Article *NIMHANS Journal*

The Description of the Malignant Neuroleptic Syndrome

Volume: 03 Issue: 02 July 1985 Page: 109-113

K S Mohan, B N Gangadhar, N Pradhan &, Dr. S M Channabasavanna, - *Department of Pathology, National Institute of Mental Health & Neuro Sciences, Bangalore 560 029, India*

Abstract

The Malignant Neuroleptic Syndrome (MNS) a rare, under diagnosed, but amenable to restitutive measures if recognised early, is here described with a description of six cases which recovered (over a period of three years) once they were recognised early and treated immediately. The cases emphasised the need for early recognition even before the full blown out picture is seen and for immediate treatment once recognized which can avert mortality.

Key words -
Malignant Neuroleptic Syndrome
Rigidity
Holoperidol
Hyperpyrexia
Stupor

The MNS is a rare but potentially lethal consequence of treatment with potent neuroleptics. It has been primarily described in the French psychiatric literature by Delay & Deniker [1] and they have suggested an approximate incidence of 0.5 to 1 percent. However, the authors themselves were not clear about its true incidence, possibly because a large number of cases go undetected or misdiagnosed. Till now there is no clear cut clinical parameters for the diagnosis of MNS. Various clinical pictures have been suggested by a number of workers [1], [2], [3].

About 60 cases with various types of clinical manifestations have so far been described in the world literature of which 3 cases have been reported from India [3].

The triad of symptoms described originally by Delay & Deniker [1] is not met with in many of the reported cases in the literature and the potentially lethal character of MNS have been over emphasized in most of the case reports. Herein we present the clinical history of 6 cases diagnosed as MNS to elucidate the presenting pictures of the syndrome.

Material and Methods

All the inpatients requiring neuroleptic medication during 1980-82 were regularly examined for MNS. The diagnosis of MNS was based on the triad of symptoms

(1) Pyrexia above 38° C
(2) Generalized rigidity of hypertonicity
(3) Altered sensorium.

All cases detected and diagnosed as MNS were under intensive care and later on O.P. treatment for a period of two months. Necessary routine clinical and bio-chemical investigations were also done for all cases. In all cases the offending neuroleptic was withdrawn and the patient was put on muscle relaxants, antiparkinsonian drugs and adequate nursing care were provided. A review of all the mortality in the Institute was also subsequently done to find out any deaths, which could have been due to unrecognized MNS.

Results

A brief clinical history of the 6 recognized MNS cases is given below :

Case 1

Mr. JGP, a 17 yr. old presented on 16.5.1980. He was earlier diagnosed as schizophrenia in 1978 and was earlier admitted in Oct 1978 and Dec 1978. The current admission was due to a relapse of schizophrenia. The patient had earlier been treated with CPZ & TFP in the dose of CPZ 400 mgm, equivalent. Occasionally parenteral CPZ 50 gms in 24 hrs. were given to him during previous episodes. Since 1 ½ yrs, the patient had stopped medication. The patient was put on CPZ and received 40 mgm parenteral haloperidol in first 24 hours. Within 24 hrs, the patient developed marked generalized rigidity, pyrexia to 40° C, altered consciousness in the form of impaired gensorium and disorientation. Haemogram, urine analysis, blood sugar, blood urea, serum creatinine, CSF investigations, ECG, X-rays of skull and chest were within normal limits. A diagnosis of MNS was made as no other cause could be found out and was treated with anti-pyretics, all other drugs stopped, general nursing measures, tepid sponging, input-output and calorie requirements were maintained, condition persisted for 5 days and then the patient started showing gradual improvement, first in sensorium, then in temperature and lastly in rigidity. Patient became mobile within one month recovered completely and was discharged on 5.8.80 with advise to take CPZ 100 mgms HS & THP 2 mgms/day.

Case 2

Mr. TBJ, aged 45 yrs, admitted on 14.7.1980 with a previous history of having recurrent manic episodes for past 20 years and treated at various places with different antipsychotics mainly CPZ upto 600 mgms/day and THP 4 mgms/day was currently diagnosed as MDP-Mania of 20 days duration. Patient was given haloperidol 10 mgm IMSOS and tab haloperidol 10 mgm tid. Patient developed symptoms of being stuporic, staring vacantly, altered sensorium, rigidity, rise of temperature to 41° C. with incontinence of bladder and bowel after receiving 30 mgs of haloperidol i.v. within 24 hrs. Haemogram, urine analysis, blood sugar, blood urea, serum electrolytes, blood creatinine & blood cholesterol, CSF examination, X-ray skull & X-ray chest were all within normal limits. A diagnosis of MNS was made, all antipsychotics were stopped, no anti parkinsonian drugs were given and anti pyretic drugs and injection diazepam 10 mgms i.v. sos given. Within 3 days patient improved with total recovery within 9 days and was started on lithium 900 mgs. & CPZ mgms HS which was stopped after a month.

Case 3

Mr. M, a 38 yrs old with no previous clinical history of mental illness or drugs intake was admitted on

27.8.1981 with a one week history of acute schizophrenia & was put on haloperidol 15 mgms. orally and THP 4 mgms/day. After 1 week during which patient received 40 mgms of i.v. haloperidol along with 15 mgms haloperidol orally daily symptoms characterized by generalized rigidity and confusion which progressed to altered sensorium developed. Pyrexia of 41° C. with brisk DTR & ankle clonus was also present. Haemogram, urine analysis, X-ray of chest & skull and ECG were normal. A diagnosis of MNS was made, all antipsychotics were stopped, careful nursing care in ICU and inj Promethazine HCL 25 mgms i.v. tid for 3 days was given. Unconsciousness improved, autonomic dysfunction (bladder retention) improved, then pyrexia came down and later rigidity improved. Within 3 days his condition had improved considerably and the patient was ambulant by the 2nd week. After total recovery patient was discharged on CPZ 400 mgms/day and tab. THP 4 mgms/day.

Case 4

Mr. S, 38 yrs old known epileptic on treatment with tab phenobarbitone 120 mgms HS since 2 yrs was admitted on 27.9.1982 with a psychosis of 3 weeks duration diagnosed as epileptic psychoses and was put on tab. haloperidol 15 mgms/day and inj. haloperidol 10 mgs i.v. sos along with tabs DPH 200 mgms and tab phenobarbitone 120 mgms/day. Within a week generalized lead pipe rigidity with confusion which progressed to altered sensorium and pyrexia of 41° C. with brisk DTR & ankle clonus developed. Haemogram, urine analysis, blood sugar, blood urea, serum creatinine, CSF investigations, ECG, X-rays of skull and chest were normal. All drugs were stopped and inj. promethazine HCI 25 mgms i.v. sos, antipyretics, nursing care and inj. diazepam 10 mgms i.v. 6th hourly for 3 days were given. Rigidity and neurological sings improved and later the pyrexia, within a week symptoms improved and within 2 weeks the patient had finally recovered. The patient was discharged with only antiepileptic medication.

Case 5

Mr. J, a 33 year old man diagnosed as schizophrenic in Feb. 1980 was admitted for1 week. The patient had been on irregular medication. Had been prescribed tab. CPZ 400 mgm/day and 6 mgm THP/day and had developed TD since Octr. 1981. The patient came in Novr. 1981 with exacerbation and schizophrenia and persistent TD and was put on tab. haloperidol 5 mgm HS for one week which was subsequently changed to 1.5 mgm tid. 2 weeks after starting oral haloperidol patient became incontinent of bladder and bowel with lead pipe rigidity, altered sensorium and pyrexia of 44° C. and was admitted on 2.12.1981. Haemogram, urine analyses, blood sugar, blood urea, serum creatinine, CSF investigations, ECG, X-rays of skull and chest were normal.

A diagnosis of MNS was made, all antipsychotics stopped, general nursing care, tepid sponging, ice packs and inj. promethazine HCL 50 mgms i.v. sos with antipyretics were given. Sensorium improved first followed by pyrexia and lastly rigidity, the whole episode lasted 40 days and patient was discharged without any medication.

Case 6

Mr. MD, a 58 year old man had a psychotic episode 21 years back, was prescribed CPZ 100 mgms/day which was discontinued 3 months later and this time was brought on 7-12-82 and was diagnosed as MDP-Mania of 5 days diagnosed as MDP-Mania of 5 days duration. He received a single dose of 20 mgms of haloperidol i.v. in the emergency room, later CPZ 200 mgms orally and then developed unconsciousness with lead pipe rigidity with dehydration and pyrexia of 39° C. Haemogram, urine analyses, blood sugar, blood urea, serum creatinine, CSF investigations, ECG, X-rays of skull and

chest were normal, a diagnosis of MNS was made, antipsychotics stopped and inj. promethazine HCl 50 mgms i.v. sos given. Within 48 hours sensorium began to clear and within the next 48 hours was normal, pyrexia had come down and over the next 24 hours rigidity disappeared. The episode lasted 4 days with total recovery and no antipsychotics were subsequently prescribed.

A perusal of the records of all the cases of deaths which occurred in the hospital during the 3 year period and in emergency receiving wards were done and it was found that 2 cases of death were associated with rigidity, fever and altered sensorium following the introduction of haloperidol. In one case only oral haloperidol 15 mgms/day for 1 week was used and in another i.v. haloperidol 10 mgm was used in addition to tab. CPZ 300 mgms HS on which the patient was being treated. These two deaths in all probability are due to MNS which may not have been recognized early enough.

The total number of inpatients requiring neuroleptic medication during 1980-1983 ... 6663.

Number of patients who developed MNS ... 8.

Incidence of MNS in inpatients requiring neuroleptics ... 0.1% (approx.) mortality as a result of MNS ... 2/8 ... 25%.

Discussion

It has been found from the present study that MNS is very rare and the incidence is about 0.1% with a mortality of 25%. The literature quotes an incidence of 0.5% with a mortality of about 20% (12 deaths out of 60 cases reported) [1]. It is evident that MNS develops in a short time in certain physically healthy individuals within 24 hours following high potency neuroleptics. Hypertonicity or rigidity develops along with the elevation of temp. upto 42° C. The consciousness gradually becomes impaired from disorientation, confusion to stupor. The marked rigidity produces prolonged immobilisation and can complicate the picture by aspiration and dysphagia. The authors have never been able to detect the pallor due to hypotension originally described by Delay, in the above six cases. There was no liability of blood pressure or marked tachycardia, and other autonomic dysfunctions like profuse diaphoresis, dyspnoea, urinary retention and incontinence. The incontinence seen in cases 2&5 are understandable in terms of the patients stuporous state.

The autonomic dysfunctions described in the literature are rare or are confused with the sequelaes of marked generalized rigidity. In most of the cases the rigidity was highly prominent which proceeded in a few hours into a board like rigidity. Dyskinesia and other involuntary movements have been absent in all these cases.

There have been no clear cut descriptions in the literature about the symptom complex of MNS. Hyperthermia has been considered as the presenting symptom by Moyes [4] and Haberman [5] whereas catatonic stupor with fatal outcome has been stressed by Regestein [6] et al, Weinberger & Kelly [7], and Meltzer [8]. Others have stressed the autonomic dysfunctions as characteristic of MNS. They have been no laboratory investigations which would be of diagnostic value in MNS, leucocytosis and increased CPK was reported by Fabry et al [9] and it is probably an effect of pyrexia and acute psychosis respectively. The authors have not been able to detect any abnormal biochemical profiles in the above six cases. In most of the reported cases the minimum temp. ranges have been variable, minimum being 40° .C. Hyperthermia in MNS has been thought to be due to hypothalamic disturbances. But similar hyperthermic states are found in other catatonic states too. Hence the nature

of relationship of MNS to clinically similar adverse hyperthermic reactions implicating psychotropic medication is unclear. All ages and both sexes are equally effected by MNS and in all different categories of psychoses. One of the most general principle that emerges from these reports is that MNS is likely to develop with an acute insult of high potency neuroleptics and the syndrome should be described in a more restricted term. The authors are inclined to describe the syndrome as a triad of pyrexia, generalized rigidity and altered sensorium. These should be the necessary and sufficient conditions to call it as MNS. The 2 cases of death occurred in cases which were not recognized early but all 6 cases which developed while being in hospital and were given adequate supportive measures could survive within 3-4 days.

Conclusions

MNS is very rare complication of high potency neuroleptic medication, the exact aetiology and pathogenesis remains to be understood. Early detection and withdrawal of neuroleptics and treatment with muscle relaxants and supportive measures can give rise to full recovery, however there is no definite predisposition for development of MNS. The acute insult of high potency neuroleptics has been found to be the most common variable in all cases, therefore extra caution must be observed in prescribing high potency neuroleptics.

Acknowledgement

We thank Mr. Sanjeev Sarmukaddam, Lecturer in Biostatistics for his kind help in preparing the mortality statistics of patients receiving neuroleptics.

1.Delay J & Deniker P, "Drug induced extra pyramidal syndromes" In: Vinken P T & Bruyn G W (Eds.)
Handbook of Clinical Neurology, Amsterdam, North Holland Publishing Co Page: 248-266, 1968
2.Caroff S N, The Neuroleptic malignant syndrome
Journal of Clinical Psychiatry Page: 41:79-83, 1980
3.Gurmeet Singh, The Malignant neuroleptic syndrome
Indian Journal of Psychiatry Page: 23:179-193, 1981
4.Moyes D, Malignant hyperpyrexia caused by trimeprazine
British Journal of Addiction Page: 45:1163-1164, 1973
5.Haberman M, Malignant Hyperthermia - an allergic reaction to thioridazine
Annals of Internal Medicine Page: 138:800-801, 1978
6.Regestein G, Alpert J and Reich P, Sudden catatonic stupor with disastrous outcome
Journal of American Medical Association Page: 238: 618-620, 1977
7.Weinberger D & Kelly M, Catatonia and the malignant syndrome, a possible complication of neuroleptic administration
Journal of Nervous & Mental Diseases Page: 165: 263-268, 1977
8.Meltzer H Y, Rigidity, Hyperpyrexia and Coma following fluphenazine. Enanthate
Psychopharmacologia Page: 29: 337-346, 1973
9.Faber S, Gervais C & Manuel C, Le Syndrome malin des neuroleptiques a propos de 7 cas

Encephale Page: 3: 321-6, 1977