. Malignant neuroleptic syndrome or neuroleptic overdose (pipothiazine). Case report. *Ann Med Psychol (Paris)* 1972;2:550-554.
4. Rothke S, Bush D. Neuropsychological sequelae of neuroleptic malignant syndrome. *Biol Psychiatry* 1986;21:838-841.
5. Van Harten PN, Kemperman CJ. Organic amnesic syndrome: a long-term sequel after neuroleptic malignant syndrome. *Biol Psychiatry* 1991;29:407-410.
6. Naramoto A, Koizumi N, Itoh N, Shigematsu, H. An autopsy case of cerebellar degeneration following lithium intoxication with neuroleptic malignant syndrome. *Acta Pathol Jpn* 1993;43:55-58.
7. Lal V, Sardana V, Thussu A, Sawhney IM, Prabhakar S. Cerebellar degeneration following neuroleptic malignant syndrome. *Postgrad Med J* 1997;73:735-736.
8. Cohen WJ, Cohen NFH. Lithium carbonate, haloperidol, and irreversible brain damage. *J Am Med Assoc* 1974;230:1283-1287.
9. Kontaxakis V, Stefanis C, Marbidis M, Tserfe V. Neuroleptic malignant syndrome in a patient with Wilson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:1001-10002.
10. Eiser AR, Neff MS, Slifkin RF. Acute myoglobinuric renal failure. A consequence of neuroleptic malignant syndrome. *Arch Intern Med* 1982;142:601-603.
11. Mueller PS, Vester JW, Fermaglich J. Neuroleptic malignant syndrome: successful treatment with bromocriptine. *J Am Med Assoc* 1983;249:386-388.
12. Balzan MV. The neuroleptic malignant syndrome: a logical approach to the patient with temperature and rigidity. *Postgrad Med J* 1998;74:72-76.
13. Caroff SN, Mann SC, Lazarus A, Sullivan K, MacFadden W. Neuroleptic malignant syndrome: diagnostic issues. *Psych Annals* 1991;21:130-147.
14. Nisijima K, Matoba M, Ishiguro T. Single photon emission computed tomography with 123I-IMP in three cases of neuroleptic malignant syndrome. *Neuroradiology* 1994;36:281-284.
15. King DJ. Neuroleptics and treatment of schizophrenia. In: King DJ, editor. *Seminars in clinical psychopharmacology*. London: Gaskell; 1995:259-327.
16. Jefferson JW, Griest JH. Lithium. In: Kaplan HI, Sadock BJ, editors. *Comprehensive textbook of psychiatry*. 6th ed. Baltimore: Williams & Wilkins; 1995: 2022-2030.