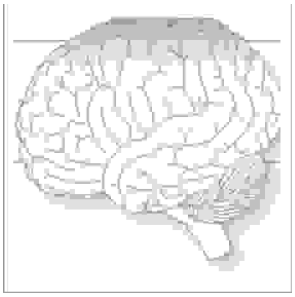
CASE REPORT PROF-972

# NEUROLEPTIC MALIGNANT SYNDROME



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**ABSTRACT ...** sohailali98@hotmail.com Neuroleptic malignant syndrome is a rare but life threatening reaction to a neuroleptic medication. Even in state-of-the-art centers, the mortality rate is reported as 5-12%. We present a report of a successfully managed patient with neuroleptic malignant syndrome, in Faisalabad, Pakistan. This is followed by a brief discussion about the syndrome, with a compilation of latest recommendations about assessment and management.

**Key words:** Neuroleptic malignant syndrome. Anti-psychotic. Lithium carbonate.

## BACKGROUND

The neuroleptic malignant syndrome (NMS) is a rare, but life-threatening, idiosyncratic reaction to a neuroleptic medication. Although potent neuroleptics (e.g., haloperidol, fluphenazine) are more frequently associated with NMS, all anti-psychotic agents, typical or atypical, may precipitate the syndrome. NMS has also been associated with non-neuroleptic agents that block central dopamine pathways, e.g., metoclopramide, amoxapine, and lithium. (1-3)

## CASE REPORT

Mr. Sami Khan (fictional name) was a 45 year old married man, hailing from a posh suburb of Lahore, Pakistan. Graduate by education, he had not been working for five years (due to his illness) when he presented to Dr. Saeed Akhtar in March 2005. He was brought to Dr. Akhtar's clinic in an unconscious state by his family members for emergency assessment and management.

There was no reported family history of serious mental

illness, but he had a past history of major psychiatric illness since the last twenty years. He had been treated by many psychiatrists and physicians, and the illness was mostly diagnosed as schizophrenia or schizoaffective disorder. The main manifestations were severe social withdrawal, loss of appetite and sleep, disorganized behavior (posturing and repetitive purposeless actions) and very poor self care, culminating in a stuporous condition.

A week before the current presentation to Dr. Akhtar, he had been receiving the following medications: haloperidol 10mg/day, procyclidin 15mg/day, alprazolam 1.5mg/day, and injectable flupenthixol decanoate 40mg every 2 weeks. Due to poor response to treatment, his family decided to get a second opinion. The second psychiatrist immediately changed the prescription to: divalproate sodium 1500mg/day, lithium carbonate 800 mg/day, and procyclidin 15mg/day.

His presenting symptoms appeared immediately after this switch in treatment. He developed diarrhea (7-8 watery non-bloody stools per day) while his intake remained very low. He developed high grade fever (upto 104 degrees Fahrenheit) which was continuous and associated with rigors and chills, but no headache or projectile vomiting. His level of consciousness began to drop rapidly, the whole body became stiff, and he developed urinary incontinence. He was brought to the clinic in a comatose state.

At initial examination, he was found to be pale, malnourished, dehydrated, and had multiple pressure sores on his feet. He had a Glasgow Coma Scale of 9/15, was haemodynamically stable but febrile (100 degrees F), respiratory and gastrointestinal systems were unremarkable, while the central nervous system examination revealed generalized lead-pipe rigidity. The list of differential diagnosis included neuroleptic malignant syndrome, lithium toxicity, schizophrenic stupor, septicemia, meningitis/encephalitis, cerebral malaria, and malnutrition.

Laboratory investigations revealed normochromic normocytic anemia (hemoglobin 8.8 gm/dl), a raised erythrocyte sedimentation rate (115 mm after the first hour), normal total and differential leukocyte counts, no detectable malarial parasites in the blood, an unremarkable urine analysis, normal blood urea nitrogen and serum creatinine levels, normal hepatic enzyme levels, a generalized serum electrolyte deficiency, serum lithium level in the therapeutic range (0.6 mEq/L), a grossly elevated creatinine phosphokinase level (2195 U/L), and unremarkable cerebrospinal fluid analysis. On the basis of these findings, a provisional diagnosis of neuroleptic malignant syndrome was made, due to an inappropriate combination of heavy dosage potent neuroleptics and lithium carbonate.

Management was initiated immediately. Fluid, electrolyte, and nutritional restoration was carried out by intravenous and nasogastric routes. Chest and limb physiotherapy was initiated. Skin, oral, bladder and bowel care was optimized. He received broad spectrum antibiotics and antimalarials: bromocryptine (10 mg/day), levodopa+carbidopa (250+25 mg/day), divalproate sodium (1500 mg/day), diazepam (15 mg/day), and promethazine (150 mg/day).

During the initial 3-4 days of his admission, he had daily spikes of high grade fever, remained comatose, had two epileptic seizures, and developed a chest infection. After that, he began to improve gradually, regained consciousness and mobility (as the rigidity subsided), and was discharged in a stable and partially recovered state after 8 days in the hospital. There were no apparent residual neurological deficits on recovery, and re-initiation of psychiatric treatment was attempted cautiously 3 weeks after recovery. The atypical anti-psychotic olanzapine was initiated at 5 mg/day, and dose titration was being carried out at the time of submission of this case report.

## DISCUSSION

All classes of neuroleptics are associated with NMS, and dopamine receptor blockade is considered the major mechanism[1]. Blockade of dopamine receptors in the striatum can cause rigidity, tremor, and rhabdomyolysis; whereas blockade of such receptors in the hypothalamus can cause impaired temperature regulation and

hyperthermia[2,3]. However, this theory does not explain why only some patients develop NMS. It also does not explain why patients rechallenged with neuroleptics do not always redevelop NMS[4].

Prospective studies and pooled data from the literature report an incidence rate of 0.07-0.2% among patients receiving neuroleptics[2,3]. Due to increased awareness of this syndrome and efforts at prevention, the incidence is probably less now than in the past. The mortality rate, once reported at 20-30% is now estimated at 5-11.6 %[1,2]. Death usually results from respiratory failure, cardiovascular collapse, myoglobinuric renal failure, arrhythmias, or disseminated intravascular coagulation[5].

NMS has been reported to be more common in males, probably because of increased use of neuroleptics in males. Male-to-female ratio is 2:1. NMS may occur in patients of any age who are receiving neuroleptics or other precipitating medications[5]. The syndrome is more likely to develop following initiation of neuroleptic therapy or an increase in the dose. The onset can be within hours, but on average, it is 4-14 days after initiation of therapy. However, NMS can occur at any time during neuroleptic use, even years after initiating therapy. Of those patients who develop NMS, 90% of them will do so within 10 days of starting the medication[3].

NMS is a heterogenous syndrome that spans a broad severity continuum. The diagnosis is made on clinical grounds based on the presence of certain historical, physical and laboratory findings. The diagnosis is confirmed, but not necessarily excluded, by the presence of the following 5 criteria[4].

Recent treatment with neuroleptics within past 1- 4 weeks.

Hyperthermia (above 38˚C)
Muscular rigidity
At least 5 of the following
Change in mental status
Tachycardia
Hypertension or hypotension
Diaphoresis or sialorrhea
Tremor
Incontinence
Increased creatinine phosphokinase (CPK) or urinary myoglobin
Leukocytosis
Metabolic acidosis
Exclusion of other drug-induced, systemic, or neuropsychiatric illness.
Clinical signs
Hyperthermia
Profuse diaphoresis
Generalized rigidity (lead pipe)
Mental status changes
Autonomic instability

The following risk factors have been reported in the literature[5], increased ambient temperature, dehydration, patient agitation or catatonia, rapid initiation or dose escalation of neuroleptic agent, withdrawal of anti-cholinergic medication, use of high-potency agents and depot intramuscular preparations, history of organic brain syndrome or affective disorder, past history of NMS, and concomitant use of predisposing drugs (e.g, lithium, anticholinergic agents).

The following disorders should be excluded during the process of investigation for NMS[4,5]: delirium tremens, encephalitis and meningitis, heat exhaustion and heatstroke, rhabdomyolysis, septic shock, stroke, tetanus; toxicity due to amphetamines, anticholinergic drugs, antidepressants, antihistamines, cocaine, monoamine oxidase inhibitors, phencyclidine, salicylate, strychnine or sympathomimetic drugs; parkinsonism, pheochromocytoma, serotonin syndrome, and dystonic reactions etc.

Successful treatment requires prompt recognition, withdrawal of precipitating agents, exclusion of other medical conditions, aggressive supportive care, and administration of certain pharmacotherapies[6-8].

Recommendations about specific interventions include: dopamine agonists such as bromocryptine (Parlodel, 7.5-30 mg/d), amantadine (PK-merz, 200-600 mg/d), levodopa and carbidopa (Sinemet, levodopa content 75-

100 mg/d), and apomorphine; skeletal muscle relaxants like dantrolene (10 mg/kg/d) and benzodiazepines; and electroconvulsive therapy in severe cases[9-11]. Possible complications such as infections, deep vein thrombosis, disseminated intra vascular coagulation, seizures, bed sores, and aspiration etc, should be monitored for and managed aggressively. Most recovered patients do not have residual symptoms[11,12].

In the absence of rhabdomyolysis, renal failure, or aspiration pneumonia, and with good supportive care, the prognosis for recovery is good. The syndrome may last 7-10 days after discontinuing oral neuroleptics and up to 21 days after use of depot neuroleptics (e.g, fluphenazine)[10,11].

Re-initiation of neuroleptic therapy after an episode of NMS may be necessary in light of the patient's psychiatric diagnosis[13-15]. Although there is an increased risk of NMS, re-initiation is associated with an acceptable risk/benefit ratio, and the following recommendations have been made for this intervention[3,4], a minimum of 5-14 days should elapse post-recovery, agents with lower D2-receptor blockade should be preferred, lower doses should be used with extremely slow titration, depot preparations should be avoided, and structurally dissimilar agents should be used the second time round. Gender and age factors do not affect successful re-initiation[15].

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