Neuroleptic malignant syndrome: Case report

DP Limbu, RB Tajhya, A Limbu, PM Singh, P Batajoo, B Gurung, S Lamichhane and B Rai

Department of Psychiatry, Nepal Medical College and Teaching Hospital, Jorpati, Kathmandu, Nepal.

Corresponding author: Dr. Durga Prasad Limbu, Department of Psychiatry, Nepal Medical College and Teaching Hospital, Kathmandu, Nepal; e-mail: dr.durgalimbu@gmail.com

ABSTRACT

Neuroleptic Malignant Syndrome (NMS), a potentially fatal complication of neuroleptic therapy is described. It is found to be associated with a variety of medical and psychiatric conditions. Various risk factors and non specific investigations pathognomic to various medical conditions has been proposed. The mortality and morbidity associated with NMS can be decreased with early recognition, early discontinuation of the neuroleptics and aggressive treatment.

Keywords: Neuroleptic Malignant Syndrome, neuroleptics.

Neuroleptic malignant syndrome, rare but life threatening neurological disorder most often caused by neuroleptics is characterized by hyperthermia, muscle rigidity, elevated creatinine phosphokinase and autonomic instability. A case of 20 yrs old female diagnosed with mental retardation with behavioral problem with neuroleptic malignant syndrome is reported here under.

CASE REPORT

A 20 yrs female, with mental retardation with behavioral problems, was brought to this hospital from a psychiatric rehabilitation centre. She was treated with Carbamazepine 200mg twice a day, Haloperidol 5mg thrice a day, Chlorpromazine 100mg twice a day. Due to her uncontrolled exhausting hostile behavior and disorganized behavior, she was given inj. Haloperidol 5mg i.m and inj.promethazine 25mg twice a day for 17 days. Then she developed symptoms like tremor of limbs, salivation, slurred speech, incontinence of urine, rigidity and was not able to stand or walk. All medications were then stopped and Tab Trihexyphenidyl 2mg 1 tab thrice a day was prescribed. She showed no any signs of improvement but after 7 days she developed fever .On examination, Temperature- 102^0F, pulse rate:140/min, Blood pressure: 110/80 mm of Hg, Respiratory rate:28/min. Central nervous system examination showed Clonus, lead pipe like rigidity of limbs. Babinski sign: negative. On examination of Chest, Cardiovascular system, Per abdomen examination showed no abnormality.

Toxicology Screening showed Total Count: 10400/cumm, Neutrophils: 73%, Erythrocyte sedimentation rate: 18, Urine examination: Within normal limits, Blood/urine Culture and Sensitivity: sterile, HbsAg: negative, HIV: negative, VDRL: non reactive. Na: 131mEq/L, K: 3.9mEq/L, CPK total: 45, Serum Creatinine: 0.8mg/dl, serum urea: 33mg/dl, SGPT: 45, SGOT: 6, ALP: 692 U/L, Total Bilirubin: 0.6mg/dl, Direct Bilirubin: 0.1mg/dl, Random blood sugar: 90mg/dl.

Along with consultation from medicine department she was kept on I.V. fluids, catheterization done and treated with Inj. Ceftriaxone 1mg twice a day, inj. Phenargan 1amp once a day, Tab Paracetamol 1 tab thrice a day, Tab Trihexiphenidyl 2mg thrice a day. She had persisting spike of fever, tachycardia and fluctuating BP with severe perspiration. Patient was not responding well up to end of 9 days and started passing sleepless nights, with minimal feeding, and passing brownish urine. However the patient looked alert, but was not speaking.

Despite management along with antibiotics and anticholinergics condition of the patient was not improving. Then preliminary diagnosis of NMS was done and conservative management was continued. After 9^{th} day Trihexyphenidyl was stopped and Tab Baclofen 1 tab twice a day, Tab Bromocriptin 1.25 mg twice a day were added. Inj. lorazepam 2 mg was given stat .Next day she slept well, tremors were reduced, but rigidity persisted. She started talking; she was then kept on oral lorazepam 1 mg twice a day along with bromocriptin & baclofen. Gradually the signs and symptoms of patient improved and all medications were tapered off. After one month of hospital stay patient's condition improved remarkably and was discharged.

DISCUSSION

Probable diagnosis of NMS was made on the basis of risk factor, persisting hyperthermia, muscular rigidity, and exclusion of other medical illnesses. Investigations done showed no findings specific for any medical conditions and patient was not improving.

Among 373 patients treated with neuroleptics during two years at psychiatric hospital, 1% developed Neuroleptic Malignant Syndrome.[1] Pooling data from 16 studies of incidence of NMS in the literature yields 66 cases among 33,720 neuroleptics treated patients i.e. an incidence of about 0.2%.[2,3] NMS has been reported in all age groups, in cold climates and throughout the seasons in parallel with the use of neuroleptics.[3,4]

From the various studies, risk factor was found to be prior exhaustion, psychomotor activity, dehydration[3] in patient treated with neuroleptics. It has been reported in association with diverse psychiatric illnesses –mood disorder,[3,5] Catatonia, schizophrenia.[6,7]

Data on dosage indicate that NMS is not a result of overdose and usually occurs with dosage within the therapeutic range.[3,4] Moreover, Carroff *et al*[4] and Shalev and Menitz[6] found that high potency agents increased the risk, whereas in a prospective study Rosebush *et al*[8] found no relationship between potency or dosage and recurrence of NMS. Shalev and Munitz[6] further proposed that loading rate of neuroleptics is key factor, supported by Keck *et al*[9] in which pt with NMS received significantly higher doses of neuroleptics at greater rates of increase and more intramuscular inj. than control. Deng *et al*[9] compared treatment data on 12 NMS Patient and 102 control, NMS per treated with i.m fluphenazine Deconate, had 3 times rate of NMS rising to 10 times if administered without antiparkinsonian. Concomitant use adjunctive psychotropic drugs like Lithium carbonate, Tricyclic, Monoamine Oxidase, anti parkinsonian, BZD, have been proposed another potential risk factor.

Although NMS may progress within hour, it is usually preceded by insidious neurologic and autonomic signs that defy diagnosis and prove refractory to conventional treatment.

Hyperthermia associated with profuse sweating occurs in 98% of reported NMS Cases, exceeding 38 c in 87%and 40 C in 40%.[4,10] Generalized rigidity described as lead pipe rigidity in its most severe form is reported in 97% of NMS cases and was associated with myonecrosis.

The classic NMS patient appears to be alert but dazed and mute. Autonomic activation and instability, manifested by sinus tachycardia in 88% of fluctuation of BP (61%) have been reported in 95% of cases. Moderate to severe respiratory distress may result from metabolic acidosis, hyperthermia, chest wall restriction aspiration pneumonia or pulmonary emboli was observed in 31% of cases.[7]

Nevertheless none laboratory findings are specific or pathognomic, elevated serum creatinine phosphokinase has been reported in 95%of NMS cases and myoglobinuria in 67% of cases.[10] Non specific leucocytosis in 98%, metabolic acidosis in 75% of cases[4,10] non focal generalized slowing on EEG in 54% of cases.[5,11] CT scans of head have been negative in 95%of cases.[4,10]

Caroff and Mann[4] reported 16% of patients developed NMS within 24hr of initiating neuroleptics, 66% by 1 week, 96% within 30 days and is found to be less likely after 30 days.

Broad range of disorders presenting with fever, rigidity, mental status changes, autonomic dysfunction need to be assessed. Viral encephalitis or post infectious encephalomyelitis confers great difficulty to distinguish from NMS. Several cases have been reported in patient infected with HIV. Clinical examination and brain imaging need to be done to reveal anatomic lesions particularly damage to anterior cingulated gyri, mamillary bodies, periventricular nuclei in the hypothalamus or brain stem may produce akinetic mutism resembling NMS, probably due to dopamine tract passing through these regions.[3,12]

Though seizure is not common with NMS, fever with elevation of creatinine phosphokinase has been reported in status epilepticus. Uncontrolled hyperactivity in major psychosis (lethal catatonia) can cause exhaustion, stupor, hyperthermia and death.[13,14]

Intercurrent infections or metabolic disorder that also has Parkinsonism or catatonia needs to be ruled out. Endocrinopathies like thyrotoxicosis; pheochromocytoma may present with extreme hyperthermia and raised plasma or urine catacholamines. Also SLE or mixed connective tissue disease may present with fever, altered mental status and movement disorder. Most cases of heat stroke associated with neuroleptics resemble classic heat stroke characterized by anhidrosis and respiratory alkalosis but not associated with muscle rigidity. NMS may occur in patients at rest independent of ambient temperature[2].occupational exposure to phenolic compounds can cause hyperthermia , and with muscle rigidity has also followed carbon monoxide and L asparaginase toxicity.[3,10] Malignant hyperthermia associated with the use of anesthetic gases and succinylcholine is another drug induced hypermetabolic disorder indistinguishable from NMS that results from the effects of triggering drugs on skeletal muscle.[3] Antidopaminergic drugs like metoclopramide , amoxapine , tetrabenazine and resrpine have been associated with NMS.[10] Lithium in combination with neuroleptics may increase the risk of NMS.[3,10]

Withdrawal from alcohol or sedative –hypnotics may present with mental status changes, autonomic dysfunction and elevated temperature. Withdrawal also may increase the risk of NMS. In view of this, as well as their tendency to lower the seizure threshold, neuroleptics should be used cautiously in these patients.

Based on recent prospective studies.[2,15-17] Basis of treatment is reduction of risk factors, early recognition, cessation of neuroleptics, and institution of intensive medical care focusing on fluid replacement, reduction of temperature and support of cardiac, respiratory and renal functions. Based on retrospective data, Rosenberg and Green[18] found both Datrolene sodium and Bromocriptine effective in ameliorating the signs and symptoms.

Dopamine has been implicated by several evidences in pathogenesis of NMS. Drug dosage or potency[2,16] rate and route of drug administration[19] and recurrences[4,20] has supported the correlation of NMS and neuroleptics. Besides metoclopramide and amoxapine which are dopamine antagonists have been also known to cause NMS. Moreover, dopamine agonists for idiopathic Parkinson's disease have developed NMS like states when drugs were withdrawn or lost effectiveness. Ultimately, dopamine agonists appear to be effective in treating NMS and contribute to recrudescence of symptoms if withdrawn prematurely.[21,22]

It has been reported that hyperthermia of NMS is due to peripheral heat production associated with severe muscular rigidity secondary to withdrawal of striatal dopamine drive, rather than being initially mediated by the hypothalamus, which is not involved in striatonigral degeneration.[23]

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