

Risk Factors in Neuroleptic Malignant Syndrome

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially serious idiosyncratic response to neuroleptic antipsychotics. It usually affects young males, but the risk has been seen to increase with certain factors including the administration practices of antipsychotic neuroleptics in these individuals. Even though no predictors for NMS are yet known, this article highlights the findings on certain risk factors as seen from a series of fifteen patients who developed NMS. Cautious use of neuroleptics in those at risk, early recognition and institution of immediate management is important.

Key Words : neuroleptic, malignant syndrome, risk factors

Neuroleptic Malignant Syndrome (NMS) (Delay & Deniker, 1968) is a rare, but potentially life threatening idiosyncratic reaction to neuroleptics and other drugs affecting dopaminergic transmission.

The syndrome tends to develop when neuroleptic treatment is initiated, or the dosage is rapidly increased, particularly when the dosage is high or parenteral. It mostly affects young males (Ebadi et al, 2000). Estimation of the frequency of NMS in prospective studies range from 0.07%-0.2% (Gelenberg et al., 1988; Caroff & Mann, 1993) to 2.2% (Hermesh et al., 1992; Keck et al., (1989a). Pathogenesis of NMS is mainly attributable to dopamine blockade (Caroff & Mann, 1993; Ebadi et al., 1990; Heiman Patterson, 1993), and dysregulated sympathetic nervous system hyperactivity is responsible for most features of NMS (Gurrera, 1999). NMS may present suddenly but more often the course is indolent, with autonomic hyperactivity and unexplained episodic tachycardia and blood pressure fluctuations observed early (Velamoor et al., 1994). Altered consciousness is considered by some to be sine qua non for the diagnosis of NMS (Adityanjee and Chawla 1989).

In a review of 53 patients of NMS, Levenson (1985) found that 50 of them were receiving neuroleptics, many for a long time without any history suggestive of previous NMS. Nearly half of the patients received anticholinergic drugs and about 20% were taking lithium. NMS occurred in 3 patients without any described exposure of neuroleptics Toru et al., 1981). NMS can occur in patients on atypical antipsychotics and resembles "classical" NMS (Hasan and Buckley, 1998). Cases of NMS have been attributed to clozapine (Reddig et al., 1993; Sachdev et al., 1995), and to risperidone (Bonwuk et al., 1996; Gleason & Conigliaro, 1997). Metaclopramide, prochlorperazine, and droperidol are all frequently used dopamine antagonists and NMS has also been attributed to all (Caroff and Mann, 1993).

Agitation and dehydration in patients on neuroleptics increases the likelihood to the development of NMS. In fact any central nervous system compromise may increase the risk of developing NMS, as also the morbidity and mortality associated (Modestin et. al, 1992; Rosebush & Stuart, 1989).

Differential diagnosis is of prime importance in any patient suspected to have NMS. Conditions which have to be ruled out include i) Infection plus neuroleptic side effects, ii) anticholinergic toxicity, iii) lithium toxicity, iv) catatonia, v) lethal catatonia, vi) malignant hyperthermia, vii) heat stroke, viii) status epilepticus and ix) serotonin syndrome.

Discontinuation of the causative agent is the primary treatment of NMS. In addition specific drug treatment such as bromocriptine and/or dantrolene are frequently used. Mortality from NMS is high but most reports put the range between 10-20% (Shalev et al., 1989).

Here we report on some of the factors that appear to predispose subjects to development of NMS. The aim of reporting our findings is to emphasize the risk factors leading to NMS.

MATERIAL AND METHOD

Patients who developed fever, rigidity and mental status changes rapidly or suddenly during concurrent psychotropic (mainly neuroleptics) medication use, and where the clinical features could not be fully explained by any other medical condition, were screened as potential NMS suspects. Neuroleptic malignant syndrome was confirmed in patients fulfilling Levenson's criteria (1985), which comprises three major and six minor manifestations. The major manifestations are i) fever, ii) rigidity and iii) elevated creatine phosphokinase level. The minor manifestations are 1) tachycardia, ii) abnormal blood pressure, iii) tachypnea, iv) altered consciousness, v) diaphoresis and vi) leukocytosis. The presence of all three major, or two major and four minor manifestations, supported by clinical history, indicates a very high probability of the presence of NMS.

We documented 15 episodes of NMS in 15 patients admitted to our hospital, in a prospective study, over a period of 48 months (from October 1997 to October 2001). Thirteen of these 15 patients were referred and were not on treatment from our hospital.

TABLE 1 : Age & Sex Distribution on Patients

Sex	Range (in years)	Mean (in years)
MALE (n=12)	24-65	41.4±11.1SD
Female (n=3)	21-57	39.0±25.5 SD
All patients (N=15)	21-65	41.0± 13.0 SD

TABLE 2 : Primary Psychiatric Illness & Associated Conditions

Primary Psychiatric Diagnosis	Percentage Cases (N=15)
Mood Disorder	73.4%(11/15)
Bipolar mood disorder	66.7% (10/15)
Recurrent depressive episode (depressive episode with psychotic features)	6.7%(1/15)
Alcohol withdrawal	13.3%(2/15)
Poorly Described	13.3%(2/15)
Secondary associated diagnosis Diabetes Mellitus	13.3%(2/15)
Alcoholic liver disease-cirrhosis with portal hypertension	6.7%(1/15)
Ischemic Heart Disease	6.7%(1/15)
Infection (Enteric)	13.3%(2/15)
Lithium Toxicity	6.7%(1/15)

TABLE 3 : Clinical Features on NMS

Symptoms	Percent Cases (N=15)	Mean duration (in days)
Hyperthermia	100%(15/15)	14.1±5.7 SD
Rigidity	100%(15/15)	13.0±4.8 SD
Elevated CPK Levels	100%(15/15)	13.2±3.9 SD
Altered sensorium	100% (15/15)	
Unconsciousness	(12/15)	13.8±4.1 SD
Delirium	(3/15)	
Labile Pulse Rate	100%(15/15)	13.6±6.27 SD
Sustained Hypertension	13.3% (2/15)	8.0
Labile Bood Pressure	86.7%(13/15)	14.1±6.3 SD
Tachypnea	26.6%(4/15)	13.5±3.5 SD
Diaphoresis	26.6%(4/15)	14±6.1 SD
Tremors	93.3%(14/15)	12.5±4.4 SD

Informed consent from the attending and legally responsible relative(s) was obtained as per the norms of our hospital, specifically to carry out (i) a full assessment of the patient, (ii) for all necessary investigations and (iii) for treating the patient. In addition permission to use the data on clinical findings for scientific analysis was also taken. This was neither an incidence nor a prevalence study, and there might have been cases lost to documentation. Diagnoses of the primary psychiatric illness was made separately and independently by two consultant based on the history and available medical records and ICD-10 criteria. Medical diagnoses if any, were based on the opinion of the attending consultant. All patients underwent necessary laboratory examination i.e. a full haemogram, renal function test, liver function test, CSF examination, ECG, chest X-ray, cultures of blood and urine etc. EEG and serum lithium estimation were possible only in four patients each. Altered sensorium was assessed clinically, also using the Glasgow Coma Scale. Dehydration considered to be an important factor in the pathogenesis of NMS, was said to be present, if the following conditions were met (1) a 40% or greater decrease in serum level of BUN and (2) a 50% or greater decrease in serum creatinine concentration, taken from the time of admission. These were recorded as within normal range in all patients on full recovery. Lithium toxicity was defined as a serum blood level of or greater than 1.5 MEq/L.

Table 1 shows the age and sex distribution of our patients. There were 12 male patients with a mean age of 41.4 (± 11.1) years (range of 24-65 years), and 3 female patients with a mean age of 39.0 (± 25.5) year (range of 21-57). The overall mean age was 41.0(± 13.0) years (range 21-65 years).

The primary psychiatric diagnosis was established from the available history and treatment records and based on ICD-10 classification. Mood disorder was the commonest psychiatric diagnosis, seen in 73.4% (11 of 15) patients with bipolar mood disorder present in 66.7% (10 to 15) patients.

Recurrent depressive episode was diagnosed in a patient, alcohol withdrawal syndrome was seen in two patients and in another two patients a correct psychiatric

TABLE 4 : Medication when patients developed NMS

Medication	Percent (Cases)	Dosage (mg/day)
Antipsychotics		
Haloperidol	66.7% (10/15)	20-80
Chlorpromazine	26.6% (4/15)	150-300
Thioridazine	20% (3/15)	50-100
Fluphenazine (in 3 weeks time)	13.3% (2/15)	150
Trifluoperazine	13.3% (2/15)	15
Clozapine	13.3% (2/15)	100-300
Mood Stabilisers		
Lithium	53.3% (8/15)	900-1200
Carbamazepine	20% (3/15)	600-800
Antidepressants		
Imipramine	13.3% (2/15)	75-150
Fluoxetine	6.6% (1/15)	20
Others		
Lorazepam	53.3% (8/15)	4-6
Diazepam	40% (6/15)	10-30
Oxazepam	13.3% (2/15)	15-30
Trihexiphenidyl	13.3% (2/15)	4-6
Clonidine	13.3% (2/15)	0.2-0.3
Combination Medication		
Neuroleptics+anticholinergic	33.3% (5/15)	
Neuroleptics+lithium	26.6% (4/15)	
Neuroleptics+lithium+anticholinergic carbamazepine	13.3% (2/15)	
Neuroleptics+carbamazepine+lithium	13.3% (2/15)	
Anticholinergic+benzodiazepine	6.7% (1/15)	
Neuroleptics+benzodiazepine	6.7% (1/15)	

TABLE 5 : Duration and Outcome of NMS

Outcome	Percent cases	Main Duration (days)
Recovered	80(12/15)	16.7±6.3SD
Expired	20(3/15)	12.0±4.6 SD

diagnosis could not be established although they seemed to have been treated for psychotic condition.

No additional active medical illness was identified in 53.3% (8 of 15) patients. Of the remaining 46.7% (7 of 15) patients, two had diabetes mellitus, one each had alcoholic liver disease with cirrhosis and portal hypertension, and ischemic heart disease. Two patients tested positive on widal test and were treated

for enteric fever. Of the 8 patients receiving lithium, serum estimation was done in only 4, and one patient had lithium toxicity.

Five features were present in all 15 patients in our series. There were, (i) Hyperthermia with a mean duration of 14.1(±5.7) days and a mean peak recording of 103.6 (±1.8) °F, peaking at 7.8(±4.04) days' (ii) muscular rigidity of all limbs with a mean duration of 13.2(±3.9) days and mean peak day of 8.2 (±4.8);(iii) Elevated

CPK levels (5759 U/L), with mean duration of 13.2 (±3.9) (iv) altered sensorium with a mean duration of 13.8 (±4.1) days and (v) a labile pulse rate with mean duration of 13.6(±6.3) days. Blood pressure was persistently high in 13.3% (2 of 15) patients, and labile in 86.7% (13 of 15) patients. Tachypnea was present in 26.6% (4 of 15) patients and 26.6% (4 of 15) patients were diaphoretic. Tremors were present in 93.3% (14 of 15) patients with coarse tremulousness of the trunk and extremities in 60% (9 of 15). We can not comment on incontinence, as most patients had been catheterized before admission.

While all patients were receiving neuroleptics, these had been used for the first time in 7 of the 15 patients and reintroduced after a drug free period in another 7 of 15 patients. Only 1 patient developed NMS on a maintenance regimen of stable neuroleptic treatment. As can be seen from Table 4, six different neuroleptic drugs had been prescribed to these patients.

Haloperidol (dose range of 20-80 mg/day) the commonest offending agent, was administered to 66.7% (10 of 15) patients, either alone or in combination with another neuroleptic, Chlorpromazine in 26.6% (4 to 15) patients (dose range of 150-300 mg/day), and Thioridazine was prescribed in 20% (3 of 15) patients (dose range of 50-100 mg/day). 13.3% (2 of 15) patients had received fluphenazine depot injection (150mg in 3 weeks time) and trifluoperazine was prescribed in 13.3% (2 of 15) patients (dose range of 15-20 mg/day). Clozapine had been used in 13.3% (2 of 15) patients in the dose range of 100-300 mg/day.

Various other drugs in combination with neuroleptics were given to the patients developing NMS. Lithium (900-1200 mg/day) was being taken by 53.3% (8 of 15) patients. Serum lithium estimation was carried out in 4 of these 8, and toxic level was measured in 1. However, it was not possible to discern the exact sequence of lithium toxicity with NMS in this patient. The other mood stabiliser used concurrently with neuroleptics was carbamazepine in 20% (3 of 15) patients (dose of 600-800 mg/day). Strangely, there was no patient on sodium valproate, which is a commonly prescribed mood stabiliser. Other drugs used were

anticholinergics i.e. imipramine and trihexyphenidyl (2 patients each) fluoxetine, while benzodiazepines were prescribed to all.

Furthermore, 40% (6 of 15) patients were receiving two or more neuroleptics in combination, of which at least one was by parenteral route. 33.3% (5 of 15) patients were receiving neuroleptics plus an anticholinergic; 26.6% (4 of 15) patients a neuroleptic plus lithium; 13.3% (2 of 15) were receiving neuroleptics plus lithium plus carbamazepine plus anticholinergics; 6.7% (1 of 15) an anticholinergic plus benzodiazepine and another 6.7% (1 of 15) a neuroleptic plus benzodiazepine combination. In 6.7% (1 of 15) patients, there was history of abrupt neuroleptic withdrawal preceding NMS.

There were 3 (20%) deaths in 15 patients who developed NMS in our series. Mean duration of syndrome in patients who expired was 12.0(\pm 4.6) days. However, 80% (12 of 15) patients recovered fully after a mean duration of 16.7 (\pm 6.3) days. Following recovery a neuroleptic of a different class was safely reintroduced in 4 patients, who were required to be treated. There was no recurrence of NMS in these 4 patients on a follow-up of six months.

DISCUSSION

Despite a considerable increase in the recognition of NMS, risk factors predisposing to this potentially fatal condition are frequently ignored. Our study intends to highlight some of these risk factors.

The male of female (M:F) ratio of patients in our sample was 4:1, a mean age of 41(\pm 13.0) years, mean time to full recovery was 16.7(\pm 6.3) days and a mortality of 20%. In a recent study from India, Chopra & Raguram (2001) reported a M:F ration of 3:1 a mean age of 29.5(\pm 9.9) years, mean time to full recovery for those who recovered 13 (\pm 7.5) days and mortality of 38.5%. In keeping with the earlier suggestions that NMS is commoner in males, our data also shows a male preponderance though not exactly in the young. We found a higher mean age in our sample, which is probably reflective of the

age trend of the primary psychiatric disorder in our patients.

All 15 patients were receiving neuroleptics, but these were newly introduced in 7 of 15 cases and the dose increased rapidly in 11 of 15 Patients. In one patient, NMS followed abrupt withdrawal of neuroleptics. Neuroleptics were administered parentally in 40% patients, and 40% patients received a combination of 2 or more neuroleptics.

These findings together with neuroleptic dosages used as shown in table IV suggest that rather than the total daily dose of the neuroleptics, it is (i) the parental administration of neuroleptics, (ii) a rapid increase of dose (iii) a combination of neuroleptics, and (iv) new exposure, along with other non pharmacological factors, that probably act as the risk for NMS. The use of IV/IM medication is tantamount to using higher oral dose since parenteral anti-psychotics have a greater bio-availability than an equivalent oral dose. Beradi et al (1998) and Rosebush & Stewart (1989) have also identified risk indicators in their studies which support our observations. While early reports suggest no relationship between new exposure to neuroleptics and the occurrence of NMS, in our series, nearly half had received neuroleptics for the first time. This finding may reflect upon the trait vulnerability of these patients for developing NMS. The handful of studies carried out (Iwahashi, 1994; Ram et al., 1995) have failed to identify any genetic defects causally related to NMS. Considering the many clinical features shared by NMS and malignant hyperthermia, it seems reasonable to hypothesise that similar but distinct mutations of a heterogeneous group of regulatory proteins might also form some basis of vulnerability to develop NMS (Gurrera, 2000).

Neuroleptic withdrawal can cause autonomic and behavioural symptoms (nausea, vomiting, diarrhoea, diaphoresis, myalgia, anxiety, restlessness) and movement disorder (withdrawal emergent parkinsonism, withdrawal dyskinesia, covert dyskinesia). Withdrawal NMS is a rarer condition with only 7 cases reported to date. The pathophysiology of withdrawal medical symptoms may be related to cholinergic rebound. Withdrawal NMS may be attributed

to an "imbalance" in the dopaminergic systems. In our series, 1 case was related to abrupt withdrawal of neuroleptics. The abrupt withdrawal of dopaminergic drugs have also produced an NMS-like condition in patients with Huntington disease and Parkinsonism (Ebadi et al.,1990). Implicated drugs include levodopa, bromocriptine, and amantadine. NMS has also been associated with abrupt withdrawal of anticholinergic agents. It is suggested that simultaneous withdrawal of both anticholinergic and neuroleptic medication, mainly long acting neuroleptics, seems to be a risk factor for NMS (Spivak et al., 1990).

A striking finding from our data is that majority of patients had a mood disorder. Affective illness has been described as a risk factor for NMS (Addonizio et al.,1986; Gurra,1999; Rosebush & Stewart,1989). Interestingly 60% patients in our series were being treated for extreme agitation when NMS developed. However, agitated patients are more likely to receive a higher dose of potent antipsychotics. Aho, psychomotor overactivity leads to physical exhaustion and dehydration (Harsch, 1987). It may not be possible to delineate the independent risk associated with each of these factors. Either factor alone, or in combination may predispose to NMS. Several authors (Itoh et al., 1977; Keck et al., 1989b; Rosebush & Stewart, 1989) have commented on the remarkably frequent occurrence of psychomotor agitation and/or excitement before development of NMS, such that this must rank as a highly reliable risk factor in association with neuroleptic treatment. In our series 53.3%(8 of 15) patients were dehydrated. Dehydration in NMS can have different reasons. Diaphoresis is common in NMS with rates varying from 50% to 100% (Mann et al., 1991; Rosebush et al., 1989). In contrast to its role in true fever, diaphoresis in NMS is not part of a coordinated effort to lower temperature, and excessive sweat gland activity is probably responsible for associated dehydration, which may contribute to hyperthermia. Whether primary or secondary feature of the illness, dehydration may contribute to the development of fulminant NMS by

increasing the effective concentrations of neuroleptics in extravascular fluids (Rosebush & Stewart, 1989; Sachdev et al., 1997). Proper hydration and good supportive care can perhaps reduce the mortality in NMS. Tachycardia and tachypnea in NMS reflect a hyper-adrenergic state, but increased metabolism makes additional cardiopulmonary demand. Urinary incontinence is another clinical manifestation of autonomic dysfunction.

Majority of our (8 of 15) patients were taking lithium, raising the important question of relationship of lithium with NMS. It has been suggested that lithium may predispose to NMS by rendering the brain more vulnerable to neuroleptic side effects (Addonizio, 1985). In addition lithium can cause diabetes insipidus leading to increase in neuroleptic concentration. Lithium toxicity in itself is not associated with fever. Typically it produces weakness, lethargy, cerebellar dysfunctions, facilitation, myoclonus and seizures, a clinical picture quite easily distinguishable from NMS. From amongst 8 patients who were receiving lithium when they developed NMS, lithium toxicity was picked up in 1. Increased random blood sugar with hyperosmolar state was another finding in 1 patient.

Clinicians should not be reluctant to make a diagnosis of NMS in presence of an infection, as they often coexist. Infection may predispose subjects to NMS by producing dehydration. Conversely, NMS may create a setting for infection as a result of respiratory compromise, immobility and urinary catheterization (Rosebush & Stewart, 1989). Urine infection in 1 of the 15, and enteric infection in 13.3% (2 of 15) patients were identified our series. Left lower zone infiltration on chest X-ray was found in one. However, the role of these infections as risk in development of NMS is not clear.

The most common serious complication of NMS is rhabdomyolysis, due to an acute, diffuse breakdown of muscle tissue. It produces extremely high serum creatine phosphokinase levels, hyperkalemia, myoglobinuria and acute renal insufficiency.

All patients received supportive

treatment in an intensive care unit. Bromocriptine was used in 80% (12 of 15) with a mean dose of 11 mg/day. No patient was given dantrolene. In keeping with previous observations of Rosebush & Stewart (1989), our data suggests that the pattern of illness in NMS tends to follow the natural course regardless of treatment.

Shalev et al (1989), found no significant difference in mortality due to NMS in those who received only supportive care, and those who received a specific medication such as bromocriptine, dantrolene or amantadine, alone or in combination. These findings suggest that specific treatment may have little or no effect in reducing mortality in patients with NMS. In our opinion good intensive care and discontinuation of neuroleptics at the earliest are more likely to save the patient's life.

CONCLUSIONS

Based on the findings of this small series of neuroleptic malignant syndrome, we conclude that NMS, has increased likelihood of developing in those individuals who are receiving neuroleptic medications. The nature of their psychiatric illness seems to be mostly a affective disorder where a combination of different neuroleptics, and/or neuroleptics with mood stabilisers are given. The route of administration is more likely to be parenteral with a rapid upward dose titration. The presence of agitation, dehydration, systemic infections, compromised brain functions and the male sex are somehow more common associations. The early presence of autonomic dysregulation and development of hyperthermia and rigidity warrant immediate cessation of neuroleptic and psychotropic medication and institution of supportive care. NMS is a life threatening condition, and we maintain that in all patients exhibiting potential risk factors, caution should be exercised in the use of neuroleptics.

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