Original Article

Neuroleptic Malignant Syndrome Revisited in the Perspective of Pakistan

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Abstract

Objective: Neuroleptic malignant syndrome (NMS) is a life threatening adverse reaction of antipsychotic drugs, especially of dopamine receptor antagonists (DRA's). In addition to clinical and pharmacological risk factors, legal and ethical risk factors may be contributory towards the incidence, diagnosis and prognosis of NMS in Pakistan.

Study Design: Experimental case study.

Place and Duration of Study: The department of psychiatry and behavioral sciences of Bahawal Victoria Hospital affiliated with Quaid-e-Azam Medical College, from July 2011 to October 2012.

Subjects and Methods: All the patients with probable NMS, received consecutively at the inpatient department of psychiatry, were included and investigated to rule out any other medical condition mimicking the syndrome. The patients were treated till complete recovery from the syndrome. The psychiatric diagnoses were confirmed, during their hospital stay, according to ICD_{10} Diagnostic Criteria for Research, the residual symptoms were recorded and tabulated along with other important characteristics of the patients.

Results: Reckless use of DRA's in the form of intramuscular depot injections or high initial oral doses, along with certain other previously perceived clinical risk factors, increased the chance of developing NMS. Female gender and younger age along with early detection and prudent management proved to be good prognostic factors for NMS in our study. The diverse categories of the first hand attending health providers e.g. doctors, quacks and faith healers of our psychiatric patients frequently used antipsychotics. This scenario points towards the lapses in determination of pathways to care, legality and ethics governing the mental health care in Pakistan.

Conclusion: Standard protocol must be followed to start antipsychotics in psychotic patients, especially while planning to use depot DRA's. The manic patients are even more sensitive to develop extrapyramidal side effects and neuroleptic malignant syndrome; these patients can better be managed with zuclopinthixol acetate (colpixol acuphase) injections when oral medication is not feasible. These drugs should not be used in neurotic patients. The introduction of depot injections of serotonin and dopamine antagonists (SDA's) may minimize the incidence of NMS. In Pakistan, a task force should immediately be constituted to include Mental Health Ordinance (MHO) 2001 into the

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constitution so that the serious legal and ethical issues of the mental health care are solved, accordingly.

Key Words: Neuroleptic Malignant Syndrome (NMS), risk factors, adverse reaction, antipsychotics.

Introduction

Neuroleptic Malignant Syndrome (NMS) is a rear adverse reaction of neuroleptic or antipsychotic drugs.[1-4] The name neuroleptics owes to the extrapyramidal side effect of these drugs.[3] NMS is a life threatening complication, commonly of dopamine receptor antagonists (DRA's) or typical antipsychotics but rarely of serotonin and dopamine antagonists (SDA's) or atypical antipsychotics.[3,4] The DRA's exhibiting affinity for receptors other than D_2, namely $5HT_2$, $alpha_1$-adrenergic and H_1-receptors are less likely to produce extrapyramidal symptoms (EPS) and NMS[2]. SDA's having low affinity for D_2 – receptors like quetiapine don't cause NMS.[4] The overall incidence of NMS is about 0.2 percent in patients treated with antipsychotic drugs,[1] it amounts to 2.4 percent when the patients exposed to only DRA's are considered.[2] The mortality rate can reach 10 – 20 percent or more, when depot preparations of DRA's are involved,[4] due to cardiopulmonary and renal complications.[5] The clinical picture includes the rapid onset of severe motor, mental and autonomic disorders together with hyperpyrexia. Motor symptoms, similar to those seen in Parkinson's disease, result from D_2 – receptor blockade at basal ganglia. The generalized muscular hypertonicity makes the throat and chest muscles stiff, resulting in dysphagia and dysnoea. The mental symptoms include akinetic mutism, stupor or impaired consciousness[3]. Hyperpyrexia is believed to be caused by hypothalamic dopamine receptor blockade, along with autonomic disturbances like unstable blood pressure, tachycardia, excessive diaphoresis, salivation and urinary incontinence.[8]

In the blood, white blood cells and creatinine phosphokinase (CPK) levels increase, probably due to increased muscular activity and resulting rhabdomyolysis.[6] The patient may suffer from hypertensive crisis and metabolic acidosis. A non-generalized slowing of EEG is found in 50% of the cases.[9] Secondary complications include pneumonia, thromboembolism, cardiovascular collapse and renal failure. NMS is differentiated from encephalitis, heat stroke, acute lethal catatonia, status epilepticus, toxic encephalopathy and serotonin syndrome.[9]

The mechanism for production of NMS by D_2 blockade does not fully explain the variations of incidence with the same DRA and occurrence of NMS with SDA's having low dopamine affinity[9]. Genetic studies indicate over – representation of specific allele of D_2 – receptor gene in some NMS patients. This allele is associated with reduced density and function of dopamine receptors in these patients.[7]

The latency period is the time elapsed between the administration of an antipsychotic and appearance of the signs of NMS. Usually signs start developing within 24 hours of initiating antipsychotic in 16% of the patients, by one week in 66%, within 30 days in 90% and NMS is less likely to occur after thirty days.[2]

The risk factors for the development of NMS which have extensively been studied by the researchers worldwide are as follows:

"Men are affected more frequently than women. Poly – pharmacy, history of EPS / NMS, agitation, affective disorder, intellectual disability, escalation of the dose of antipsychotics in short time,[2,7,13] use of depot preparations of DRA's, concomitant use of lithium, dehydration and dementia (Lowy body).[2,9] Chronic use of psychostimulants such as methamphetamine or cocaine, by working through dopamine depletion, may also predispose the individuals to NMS.[10] Other drugs, even without known anti-dopaminergic activity such as metochlopramite, desipramine, dothiepin, phenelzine, tetrabenazine and reserpine are known to trigger NMS.[11] Sudden withdrawal of L – dopa or dopamine agonist therapy, its dose reduction and a switch from one agent to another has also been associated with the production of NMS – like syndrome.[7,9] Previous episodes of NMS do not make the patient vulnerable to the NMS[12]."

This experimental study was designed to look into various risk factors for the development of neuroleptic malignant syndrome in our settings. We hypothesized that in addition to previously studied pharmacological and clinical risk factors, legal and ethical risk factors may contribute, adversely, to the incidence, diagnosis and prognosis of NMS in Pakistan.

Subjects and Method

This experimental case study with consecutive sampling was conducted between July 2011 and April 2012, in the department of Psychiatry and Behavioural Sciences of Bahawal Victoria Hospital affiliated with Qua-

id-e-Azam Medical College Bahawalpur, Pakistan. Nine cases consecutively received at the department were included and diagnosed as probable cases of NMS with possible effort to exclude other causes of the symptom – complex (relevant investigations with results are included in table 1). After taking detailed history and performing serial mental state exami-nations of the individual cases, during their stay in the hospital, psychiatric diagnoses were finalized according to the ICD – 10 Diagnostic Criteria for Research.[14] On the day of discharge of each case, the residual symptoms and other characteristic features were recorded and tabulated in Table 1.

Results

Table 1: Tabulation of Characteristics of NMS Study Patients (n = 9).

Serial No.	Age in Years	Sex	Diagnosis	Drugs Precipitating NMS with Dose and Route of Administration	First Treated By	Complications
Case 1	17	Female	Acute and Transient Psychotic Episode	Haloperidol 30 mg / Day Per Oral Inj. Flupenthixol Deconate 40 mg / IM	Neurosurgeon	Dehydration Cognitive Impairment Confusion
Case 2	16	Female	Conversion Disorder	Inj. Flupenthixol Deconate 40 mg / IM	Neurosurgeon	Dehydration
Case 3	17	Male	Acute and Transient Psychotic Episode	Inj. Fluphenazine Deconate 25 mg / IM	Quack / Faith Healer	Dehydration Cognitive Impairment Confusion Incontinence
Case 4	18	Female	Acute and Transient Psychotic Episode	Inj. Fluphenazine Deconate 25 mg / IM	Quack / Faith Healer	Dehydration Cognitive Impairment Confusion
Case 5	18	Male	Conversion Disorder	Inj. Flupenthixol Deconate 40 mg / IM	Neurosurgeon	Dehydration Cognitive Impairment Confusion
Case 6	22	Male	Manic Episode	Inj. Fluphenazine Deconate 25 mg / IM Risperidone 6 mg Per Oral	Psychiatrist	Dehydration
Case 7	14	Male	Manic Episode	Inj. Fluphenazine Deconate 25 mg / IM Risperidone 6 mg Per Oral	Psychiatrist	Dehydration Cognitive Impairment Confusion
Case 8	20	Female	Conversion Disorder	Inj. Flupenthixol Deconate 40 mg / IM	Neurosurgeon	Dehydration Cognitive Impairment

						Confusion
Case 9	12	Male	Acute and Transient Psychotic Episode	Inj. Fluphanazine Deconate 25 mg / IM	Quack / Faith Healer	Dehydration

Table 1 (continued): Tabulation of Characteristics of NMS Study Patients (n = 9).

Serial No.	Laboratory Findings					Treatment Given	Duration of NMS Treatment in Days	Outcome
	CSF Examination	TLC	CPK (IU)	CT Scan Brain	X-ray Chest			
Case 1	Normal	11000 / mm^3	279	Normal	Clear	• Diazepam • I/v Rehydration • Bromocryptine	10	• Full Recovery from NMS • Discharged on Sodium Valproate and Olanzapine
Case 2	Normal	7000 / mm^3	149	Normal	Clear	• Diazepam • I/v Rehydration	18	• Full Recovery from NMS • Discharged Drug Free
Case 3	Normal	9000 / mm^3	1556	Normal	Clear	• Diazepam • I/v Rehydration • Bromocryptine	12	• NMS Recovered with Slight Cognitive Deficit • Discharged on Quetiapine
Case 4	Normal	7900 / mm^3	678	Normal	Clear	• Diazepam • I/v Rehydration	15	• Nms Fully Recovered • Discharged on Olanzapine
Case 5	Normal	10140 / mm^3	834	Normal	Clear	• Diazepam • I/v Rehydration • Bromocryptine	19	• NMS Fully Recovered • Discharged Drug Free
Case 6	Normal	11200 / mm^3	2255	Normal	Clear	• Diazepam • I/v Rehydration • Bromocryptine	12	• NMS Fully Recovered • Discharged on Sodium Valproate and Olanzapine
Case 7	Normal	12900 / mm^3	4384	Normal	Clear	• I/v Rehydration • ECT • Bromocryptine	22	• NMS + Manic Symptoms Improved • Mild Cognitive Impairment • Discharged on Sodium Valproate + Olanzapine
Case 8	Normal	7800 / mm^3	1423	Normal	Clear	• I/v Rehydration • Bromocryptine	18	• NMS Fully Recovered • Discharged Drug Free

Case 9	Normal	9150 / mm^3	680	Normal	Clear	• Inj. Diazepam • I/v Rehydration • Bromocryptine	14	• NMS Fully Recovered • Discharged on Olanzapine

NMS = Neuroleptic Malignant Syndrome, IM = Intramuscular, Inj. = Injection, I/V = Intravenous, ECT = Electroconvulsive Therapy, CPK = Creatinine Phosphokinase

Out of nine cases 4 were female and 5 male, with the age ranging from 12 years to 22 years. All 6 cases of psychotic illness (case 1, 3, 4, 6, 7, and 9) were presenting for the first time and were neuroleptic – naïve (Table 1). Three non-psychotic patients (case 2, 5, 8) and four psychotic cases (case 1, 3, 4 and 9) received depot antipsychotics illegally and unethically.[15] The diverse categories of the practitioners treating our NMS – study patients indicate the variety of pathways to mental health care in Pakistan. Cases 6 and 7, treated by psychiatrists were young males with their first episodes of affective disorder with prominent excitation and aggressive behaviour.

The diagnoses of the NMS-patients, given in the column of "diagnosis" in Table1, were made by senior psychiatrist after assessing each patient on the ICD_{10} Diagnostic Criteria for Research,[14] during their stay in the psychiatry department. The laboratory findings, CSF, x-ray chest and CT scan brain showed no abnormality in all the study patients (n = 9). The leukocyte count ranges between 7000 – 12900 / mm^3 and CPK from 149 to 4384 I.U, which are non-specific findings for diagnosing NMS but serial test reports helped us monitoring the prognosis of the condition. The use of depot preparations and high initial oral doses of DRA's are associated with the development of NMS. The latency period between the exposure to DRA's and appearance of the signs of the condition was 4 – 12 days in this study. The encouraging finding of the study is the safe outcome of all the cases (n = 9) without mortality or severe disability.

Discussion

This study confirms most of the previously studied clinical risk factors for the development of NMS. Excitation, exuberant behaviour, violent behaviour and lack of insight predispose the patients to the use of depot preparations and high doses of the antipsychotics. These behaviours also make the patients suffer from dehydration leading to cognitive impairment, confusion and incontinence (Table 1).

The injectable depot preparations and high initial oral doses of DRA's, administered to the psychotic patients not tested for sensitivity to extrapyramidal symptoms, are notorious to cause NMS in up to 2.4% of the recipients.[2,9] In our study, the use of intramuscular depot preparations of DRA's and high oral doses of the same group (haloperidol) at the start of the treatment, found to be causative for the development of NMS. We could not study any case of NMS caused only by the use of any member of the SDA group of antipsychotics.

In the sixth column of Table 1, are listed the practitioners to whom our patients presented for the first time and were treated with antipsychotics; this points out the pathway to care for mentally ill patients in Pakistan. Out of total nine cases, four contacted neurosurgeon, three approached quacks / faith – healers and only two could reach the psychiatrist. This shows the hierarchy of care of mentally ill patient in the town, but in most of the rural and even urban areas quakes / faith – healers are first to be contacted. Pathways to mental health care are not specified and ethical considerations are meager at even consultant level. There is no proper referral system in the country to guide these patients to the mental health professionals.

In this study the quacks / faith – healers have been very rational to diagnose psychosis and administer antipsychotics. The neurosurgeon has been the most reckless in diagnosing and administering depot preparations of DRA's to neurotic patients (case 2 and 5). The manic patients (case 6 and 7) were also not treated prudently by the psychiatrist. To deal with excited, violent and noncompliant manic patients has been grey area for the psychiatrists. The doctors may become tempted to use initial high doses or depot preparations of DRA's to get earliest hold of such patients and thus, precipitate NMS in a few patients. According to the mental health ordinance (MHO) 2001, specialized psychiatric treatments may be carried out, after taking the informed consent of the patient on the order, in writing by the psychiatrist incharge of the treatment. The specialized psychiatric treatments include electroconvulsive therapy (ECT), long acting antipsychotic depot injections and psychosurgery.[15] The protocol for each of the treatment is also mentioned in MHO. Ironically, the MHO 2001 could not become the part of the con-

stitution of Pakistan despite utmost efforts of the concerned mental health professionals.[16]

The prior need to manage NMS has been; the early detection, prompt discontinuation of the antipsychotic and effective treatment of the syndrome and complications in experienced hands.[5] In this study all the study cases (n = 9) recovered from NMS without any mortality or serious disability. This safe outcome of the syndrome is in harmony with so many international studies which used the above gold standard guide lines of management of NMS.[1,2,5] Furthermore, preponderances of younger age and the female gender in our study also seem to contribute towards good prognosis of NMS,[2] whereas some follow up studies of NMS patients of older average age concluded into high mortality up to 25%.[1]

The results of the study support our null hypothesis that along with previously studied clinical and pharmacological risk factors, legal and ethical risk factors further complicate the menace of NMS in Pakistan.

To alleviate the sufferings of psychiatric patients and their families due to NMS, in Pakistan, immediate measures ought to be taken by a task force comprising of senior psychiatrists, office bearers of Pakistan psychiatric society, senior officials from the federal ministries of health and law to make the MHO part of the constitution of Pakistan.[16] The provincial law enforcing agencies must make this law applicable with equity and justice to all the psychiatric patients and their health providers. The federal and provincial health departments are to constitutionalize the pathways to health care for the patients of different specialties to ensure early diagnosis, treatment and prevention on the latest scientific lines. We also recommend the early introduction of injectable (plain and depot) preparations of SDA's to control the agitated, violent and non-compliant patients. This joint venture of pharmaceutical companies, federal ministry of health and psychiatrists needs swift action, if we have to save our psychotic patients from the misery of neuroleptic malignant syndrome.

References

1. P Buckley, A McCarthy and C Larkin. Neuroleptic Malignant Syndrome-Follow up Study. Irish Journal of Medical Science 1991; 160 (2): 45-47.
2. Terri Henderson. Neuroleptic malignant syndrome in adolescents: Four probable cases in the Western Cape. S Afr Med J 2011; 101: 405-407.
3. Drugs and other physical treatments. In: Shorter Oxford Textbook of Psychiatry, 5th ed. Gelder M, Harrison P.J and Cowen Philip eds. Oxford University Press NY, 2006: 536-537.
4. Medication Induced Movement Disorders. In: Kaplan and Sadock's Synopsis of Psychiatry, 10th ed. Sadock B J and Sadock V A eds. (South Asian Edition). Lippincott Williams and Wilkins / Wolters Kluwer Philadelphia, USA, 2007: 992-997.
5. Kahn H, Syed N, Sheerani M, Khealini B, Kamal A, Wasay M. Neuroleptic malignant syndrome: need for early diagnosis and therapy. Journal Ayub Med Coll Abbottabad 2006; 18: 1.
6. Latham J, Campbell D, Nichols W, Mott T. Clinical inquiries. How much can exercise raise creatine kinase level — and does it matter? (http://www.jfponline.com/Pages.asp?AID=6497). J Fam Pract, August 2008; 57 (8): 545-7.
7. Eelco FM Wijdicks author, Michael J Aminoff and Janet L Wlterdink eds. Up To Date 2012. (www.uptodate.com).
8. Strawn JR, Keck PE, Caroff SN. Neuroleptic Malignant Syndrome. (http://ajp.psychiatryonline.org/cgi/content/full/164//6/870). Am J Psychiatry, June 2007; 164 (6): 870-6.
9. Neuroleptic Malignant Syndrome. From Wikipedia, the free encyclopedia (http://www..update.com/online/cotent/topic.do?). topicKey=medneuro/5946&selectedTitle=1~123&source=search_result#26
10. Carrof SN, Mann SC. Neuroleptic Malignant Syndrome. Med Clin North Am, 1993; 77: 185.
11. Silva RR, Munos DM, Alpert M et al. Neuroleptic malignant syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999; 38: 187.
12. Pope HG Jr, Aizley HG, Keck PE Jr, McElroy SI. Neuroleptic Malignant Syndrome: long-term follow-up of 20 cases. J Clin Psychiatry, 1991 May; 52 (5): 208-12.
13. Domenico Berardi, Mario Amore, Paul E Keck Jr, Mario Troia, Meddalena Dell'Atti. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case – control study. Biological Psychiatry, 15 October 1998; 44 (8): 748-754.
14. The International Classification of Diseases and Related Health Problems 10th revision (ICD_{10}) chapter v; Diagnostic Criteria for Research. World Health Organization Geneva, 1993.
15. Specialized Psychiatric Treatments, chapter XI, Miscellaneous, article 56. Mental Health Ordinance, 2001. Government of Pakistan.
16. Rubeena Kidwani. Implementation of Mental Health Ordinance in Pakistan. Go Petition, Jan 18, 2010.