NEUROLEPTIC MALIGNANT SYNDROME — A STUDY OF 4 CASES

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SYNOPSIS

The neuroleptic malignant syndrome — a serious extrapyramidal side-effect of neuroleptic druga is being increasingly reported. We report four cases of this syndrome. The management of this condition is briefly discussed.

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INTRODUCTION

There have been increasing reports in the recent literature on the neuroleptic malignant syndrome (NMS) - a rare but serious side-effect of the neuroleptic drugs. Cardinal features of the NMS are development of hyperthermia, muscle rigidity and autonomic instability in a patient exposed to neuroleptics.(1)

It has been suggested that this extrapyramidal side-effect may

be more common than once thought. Addonizio et al(2) have reported a prevalence of 2.4% of more severe cases and in milder form in 9.8% of their sample. The pathophysiologic mechanism appears unclear though it is thought to be an idiosyncratic reaction to a therapeutic dose of a neuroleptic especially one with high antidopaminergic activity. We report two definite cases and two probable cases of this syndrome seen recently in the National University of Malaysia.

Case 1:

Mr. A is a 36 year-old Chinese man who presented with withdrawn behaviour, insomnia and lack of personal hygiene for 4 years. He had had severe head injury at the age of 7 years following which he was noted to have some mental retardation. A diagnosis of Schizophrenia with mental retardation was made and Haloperidol 1.5 mgm thrice daily with Benzhexol 2 mgm twice daily was given. On day 16 an injection of 12.5 mgm of Fluphenazine decanoate was given followed by 25 mgm on day 21. On day 24 he developed severe rigidity of the limbs and became mute. He had a pulse rate of 100 beats per minute and temperature of 38°C. A provisional diagnosis of malignant neuroleptic syndrome was made. Total white count and renal function were normal but serum creatine phosphokinase, CPK, was 571 IU/L (Normal 24 - 195 IU/L) and lactate dehydrogenase, LDH, was 975 IU/L (Normal 230 - 460 IU/L) were raised. He was treated with Benzhexol 4 mgm and Propranolol 40 mgm twice daily. After three weeks the CPK and LDH levels had fallen to 194 IU/L and 805 IU/L respectively. The patient eventually recovered one month after the onset of symptoms.

Case 2

Mr. B is a 36 year-old Indian man who presented with a three-year history of withdrawn behaviour and fear of being poisoned. He had auditory hallucinations, paranoid delusions, thought broadcasting and passivity feelings. A diagnosis of Schizophrenia was made and Chlorpromazine 200 mgm daily was commenced. On day 3 he was given 12.5 mgm of depot Fluphenazine decanoate and on day 6 a full dose of 25 mgm was administered. On day 7 he became drowsy and had headache and a temperature of 38°C. Pulse was 120 beats per minute and blood pressure fluctuated between 100/60 and 160/120 mm of mercury. On day 9 he had profuse sweating and developed severe muscle rigidity and tremors. Investigations showed a leukocytosis of 14800/cu mm rising to 17000 over the next week. Serum CPK rose from 83 IU/L to 566 IU/L and LDH from 533 IU/L to 722 IU/L. Urine for myoglobin was negative. The patient was started on Bromocriptine 5 mgm thrice daily. By day 36 he was afebrile but muscle rigidity persisted till day 53. At time of discharge a week later all investigations were normal and the patient remains clinically well on 150 mgm of Thioridazine daily.

Case 3

Mrs. C is a 35 year-old Chinese woman who had severe paranoid delusions, delusions of reference and auditory hallucinations for 5 years and diagnosed as having

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TABLE 1: SUMMARY OF CLINICAL FEATURES

Case	Psychiatric Diagnosis	Muscle Rigidity	Temperature	Leukocytosis	Neuroleptic Medication	CPK Level IU/L	Autonomic Instability	CNS Changes
1. Male Chinese 36 years old	Schizophrenia with Mental Retardation	+	38°C	absent	Fluphenazine depot	571	present	mute
2. Male Indian 36 years old	Schizophrenia	+	38°C	present	Fluphenazine depot	566	present	drowsiness
3. Female Chinese 35 years old	Paranoid Schizophrenia	+	37°C	absent	Fluphenazine depot	377	Present	drowsiness disorientation
4. Male Chinese 23 years old	Manic-Depressive Psychosis	+	37.1°C	absent	Halaperidol (oral)	752	present	disorientation

paranoid schizophrenia. She was given depot injection of Flupenthixol 10 mgm and Lorazepam 1 mgm at night. On day 3 she developed drowsiness, giddiness, disorientation, short-term memory impairment and acute dystonia and muscle rigidity. On day 5 the dystonia and rigidity had improved but she had severe giddiness with blood pressure being 90 systolic, diastolic being unrecordable. Serum CPK level was 377 IU/L. Leukocyte count was 8400/cu mm. No further medication was given and she recovered rapidly. Repeat CPK a month later was 131 IU/L.

Case 4

Mr. D is a 23 year-old Chinese man with a two-year history of Manic depressive psychosis who presented with a depressive swing and had been receiving Imipramine 150 mgm daily and Haloperidol 3 mgm twice daily. Prophylactic Lithium was commenced at a dose of 250 mgm twice daily. A week later Imipramine was increased to 200 mgm daily, and 3 days later he became restless, had profuse sweating, pulse rate of 120 beats per minute and blood pressure fluctuated between 160/110 to 110/88 mm of mercury. His temperature was 37.1°C, he was disorientated to time, and marked muscle rigidity and tremors were present. Total white count was 9000/cu mm with a relative polymorph leukocytosis of 7740/cu mm. CPK level was 754 IU/L and LDH was 512 IU/L. With the stoppage of previous medications he improved and at the time of writing, two weeks later, he had only mild rigidity. The essential clinical features are shown in Table 1.

DISCUSSION

The cardinal features of NMS were found only in Cases 1 and 2, but in the other two patients common findings such as muscle rigidity, autonomic instability and raised CPK levels were seen. CPK levels need to be cautiously interpreted because the enzyme may be raised in trauma to skeletal muscles such as in severe exercise or repeated or large intramuscular injections.(3) However in our cases, it is unlikely that the injections caused the rise of enzyme levels. Case 3 had only one injection of 1/2 ml of Flupenthixol 5 days prior to the blood test and Case 4 had no injection at all, and his CPK level was more than 3 times above the upper limit of normal. We believe these two cases are milder forms of NMS when considered together with other clinical features.

The differential diagnoses of NMS include encephalitis, meningitis, tetanus, hyperpyrexia due to heat stroke or hypersensitivity reaction and lethal catatonia. None of our cases had findings suggestive of the above.

Various treatments for NMS have been suggested: anticholinergics, ECT, amantadine, bromocriptine and dantrolene. The best combination may be bromocriptine 60 mgm/day and dantrolene 10 mgm/kg/day.(1) Active treatment is associated with much lower mortality than supportive treatment alone or in combination with benzodiazepines and anticholinergics.(4) In our cases, one was symptomatically treated with Benzhexol and Propranolol, another responded well to bromocriptine 15 mgm/day and the third and fourth cases improved after the neuroleptic medication was stopped.

Re-exposure of the patient to neuroleptics needs to be done cautiously though it often does not result in recurrence of symptoms. This suggests that other variables other than the drug is involved in the emergence of the syndrome. Since depot neuroleptics are most often implicated, it would be wiser to re- introduce with oral forms.

CONCLUSION

This syndrome is of interest not only to the psychiatrist but also to other medical professionals because of the widespread use of the neuroleptics particularly in general practice. It needs to be borne in mind that NMS has been reported in patients using dopamine-depleting drugs, following withdrawal of dopaminergic drugs such as

levodopa and amantadine, hypnotic withdrawal and there appears to be a particular predisposition among patients with organic brain impairment.(1) Addonizio et al(2) have found increased proneness among affectively disordered patients.

In view of the high mortality (20-30%) associated with NMS, clinicians need to have a high index of suspicion to detect the early signs of this syndrome, and stop medication promptly when otherwise unexplainable fever or autonomic changes occur in a patient who has been commenced on a neuroleptic. A patient developing NMS should be moved immediately into medical intensive care and supportive measures should also be used.(4)

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REFERENCES

1. Abbott R J and Loizou L A: Neuroleptic Malignant Syndrome. Brit. J. Psychiat. 1986; 148:47-5.

2. Addonizio S, Susman V L, Roth S D: Symptoms of Neuroleptic Malignant Syndrome in 82 Consecutive Inpatients. Am. J. Psychiat. 1986; 143:1587-90.

3. Tietz N W. Enzymes. In: Fundamentals of Clinical Chemistry. W B Saunders & Co. Philadelphia. 1976: 682-3.

4. Kellam A M P: The Neuroleptic Malignant Syndrome, So-called: A Survey of the World Literature. Brit. J. Psychiat. 1987; 150:752-9.