

## Drug resistant neuroleptic malignant syndrome and the role of electroconvulsive therapy

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### Abstract

Neuroleptic malignant syndrome is considered as a rare but potentially fatal complication of neuroleptic medications e.g., antipsychotics, sedatives and antiemetics. It is characterized by hyperthermia, muscle rigidity, an elevated creatine kinase level and autonomic instability. The syndrome often develops after the start of antipsychotic or a sudden increase in dosage of the neuroleptic medication or in states of dehydration. Treatment is mainly supportive and includes withdrawal of the neuroleptic medication and, possibly, administration of drugs such as dantrolene and bromocriptine. In rare cases where drug treatment remains ineffective a trial of electroconvulsive therapy is being given. The case presented is a drug resistant case of Neuroleptic Malignant Syndrome where finally electroconvulsive therapy was effective.

**Keywords:** Neuroleptic Malignant Syndrome, Electroconvulsive therapy.

### Introduction

Neuroleptic malignant syndrome (NMS) is a rare, but potentially life-threatening adverse reaction to antipsychotic drugs and other dopamine-modulating agents. Symptoms of NMS include severe muscle rigidity, fever, autonomic instability, mental status changes and laboratory abnormalities like elevated muscle enzymes, transaminases, lactic acid dehydrogenase, decreased serum iron concentrations, metabolic acidosis and leukocytosis.

Incidence rates for neuroleptic malignant syndrome (NMS) range from 0.02 to 3 percent among patients taking neuroleptic agents.<sup>1</sup> While most patients with NMS are young adults, but age is not a risk factor.<sup>3</sup> This syndrome has been described in all age groups from 0.9 to 78 years.<sup>2</sup> In most studies, men are affected more than women. Both age and gender distributions correspond with the distribution of the

exposure to neuroleptic agents.<sup>2</sup>

The presented case is of severe drug resistant neuroleptic malignant syndrome where patient remained in intensive care unit with ventilator support for a long time and finally responded to electroconvulsive therapy.

### Case Report

A 34 years old Filipino female was admitted under care of psychiatry department with the brief history of abnormal behaviour including episodic aggressive behaviour, irrelevant talk, self-talking, shouting, hallucination, restlessness and agitation. She was started on typical antipsychotic agent Haloperidol along with Lorazepam but did not improve. The next day she was started on olanzapine and procyclidine, but the patient remained psychotic, agitated, restless, and aggressive. After 2 to 3 days she was given high dose of Risperidone in injectable form. But the patient's condition deteriorated and she became more restless, along with little bit stiffness, aggressive behaviour and confusion. She also developed autonomic instability with fluctuation of blood pressure and respiration, but the temperature was normal. She was shifted to Neurology service and was started on supportive care and later transferred to high dependency unit.

On examination she was confused, restless and agitated. She had abnormal orofacial dyskinesic movements. There was no pupillary asymmetry. Extraocular movement seemed to be full. She was stiff all over with brisk reflexes and down going plantars. Initial laboratory data showed normal CBC, liver function, renal function, serum electrolyte, coagulation profile, Thyroid Function Test, and B12 levels. She had raised creatine phosphokinase (CPK) of 723 unit which increased to 4000 during the next 4 to 5 days. She continued to deteriorate with further stiffness in body and rise in temperature up to 40°C. She was shifted to medical ICU and was started on Procyclidine along with Diazepam, Sinemet, Pramipexole with gradual increment of the doses. The condition deteriorated gradually and patient became more stiff, rigid, along with autonomic compromise with fluctuation of heart rate, BP and respiration. She was sedated and put on ventilator. Dantrolene was continued with maximum recommended dose. She was also taking

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Propofol along with midazolam infusion and fentanyl in between. Despite all these medication she was totally non responsive with continuous increase in stiffness and occasional fluctuation. She started clinching her teeth and she broke her teeth. Dental consultation was arranged to save her teeth. Dental support was applied and patient was put on complete sedation. She was given trial of reduction of sedation many times during ICU stay but on reduction she became stiff and restless again

As she remained totally resistant to all these dopaminergic, anti cholinergic, muscle relaxant, sedative, anaesthetic medication and supportive care including hydration, nutrition, antibiotics and physiotherapy, it was finally decided to go for electroconvulsive therapy (ECT). She was to receive 9 sessions of ECT. During the first 7 session she remained unresponsive but after the 8th sessions of ECT, patient started showing some improvement. Stiffness lessened and she became more conscious, along with lowering of temperature and with stability of autonomic fluctuations.

Though she continued to improve and became more conscious but remained restless with same base line

abnormal behaviour. She was kept on ventilator for about 5 weeks and then finally gradually weaned off from the ventilator. She was shifted from ICU to high dependency and then to general ward when she was almost back to same base line with psychotic behaviour and restlessness.

## Discussion

This case is unusual in that it is one of the most severe form of neuroleptic malignant syndrome with autonomic instability and respiratory compromise and patient remained on ventilator for more than 5 weeks. Other unusual thing seen in this case is that this patient was exposed not only to one antipsychotic drug but heavy doses of antipsychotics both typical and atypical were given including high doses of haloperidol in injection form along with heavy doses of olanzapine and resperidone continuously for eight days.

Most likely NMS is self-limiting after antipsychotics are discontinued with average duration of recovery in the range of 7-10 days.<sup>2</sup> Successful treatment of NMS depends on early clinical recognition and prompt withdrawal of the neuroleptic agents. Neuroleptics cannot be removed by dialysis and blood concentrations decline only slowly.

**Table-1:** Algorithm proposed for individualized supportive therapy.

Woodbury status	Clinical presentation	Supportive therapy	First-line interventions	Second-line interventions
Status I: drug-induced Parkinsonism	Rigidity, tremor	Reduce or change APS	Anticholinergic drugs	
Status II: drug-induced catatonia	Rigidity, mutism, stupor	Discontinue, reduce, or change APS	Lorazepam (1-2mg IM or 4-6h)	
Status III: moderate or early NMS	Moderate rigidity, catatonia, or confusion, T $\leq$ 38°C, HR 100-120bpm	Discontinue APS, monitor progress closely, correct risk factors	Lorazepam (1-2mg IM or 4-6h)	
Status IV: moderate NMS	Moderate rigidity, catatonia, or confusion, T $\leq$ 38-40°C, HR 100-120bpm	Discontinue APS, IV fluids management, initiate cooling measures, correct risk factors, provide intensive care	Lorazepam (1-2mg IM or 4-6h), bromocriptine (2.5-5mg PO/NGT 8h) or amantadine (100mg PO/NGT 8h)	Consider ECT (6-10 bilateral sessions)
Status V: severe NMS	Severe rigidity, catatonia, or coma, T $\geq$ 40°C, HR >120bpm	Discontinue APS, IV fluids management, initiate cooling measures, correct risk factors, provide intensive care	Dantrolene (1-2.5mg/kg of weight IV 6h for 48h) combined with bromocriptine (2.5-5mg PO/NGT 8h) or amantadine (100mg PO/NGT 8h)	Consider ECT (6-10 bilateral sessions)

APS: Antipsychotics; ECT: electroconvulsive therapy; HR: heart rate; IV: intravenous; NGT: nasogastric tube; NMS: Neuroleptic Malignant Syndrome. PO: by mouth; T: temperature.

**Table-2:** Showing important case reports showing importance of electroconvulsive therapy for NMS patient.

Study	Patient age	CPK, Labs	Failed medication	ECT therapy detail	Outcome
*Adam Wysokinski at al. <sup>5</sup>	44 years Male	CPK.:8241 U/L	Lorazepam, Bromocriptine Amantadine Diazepam, Dentrolene	Total 19 Sessions	Very good
**Yousefi A at al. <sup>6</sup>	22 years Male	---	Dantrolen, Bromocriptin Amantadin	Total 10 Sessions	Good
***Harland CC at al. <sup>7</sup>	29 years Female	CPK. 1602	Bromocriptine Dentrolene Diazepam	Total 04 sessions	Very good

\*Adam Wysokinski: Intensive Electroconvulsive Therapy In Drug Resistant Neurolepticmalignant Syndrome - Case Report Psychiatria Danubina, 2012; Vol. 24, No. 2, pp 219-222

\*\*Yousefi A, Asgari F. Electroconvulsive therapy in drug resistant neuroleptic malignant syndrome: a case report. Tehran University Medical Journal . A2010;67(11) : 817-820

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General symptomatic treatment, such as hydration, nutrition and reduction of fever, is essential. Secondary complications, such as hypoxia, acidosis and renal failure, must be treated aggressively.

The algorithm proposed by Woodbury<sup>4</sup> in 1992 provides us the guideline toward the management of MNS (Table-1). Supportive care including rehydration and regulation of electrolyte changes should be basic treatment objectives, and measures may be taken to reduce the degree and duration of the hyperthermia.

Usually the effects of pharmacotherapy are thought to appear within the first few days, and if they do not, then the drug is not likely to be effective.<sup>5</sup> It is at this stage where ECT gains popularity, for it appears to be effective in not only severe but also long-standing cases, with a marked reduction in mortality (Table-2).<sup>5,6</sup> In their case series, Scheftner and Shulman<sup>7</sup> proposed ECT as an effective treatment modality when drugs are not effective. Their literature review indicates that response to treatment is usually apparent after a few sessions. This case confirms their observation as out of 9 suggested session of ECT, patient started improving after the 8th session.

Data on efficacy are limited, inconsistent, and difficult to interpret because of the conceptual heterogeneity and variability of treatments. Trollor et al.<sup>8</sup> reviewed 46 cases in the literature and 9 patients of their own. In 31 cases (56%), ECT was used after pharmacotherapy had failed, while in 40 cases (73%), it was the first-line treatment. Full recovery was seen in 25 cases (63%) and partial recovery in 11 cases (26%), with a total of 36 patients (90%) benefiting from the treatment.

Once the NMS is resolved, there remains the question of re-establishing antipsychotic therapy, for which a preliminary 2-week waiting period is suggested. It is recommended that low-potency or atypical antipsychotics be given, starting with low doses and

gradually titrating. Clozapine is the agent of choice because it has less D2 affinity.<sup>9</sup> Despite the precautions, resumption of antipsychotic drugs following NMS is associated with a 30% incidence of recurrence.

## Conclusion

Neuroleptic malignant syndrome is a rare and potentially a life threatening neuropsychiatric illness. It has wide range of clinical presentation depending upon the type and duration of exposure to inciting drugs. Sometime this condition becomes very severe and resistant to conventional drugs being used for NMS like Bromocriptine, dentrolene, benzodiazepine, amantadine and other supportive care. In this scenario we should consider the option of Electroconvulsive therapy which has proved useful and is being used in specialized centers. Our case also showed the effectivity of the electroconvulsive therapy for drugs resistant NMS.

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