NEUROLEPTIC MALIGNANT SYNDROME IN ORGANIC BRAIN DISEASE AND PHYSICAL ILLNESS

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ABSTRACT

The neuroleptic malignant syndrome is a serious complication associated with the use of antipsychotic drugs that has received a great deal of interest in recent times. Although its aetiology has not been fully understood, it often occurs in association with underlying brain disease and physical debilitation. Two such cases are described. The various hypotheses concerning the aetiology and pathogenesis of this condition are also discussed.

Keyword: Neuroleptic Malignant Syndrome

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INTRODUCTION

The neuroleptic malignant syndrome (NMS) is a serious, potentially fatal complication associated with the use of antipsychotic drugs. Although the aetiology of NMS remains uncertain, it usually occurs with the use of antipsychotics. In some cases, patients who may have been on antipsychotics for years with no adverse side-effects suddenly develop NMS. In such cases, predisposing factors such as physical exhaustion, dehydration and concurrent organic brain disease should be considered. Described below are two cases of NMS with an underlying organic basis.

CASE 1

Miss A is a 53-year old Chinese woman with a history of schizophrenia for the past 35 years, who has residual symptoms of thought disorder and inappropriate affect. She was admitted to a general hospital one week after her monthly fluphenazine decanoate injection because she became drowsy and threw a fit after drinking large amounts of water. She was treated for water intoxication and improved.

Two weeks after admission, she developed fever, hypertonicity and drowsiness. Total white cell count was 23, 700 per cubic millimeter (Normal range: 4, 000 - 11,000 per cubic millimeter) and serum creatine phosphokinase, CPK, was 674 IU/L (Normal: 38 - 164 IU/L). She was diagnosed to have NMS and treated with bromocriptine and she improved. She was eventually started on chlorpromazine with no adverse effects. On discharge she was in remission and maintained on 75 mg of chlorpromazine daily.

CASE 2

Mr B is a 26-year old Malay man who is single and unemployed. He was first diagnosed to have schizophrenia 10 years ago when he presented with persecutory delusions, auditory hallucinations and thought disorder. He was subsequently readmitted on numerous occasions because of relapses of his illness. He was admitted to a general hospital because of an acute abdomen. Laparotomy revealed tuberculous peritonitis and he was started on anti-tuberculous medication. On the seventh post operative day, he was given his usual fortnightly dose of fluphenazine decanoate. A few hours later, he developed fever and stupor. A septic workup revealed no evidence of any infection. Cerebrospinal fluid examination too was normal. Total white cell count was 33,500 per cubic millimeter (Normal range: 4,000 - 11,000 per cubic millimeter) and serum creatine phosphokinase, CPK, was 1,102 IU/L (Normal range 38-164 IU/L). He was taken off all antipsychotic medication and improved spontaneously. He was subsequently restarted on chlorpromazine, the dose of which was gradually increased to 200mg daily with no recurrence of the NMS.

DISCUSSION

The NMS is a condition whose aetiology remains unknown. Several reasons have been postulated and they include the following:

1 The use of antipsychotic agents. Although NMS has been reported following the use of a large number of different antipsychotics, used alone or in combination with other agents such as lithium, the drugs potential for inducing NMS may parallel its anti-dopaminergic potency [1-3]. Haloperidol and fluphenazine have therefore been incriminated most often [4].

2 Rapid neuroleptization is believed to be responsible for some cases of NMS [2,5].

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3 An idiosyncratic response to antipsychotic agents[1].

In some cases of NMS however, patients may have been maintained on a certain dosage of antipsychotics for years, and yet develop NMS. This is so in the two cases described earlier. The above explanations do not explain the onset of NMS in these cases and it suggests that antipsychotics may be a necessary but not sufficient cause of the syndrome [2-4].

Other predisposing factors that have been implicated are physical exhaustion, dehydration and concurrent organic brain disease [2]. These factors would explain the onset of NMS in those who are maintained on a particular dose of antipsychotics. It would also explain why it is that re-exposure of the patient to neuroleptics often does not result in recurrence of NMS[4]. Caroff (1980) suggested that organic brain disease might be a predisposing factor, since 11 out of 60 patients with NMS had either brain damage or a history of alcohol or drug abuse prior to neuroleptic exposure[3].

The two cases described illustrate patients who were previously maintained on antipsychotics and now develop NMS because of concurrent brain disease in Case 1 and because of either physical debilitation or subtle organic brain changes in Case 2.

In Case 1, Miss A developed water intoxication one week after she had been given her monthly fluphenazine decanoate injection. Water intoxication may cause hyponatremic encephalopathy which in turn causes mental symptoms like confusion, restlessness, irritability, lethargy, coma and seizures[6]. It is probably this encephalopathy that made her vulnerable to the dose of fluphenazine decanoate that she had been on for years. It is interesting to note that she developed NMS three weeks after the depot injection. Could this be because her vulnerable brain had initially tried to compensate for the "insult" produced by the depot injection or is it related to the rate of release of the antipsychotic from the injection site. It has been suggested that the appearance of NMS relates to the critical level of the drug in a predisposed patient [1]. Allan & White reported that the reduction in clinical signs coincided with a fall in the urinary concentration of fluphenazine break-down products [1,7].

Miss A was restarted on oral neuroleptics with no recurrence of NMS.

Mr B developed NMS one week after he had received general anaesthesia, on the same day that he had received his monthly dose of fluphenazine decanoate. Since there had been no operative or post-operative complications, it is difficult to speculate on what it is that may have made him vulnerable to NMS. Differential diagnosis of NMS like tuberculous meningitis were considered and excluded as the cerebrospinal fluid examination was normal. Malignant hyperthermia associated with anaesthesia is unlikely as the hypertonicity and fever occurred one week after the anaesthesia.

Malignant hyperthermia occurs within minutes of anaesthetic induction [1]. Assuming that Mr B did indeed suffer from NMS, could he have been predisposed to it because of physical debilitation or could his brain have been made more vulnerable by subtle brain changes that occurred during the anaesthesia?

A decrease in dopaminergic activity is documented in almost all cases. The central mechanisms involved in the pathogenesis of NMS is believed to result from excessive dopamine receptor blockade in the basal ganglia, which causes extrapyramidal symptoms, and in the hypothalamus, where dopamine receptors are concerned with thermoregulation and other autonomic functions [4]. The catatonic symptoms too might be attributed to dopamine receptor blockade.

Debate still exists as to whether the muscle rigidity and hyperpyrexia in NMS originate from an effect of the central action of drugs or are due to a peripheral effect within skeletal muscle as in malignant hyperthermia [1]. Muscle biopsy changes in NMS have been reported [8]. However it has not been established whether these changes are primary or whether they occur secondary to the rigidity. The rigidity and tremor in NMS are profound and must generate considerable heat. This too may contribute to the hyperpyrexia [5].

Mr B too was restarted on antipsychotics with no recurrence of NMS, suggesting that the predisposing factors viz. the physical debility had resolved.

It is interesting to note that in both these cases, the drug implicated was fluphenazine. This is in keeping with previous findings [1,4].

The finding that NMS may occur in predisposed individuals like those with concurrent organic brain disease and physical debility implies that antipsychotics, particularly those with more potent anti-dopaminergic action should be used with caution in such cases. This is especially so in the elderly, as most have pre-existing medical illnesses.

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