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NEUROLEPTIC MALIGNANT SYNDROME: NEED FOR EARLY DIAGNOSIS AND THERAPY

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Background: Neuroleptic Malignant Syndrome (NMS) is a medical entity that has received little attention in the clinical settings in Pakistan. The aim of our study was to review the predisposing factors, outcomes and characteristics of in-patients diagnosed with NMS. **Methods:** We performed a retrospective chart review of all cases (age > 15 years) at a tertiary care center in Karachi between January 01, 1990 and November 30, 2001, diagnosed using ICD 10 coding. Data was collected using a standardized data entry form and statistical analysis was performed using Epi Info 6, Version 6.02. **Results:** There were a total of 20 patients diagnosed with NMS (11 male and 9 female) in our study with a mean age of 46.6±15.9 years. Haloperidol was the most frequently responsible neuroleptic. Of the 18 patients on a neuroleptic, most developed NMS after 8 weeks of therapy. There were 5 mortalities all of which were associated with septic shock. Fourteen patients recovered completely from the episode and did not have any neurologic sequelae. **Conclusions:** NMS is an important preventable clinical entity. Early diagnosis and judicious use of antipsychotics is warranted to prevent mortality and heightened morbidity.

Key Words: Neuroleptic malignant syndrome, antipsychotics, predisposing factors

INTRODUCTION

Neuroleptic Malignant Syndrome (NMS) is a rare but potentially fatal idiosyncratic reaction associated with the use of antipsychotics. It has been seen to occur secondary to the use of a range of neuroleptics (typical and atypical) as well as various non-neuroleptic medications[1]. It can also occur following sudden discontinuation of anti-Parkinsonian medications[2-4]. NMS is characterized by hyperthermia, extra-pyramidal rigidity, autonomic dysfunction and altered consciousness. Morbidity and mortality in NMS is most often secondary to cardiopulmonary and renal complications. Early diagnosis and cessation of neuroleptics are associated with a better outcome.

NMS remains a medical entity that has received little focus in the clinical settings in Pakistan. The only study performed in Pakistan on NMS reported 7 cases in Karachi in 1986 [5]. The aim of our study, therefore, was to review the clinical features, pharmacologic variables, risk factors, complications and outcome of patients with NMS at a tertiary care center in Pakistan in order to better define the characteristics of NMS in the local therapeutic and diagnostic environment. We believe a scrutiny of the local pattern of NMS would enhance our ability to diagnose and treat NMS more effectively.

MATERIAL AND METHODS

We carried out a retrospective chart review of all cases (age > 15 years) presenting to The Aga Khan University Hospital, Karachi, between January 01, 1990 and November 30, 2001 classified as having a definite diagnosis of NMS at discharge from hospital using ICD 10 coding. Of the 25 cases identified on initial search, 20 cases were included for final analysis as there was insufficient clinical data for adequate review in 5 cases.

Diagnosis of NMS was based on previously validated criteria [6]. Autonomic dysfunction was considered in terms of high systolic (>140 mm Hg) or diastolic (>100 mm Hg) blood pressure (BP), labile BP (variability more than 30 mmHg systolic or more than 20 mmHg diastolic at different readings), tachycardia (≥ 100 beats per minute), tachypnea (≥ 25 breaths per minute), prominent diaphoresis and incontinence of urine and/or feces.

A standardized data entry form was developed and the data collected included demographics, signs and symptoms at presentation, known risk factors for NMS, primary psychiatric diagnosis, details of neuroleptic use, concomitant use of anticholinergics, tricyclic antidepressants (TCA), selective serotonin receptor inhibitors (SSRI), and lithium, laboratory abnormalities, therapeutic interventions, complications during hospital stay and outcome characterized by mortality or neurologic sequelae. Laboratory abnormalities evaluated included degree of leukocytosis and elevations of creatinine phosphokinase (CPK) [>200 IU/L]. Serial values of CPK were noted whenever available. Therapeutic interventions for the management of NMS were noted, including supportive therapy, discontinuation of neuroleptic use, administration of dopaminergic agents or muscle relaxants. Functional

outcome of NMS patients was assessed using Rankin Score [7].

Extra-pyramidal signs and symptoms noted included rigidity, choreiform movements, tremor, oculogyric crisis, dyskinetic movements, flexor-extensor posturing, trismus, sialorrhea, retrocollis, opisthotonus and festinating gait. Chronological order of symptoms (temporal sequence of appearance of autonomic instability, extra-pyramidal symptoms, hyperthermia, and altered consciousness) was assessed when symptoms had developed over 2 or more days. Past history was also assessed to include history of catatonia, mania or other affective disorder, decreased oral intake in the week preceding symptom development, significant weight loss, a previous episode of NMS, history of substance abuse, possibility of deliberate overdose or self-medication, neurologic disease and previous treatment with electro-convulsive therapy (ECT). Data analysis was carried out using Epi Info 6, Version 6.02 (A Word Processing, Database and Statistics Program for Public Health, Centers for Disease Control and Prevention (CDC), USA and World Health Organization, Geneva, Switzerland).

RESULTS

There were 11 male and 9 female patients of NMS in our study with a mean age of 46.6±15.9 years (range: 17 to 73 years). There were 5 patients over 60 years of age and 3 were less than 25 years old. Table 1 summarizes the clinical features of all 20 patients. Affective disorder was the primary psychiatric diagnosis in 12 of our patients, 9 of whom were documented to have psychotic features. The other major psychiatric diagnosis was schizophrenia (n=4), including catatonic and undifferentiated types, while 1 patient had schizoaffective disorder. Three patients were not documented to suffer any psychiatric illness. Nineteen patients were admitted through the Emergency Room (ER).

Neuroleptics prescribed included oral and depot preparations of both high and low potency anti-psychotics. Depot preparations had been used in 5 (25%) of our patients, intramuscular injections of neuroleptics in 9 (45%) patients and 5 (25%) patients received a combination of an oral and injectable antipsychotics medication. Haloperidol was the most frequently responsible drug (9 of 16 patients on neuroleptics). Eight patients were using more than 2 neuroleptics concomitantly. Duration of neuroleptic use is summarized in Figure 1. Of the 18 patients on neuroleptics, 60% developed NMS after 8 weeks of therapy. Two patients were not on neuroleptics but had abrupt discontinuation of their anti-parkinsonian drug(s) only. Recent (<2 weeks) addition of a neuroleptic was documented in 6 patients. Six patients had experienced a recent (<1 week) increase in dose of the neuroleptic and 3 patients had experienced both a recent increase in dose of neuroleptic as well as addition of another neuroleptic to their treatment regimen. Only one patient had been given neuroleptics for the first time and developed symptoms of NMS within 24 hours.

Figure 2 shows the time course for development of the symptoms of NMS. Most patients developed symptoms slowly, while 8 patients (40%) developed full-blown NMS over a period of 3 days only. Six of the patients who had developed symptoms rapidly (≤3 days) were diagnosed NMS within 24 hours of presentation. In their case CPK was >1000 IU/l at admission, while in the other 2 cases, CPK was normal or only slightly elevated. In 2 cases, diagnosis was established in >1 week: one was an elderly patient with mild symptoms and no documented fever; the other had Parkinson's disease and had presented in septic shock following sudden withdrawal of anti-Parkinsonian medications.

All patients were managed in the special care unit. Laboratory findings are summarized in Table 2. Four patients developed multi-organ failure in association with sepsis. One patient developed acute renal failure due to hypovolemic shock; 1 developed rhabdomyolysis with acute renal failure; 2 developed aspiration pneumonia. In addition to supportive treatment, dopamine agonists were used in 12 patients, bromocriptine in 11 cases and anti-cholinergics were given to 9 patients. Dantrolene was used in 2 patients and diazepam in 3 patients. EEG was done in 4 patients, 2 of which were consistent with metabolic encephalopathy while the other 2 were reported normal.

The mean number of days for resolution of NMS following cessation of neuroleptics was 17.55 ± 9.47 days (range: 6-30 days). Table 3 shows the duration of symptoms of NMS in survivors following cessation of neuroleptic(s). There were 5 mortalities all of which were associated with septic shock. Fourteen patients recovered completely from the episode and did not have neurologic sequelae or cognitive impairment after recovery or on follow up. One patient was shifted to another hospital and was lost to follow up. Of the 4 Parkinsonian patients, only one recovered fully (Rankin score = 0). Interestingly, 7 of the 20 patients were re-challenged with neuroleptics and one with lithium; however, no relapse during hospital stay was documented in these patients.

Figure 1. Total duration of neuroleptic use (n=15)

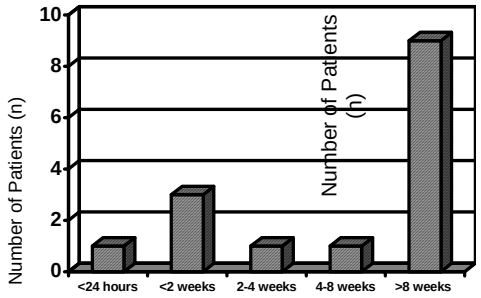

Figure 2. Time course for development of symptoms of NMS (n=20)

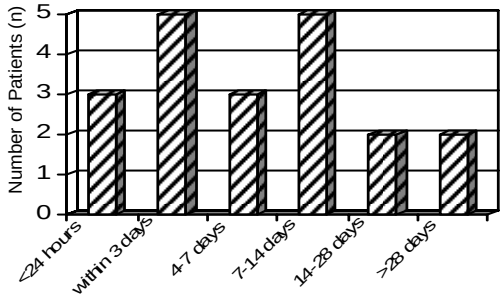

Table 1. Clinical Features of Patients with Neuroleptic Malignant Syndrome (NMS) (n=20)

	Frequency	
Feature	N	%
Clinical		
Tmax		
> 38^0 C	19	95
Afebrile	1	5
Autonomic Dysfunction		
Hypertension	13	65
Labile BP	4	20
Tachycardia >100 bpm	14	70
Tachypnea >25 resp/min	8	40
Diaphoresis	2	10
Incontinence	5	25
Total	20	100
EPS		
Rigidity	17	85
Tremor	2	10
Dyskinetic movements	2	10
Flexor-extensor posturing	4	20
Sialorrhea	3	15
Retrocollis	11	55
Total	20	100
Altered consciousness		
Confused but verbalizing	2	10
Unintelligible sounds	8	40
Coma	9	45
Total	19	95

BP= blood pressure, bpm= beats per minute, resp/min= breaths per minute, EPS= Extrapyramidal signs,

Table 2: Biochemical Characteristics of Patients with Neuroleptic Malignant Syndrome (NMS)

		Frequency	
Feature	Total	N	%
Labs:			
CPK (IU/L)	16	9	56
>1000		6	38
400-1000			
200-400		0	0
<200		1	6
Total Abnormal		15	93.8
WBC (cell/ul)	19		
>15000		8	42
10000-15000		6	32
<10000		5	26
Total Abnormal		14	73.7
Lumbar Puncture (LP)	10		
High protein (moderate elevation)		2	20
High cells (minimal), with normal protein		1	10
Total Abnormal		3	30
Renal Function Tests Abnormal	20	10	50
Liver Function Tests (LFT) Abnormal	14	4	28.6

Table 3: Duration of symptoms of NMS in survivors following cessation of neuroleptics

Duration of syndrome	Frequency	%
< 7 days	2	18.2
7-14 days	2	18.2
14-21 days	3	27.3
> 21 days	4	36.4
Total	11	100

DISCUSSION

Virtually all neuroleptics are capable of inducing NMS, including the newer atypical antipsychotics. NMS should feature in the differential diagnosis of any patient receiving a neuroleptic who develops fever or rigidity. In our study, Haloperidol was by far the most commonly responsible antipsychotic (56.3%) for NMS in the local population. One patient was receiving 4 different oral and depot preparations of high potency neuroleptics in combination with one low potency one. Use of newer (atypical) antipsychotic medications instead of haloperidol may be associated with lower rates of NMS and extra-pyramidal symptoms [8].

Factors that have been suggested as being more provocative include the rate of introduction of neuroleptics, the use of depot preparations, a preceding attack of NMS, and the concomitant use of other drugs, in particular, lithium[9-13]. Depot preparations, intramuscular injections of anti-pscyhotics and combinations of these with oral preparations were being used by 25%, 45% and 25% of our patients, respectively. Concomitant use of lithium was seen in only one patient in our study. High potency neuroleptics in combination with a

tricyclic antidepressant were being prescribed in 4 others.

Our results show that where the full-blown syndrome developed over 3 days or less, no difficulty in making a diagnosis of NMS was encountered especially when supported by high CPK levels. In NMS, the rise in CPK is often significant, sometimes reaching levels above 100,000 IU per liter (IU/l). We noted a level of >100,000 IU/l in one patient. However, high CPK values alone should not be regarded as diagnostic markers for NMS.[14] Prominent increases have been found in upwards of 70% of patients taking neuroleptics who become pyrexial due to infection,[15] and some 30% of medically ill patients (not receiving neuroleptics) show a similar, albeit less exaggerated, rise in CPK.[16] Furthermore, asymptomatic CPK elevations can occur in patients with psychotic disorders, whether clinically stable or acutely ill, following oral treatment with typical or atypical neuroleptics.[17-19] These findings suggest the need for a high index of suspicion for NMS in patients whose clinical findings evolve subacutely.

Quantitative CPK values were available for 3 of the 4 Parkinson's disease patients. CPK levels were >1000 IU/l on admission in all 3 patients. This trend for the Parkinson's subgroup is interesting because in these patients CPK may perhaps play a role in the early diagnosis of NMS. Among the 4 Parkinson's disease patients, there were 3 mortalities; only one recovered fully (Rankin score = 0). Our results are consistent with those of other studies [20,21] where it has been shown that Parkinsonian patients in particular have very poor prognosis. These findings suggest the need for particularly aggressive monitoring and early intervention in case of NMS occurring in patients suffering from Parkinson's disease.

Velamoor et al[22] found that of all order implications, 70.5% were consistent with the sequence of mental-status changes followed by rigidity, hyperthermia, and autonomic dysfunction. Changes in either mental status or rigidity were the initial manifestations of NMS in 82.3% of cases with a single presenting sign and were significantly more likely to be observed before hyperthermia and autonomic dysfunction. One of our patients did not develop fever at any time throughout the episode of NMS. Extrapyramidal features and autonomic instability, however, were present in this patient. Several authors have reported such variants of NMS which suggests that NMS is a spectrum disorder[23-26] and a number of cases of NMS with no rise in temperature or negligible temperature elevations have been described. This underlines the importance of looking at the complete clinical picture rather than relying on individual signs and symptoms meeting arbitrarily fixed thresholds for disease.

Agitation and dehydration are known to make independent contributions to risk[12,13,23,25,27]. Six of our patients had concurrent medical illnesses leading to agitation and dehydration. Two others had refused oral intake for 1 and 5 days respectively. Both developed symptoms within the next 24 hours. Two of our patients had received ECT within the previous year; in one case, the last cycle of ECT had been completed 2 weeks before symptoms began. Our findings are supported by a case-control study of NMS patients where ECT emerged as a significant risk factor[27].

Most frequently considered differentials in our patients were Central Nervous System (CNS) infections (30%) and neuroleptic-induced dystonia or Parkinsonism (20%). CNS infection which can present with fever and altered consciousness can pose a special problem. An LP can be particularly helpful in such cases. Other infections can often co-exist with NMS and clinicians should not hesitate to make a diagnosis of NMS and a concomitant infection. Infection may predispose patients to NMS by causing dehydration and agitation. Conversely, NMS may create a setting for infection as a result of respiratory compromise, immobility, and urinary catheterization. It is important that clinicians are able to make a diagnosis of NMS in the presence of a non-CNS infection as the two may often co-exist. Attributing the patients' symptoms to sepsis in this setting could be a costly mistake as delays in instituting appropriate therapy may result.

In the management of NMS, the most effective measures include prompt recognition, withdrawal of neuroleptic medication, and transfer to an intensive/special care unit, with attention to hydration, fever reduction, sedation with benzodiazepines, if indicated, and control of rigidity with bromocriptine or dantrolene.

CONCLUSION

NMS is an important preventable clinical entity. Judicious use of antipsychotics including cessation of rapid neuroleptization, better hydration of patients during titration of medication, avoiding use of multiple anti-psychotics simultaneously, and use of non-depot neuroleptics whenever possible, is warranted. Use of the newer atypical agents may also be considered. Early diagnosis can prevent both morbidity and mortality therefore heightened clinical awareness with regard to its varied presentation and special high risk groups (the elderly and Parkinson's disease patients) and careful investigation to rule out alternative diagnoses are important.

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