NEUROLEPTIC MALIGNANT SYNDROME: A SIXTEEN YEARS RETROSPECTIVE REVIEW

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ABSTRACT

Objective: To study demographic characteristics, psychiatric diagnosis, type of neuroleptic drugs administered, course of illness, management and outcome.

Design: Retrospective chart review study.

Place and duration of study: This study was carried out for sixteen years (1988-2004) in the Psychiatry unit, Aga Khan University Hospital, Karachi.

Subjects and Methods: Sample consisted of 25 cases of Neuroleptic Malignant Syndrome in which 13 were males and 12 were females. The record was taken from the health information management system which keeps a comprehensive chart of each patient. This renders the files retrievable through computer generated search. A specific data collection form was designed for extraction of relevant data. The data was analyzed using SPSS version 13.0.

Results: Twenty five cases were identified, of which thirteen were males. Mean age was 45 years (range 20-74 years). Bipolar affective disorder was the most common diagnosis followed by schizo-affective disorder, schizophrenia, postpartum psychosis, dementia and Parkinsonism. 48% of the patients had previous history of neuroleptic use, while 28% received neuroleptics for the first time. Among neuroleptic users, 20% were on long-acting depot antipsychotics. 52% received per-oral dose (PO), while 32% received intramuscular (IM) dose. 56% patients were on other concomitant medications among which Lithium was the most common (16%). 96% patients had the cardinal symptoms of fever, rigidity and increased creatine phosphokinase (CPK). 96% had associated delirium, 80% showed autonomic instability with fluctuation in pulse and blood pressure. Electrolyte disturbance was seen in 84% and diaphoresis with leukocytosis was present in 68% patients. NMS was associated with high ambient temperature with mean temperature of 39.2^0 C (S.E. 0.3). Discontinuation of neurolpetic medications and supportive care was carried out in all cases. In our case series we observed mortality rate of 16%. Out of 25 patients, 21 recovered with early diagnosis and adequate management.

Conclusion: Risk of NMS can be minimized by use of low potency or atypical antipsychotics, cautious use of concomitant medications and depot preparations and initiation of neurolpetics at lower dose with careful monitoring. With good supportive medical care mortality can be substantially mimimized.

Key words: Neuroleptic malignant syndrome (NMS), neuroleptics, creatine phosphokinase (CPK).

INTRODUCTION

Neuroleptic Malignant Syndrome (NMS) is a rare idiosyncratic but life threatening complication of treatment with neuroleptic medications. It is characterized by high grade fever, whole body rigidity, altered consciousness and signs of autonomic instability[1]. The syndrome follows the administration of drugs with anti-dopaminergic activity or more rarely sudden withdrawal of dopaminergic medications[2].

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NMS was first described and so named by Delay and Deniker in 1968.[3] Estimates of incidence ranges from 0.5% - 1% of all patients exposed to neuroleptics.[4] There is no known sex or age predilection but most reviews have shown a male-to-female ratio of 2: 1, with young males in age group 16 - 44 years to be over represented[5].

Among various hypothesis is dopamine blockade in specific areas of central nervous system (CNS), particularly meso-limbic and meso-cortical dopaminergic pathways.[5, 6] The additional blockade of dopaminergic pathways in hypothalamus leads to hyperpyrexia while blockade in nigro-striatal pathway leads to rigidity.[7] The antagonism in the cortico-limbic tracts leads to altered consciousness. The syndrome of NMS has also been described following withdrawal of dopaminergic drugs e.g. levodopa[2,8,9].

The diagnosis of NMS has been operationalized to improve diagnosis and for research. It requires presence of three cardinal or alternatively two cardinal with four associated features[4]. The cardinal features include hyperpyrexia, whole body rigidity and raised serum creatine phosphokinase (CPK). Associated features include altered level of consciousness, autonomic instability and leukocytosis[4].

The evidence from literature points towards increased vulnerability of patients with affective disorder for developing NMS as they may be more likely to be agitated, which in turn results in dehydration and exhaustion[10-12]. The clinical state of these patients may also invoke aggressive management from physicians. Combined lithium carbonate and neuroleptic drug treatment has a controversial history of association with NMS. Some retrospective case studies have identified a significant number of patients developing NMS while receiving a combination of neuroleptic medications and lithium[13-15].

On the basis of numerous published case reports it is clear that NMS can be caused by any type of neuroleptic medication in both psychiatric and non psychiatric patients[5]. High potency antipsychotics such as haloperidol and fluphenazine are most commonly implicated but cases of NMS occurring with low potency neuroleptics such as chlorpromazine are not uncommon[4]. NMS usually lasts five to ten days after the discontinuation of treatment with a neuroleptic. Duration may extend longer after depot antipsychotic medications.

It is generally accepted that higher doses of neuroleptics is a risk factor for NMS[16,17]. In addition to potency and dose the rapid dose escalation is also a potential risk factor for NMS[14]. There are case reports of patients with neurological and organic mental disorders developing NMS even on low doses of antipsychotics[15, 18].

The role of temperature though somewhat controversial also deserves attention. There are narrative literature reviews which states that factors such as disturbance in thermoregulatory processes and dehydration could be potential triggers for NMS[19]. There is an ongoing controversy on whether high ambient temperature plays a causal role in the development of NMS.

There are very few studies on NMS from Pakistan, a developing country with poorly established mental health services. There are few reports on NMS from Pakistan. This is despite the fact that neuroleptic drug usage in Pakistan is quite high. Sale figures of only one year (2003-2004) amounted to Rs. 377.02 million (US$6.39 million)[20]. With such high usage it is quite likely there would be many more cases of NMS than is currently known

First ever report of NMS from Pakistan was a case series by Ahmed HS in 1989[21]. They reported seven cases of NMS admitted in the Department of Nueropsychiatry, Jinnah Postgraduate Medical Center, Karachi. All were acutely disturbed psychotic patients seen during hot and humid months of May to October during 1986. Since then NMS has been a focus of few reports and reviews however specific questions related to characteristics of patients their predisposing factors and outcome have remained unanswered[22]. There is therefore a need for more information on NMS from Pakistan.

Aims and Objectives

The aims of this descriptive study were to assess the association of NMS with psychiatric diagnosis, type of neuroleptic use and concomitant therapy in patients admitted to the Aga Khan University Hospital between 1988 and 2004. Socio-demographic characteristics, possible seasonal variations and outcome of management on mortality were also studied.

SUBJECTS AND METHODS

The Aga Khan University hospital is a 500-bed tertiary care teaching hospital. The Health Information Management System (HIMS) keeps a comprehensive chart that documents the details of in-and-out patient's clinical care. The chart contains information on all prescribed medications, investigations and progress notes of physicians and nurses. The diagnosis of NMS is coded separately based on the clinical version of International Classification of Disorders (ICD-9). This renders the files retrievable through computer generated search. A specific data collection form was designed for extraction of relevant data. The data was analyzed using SPSS version 13.0.

RESULTS

Socio-demographic characteristics

During the study period twenty five cases of NMS were identified. Thirteen were males and twelve were females. There was no significant gender difference in our sample. The mean age was 45 years (range 20-74 years). 52 % (n=13) of the sample was above 50 years of age. 48% were in the age range of 20-50 years while 52% were 50 years or older.

Diagnosis

The most common diagnosis was bipolar affective disorder in 24% (n = 6) of patients. Other diagnosis included schizoaffective disorder (n =3), schizophrenia (n =3), postpartum psychosis (n=1), psychotic depression (n=2), dementia (n=2) and Parkinsonism N= 2). There were two patients who had co-morbid Parkinsonism along with bipolar disorder and schizophrenia. The primary psychiatric diagnosis was not known in the six patients.

Neuroleptic exposure

48% (n= 12) patients had a history of earlier neuroleptic exposure but none had a previous documented episode of NMS. 28% (n=7) patients had their first exposure to neuroleptics while 12% (n =3) patients had a documented escalation of dose from the previous prescribed drug regimen.

20% (n=5) had received depot antipsychotic (AP) injections alone. These were either zuclopenthixol decanoate, fluphenazine decanoate or flupenthixol decanoate on monthly, fortnightly or weekly basis. 16% (n = 4) of the patients were receiving per-oral butyrophenones (haloperidol), the range of dose (in chlorpromazine equivalents) ranged from 100-800mgs daily.

44% patients were receiving two or more neuroleptics concomitantly. 20% (n = 5) were receiving haloperidol with depot antipsychotic while 24% (n=6) received haloperidol in combination with other neuroleptics i.e. trifluoperazine, chlorpromazine, flupenthixol or metaclopromide (an anti-emetic).

Depot antipsychotics and haloperidol were implicated in 88% cases.

52% (n = 13) received per oral (PO) dose whereas 32% (n = 8) received intramuscular injections (IM). The remaining four patients received both PO and IM doses.

In our sample 66% (n=14) patients were on concomitant medications beside an antipsychotic. Among the concomitant medicines lithium was being used in 16% (n =4) cases while 40% (n =10) patients were taking a variety of psychotropic medications including antidepressants, benzodiazepines or anticholinergic drugs.

All patients were profoundly ill and required initial intensive care management. 96% (n=24) had all the cardinal features of NMS i.e. fever, rigidity and increased serum CPK. In only 1 patient there was absence of fever but the associated diagnostic features were present.

23 patients had the associated feature of delirium. 80% (n=19) patients had documented evidence of fluctuation in BP and pulse. Electrolyte disturbances were also seen in 84% (n=20) of the sample. Diaphoresis and leukocytosis were noted in 68% n=17) of patients.

Most of our sample (68%; n=17) had these episodes in summer whereas only 32% (n=8) developed NMS during the winter months (December- February).

Twelve of the patients (48%) were treated with bromocriptine. One patient received Dantrolene along with bromocriptine.

Mean length of stay (LOS) or course of illness was 11 + 8 days (Range 2–30 days). There was no statistically significant difference in the duration of illness in patients who were treated with bromocriptine compared to those who did not receive bromocriptine.

In our case series the mortality rate in patients with NMS was 16% (n=4). None of these received bromocriptine. Three of them were above 50 years and 2 had concurrent neurological impairment.

DISCUSSION

This report has a number of limitations. It is a tertiary-care hospital based study and the findings cannot be generalized to other health care settings in Pakistan. The small sample size and lack of control group are other limitations.

Despite the limitations, the study highlights some important aspects of this rare but life-threatening condition. This is highly pertinent in the context of Pakistan, a developing country with poorly developed health systems. Mental health fares even worse. While prevalence rates for mental disorders show very high figures, there is an extreme dearth of mental health professionals. Improper and unsupervised use of neuroleptics, over-the-counter (OTC) availability of neuroleptics, use of more than one neuroleptic and lack of timely and proper medical management puts psychiatric patients at high risk of morbidity and mortality from NMS in Pakistan.

Eighty eight percent (n=23) patients in our study were on both depot as well as a high potency neuroleptic (haloperidol) and almost 50% were taking two or more anti-psychotics at the same time. Two-thirds of patients were on other concomitant medications, amongst them serotonin modulators and lithium.

Although two-thirds of our cases presented during the summer months, reports of association of NMS with season give conflicting results. Caroff and Mann reported the syndrome to occur independently of climate and ambient temperature[23]. While patents' inability to maintain body temperature in extreme conditions is a recognized side-effect of neuroleptic treatment, this does not fully explain the occurrence of NMS, which has been reported in cold climates and in different seasons. While high temperatures and humidity may augment the risk of NMS, they need not be present for NMS to occur.

NMS is not specific to any neuropsychiatric diagnosis[24]. Various authors have proposed that patients with disorder of mood, catatonia, schizophrenia, or organic syndromes may be at risk. In our case series one third of the cases had affective illness.

Risk of NMS can be minimized by use of low potency or atypical antipsychotic, cautious use of concomitant medications and depot preparations, initiation of neuroleptic at lowest possible dose with careful monitoring, careful dose increment and cautious use in elderly and neurologically impaired.

Our study indicates that with early diagnosis and prompt treatment i.e. good supportive care, the illness need not be fatal and in fact can have a good prognosis. This study also highlights the need for more information on this disorder looking at associated risk factors, complications and mortality rates from other centers in Pakistan.

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