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OCCURRENCE OF NEUROLEPTIC MALIGNANT SYNDROME ON TRIHEXYPHENIDYL DISCONTINUATION

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ABSTRACT

The neuroleptic malignant syndrome (NMS) commonly occurs on treatment with neuroleptics, it is also reported in patients who suddenly stop drugs like levodopa, amitriptyline and imipramine. We report a case of NMS, which occured in a patient on lithium, haloperidol and trihexyphenidyl (THP) after sudden discontinuation of THP. The cholinergic system, through its effect on the dopaminergic system, may play a role in the genesis of NMS. Alternatively , anticholinergic withdrawal may produce extrapyramidal symptoms (EPS), and the consequent alteration in food and fluid intake may produce electrolyte imbalance which increases the risk for NMS.

KEY WORDS : Neuroleptic Malignant Syndrome, Trihexyphenidyl discontinuation, Anticholinergic withdrawal.

INTRODUCTION

Rigidity, hyperthermia, alteration in consciousness and autonomic instability are considered to be the core features of neuroleptic malignant syndrome (NMS) (Addonizio & Susman, 1991; Caroff & Mann, 1993). Neuroleptics, especially high - potency ones or high doses of low - potency ones, are implicated in the genesis of NMS. (Addonizio et al ,1987). However, syndromes identical to NMS have been reported in patients not taking neuroleptics (Addonizio & Susman, 1991). Recently, there have been many case reports of a syndrome identical to NMS, developing after withdrawal of dopaminergic drugs, especially levodopa, in patients with Parkinson's disease. (Gibb&Griffith, 1986, Keyser and Rodnizky, 1991).

NMS occurring in psychiatric patients on withdrawal of drugs with anticholinergic action are only sparsely reported (Merriam, 1987; Corrigan & Coutter, 1988). To the best of our knowledge there are no reports of patients developing NMS following primary anticholinergic drug withdrawal. We report a case of NMS occurring in a patient on sudden stoppage of trihexyphenidyl (THP).

CASE REPORT

Mr. P, a 55 year old man, was brought to our outpatient department in January 1994 with a history of irritabillity, increased psychomotor activity, grandiosity, reduced need for sleep, oversociability and impaired judgement. There were past episodes of mania in 1984, 1991,1993, and depression in 1986. There was no history of NMS, contributory organic illness or substance abuse. Physical examination was unremarkable. An ICD-10 (World Health Organisation , 1992) diagnosis of bipolar affective disorder, currently mania with psychotic features, was made. The patient was admitted and started on lithium 600 mg per day and haloperidol 30mg per day. A week later, he developed mild extrapyramidal symptoms (EPS) and THP 4mg per day was added. Over a period of two weeks, his manic symptoms remitted and he was discharged in early February on haloperidol 20 mg per day, lithium 600mg per day and THP 4mg per day. At the time of discharge, serum lithium was 0.5 mEq/L and there was no EPS. He was asked to come for follow - up after two weeks.

The dispensary inadvertently gave the patient THP for 10 days instead of for 14 days. So, from the eleventh day of discharge, he was not

taking THP, though he continued to take lithium and haloperidol. Within two days, he developed difficulty in speaking and swallowing, muscular rigidity and mild rise in temperature. He was brought to our outpatient department the next day.

On examination, he was mildly dehydrated, disoriented to time, though orientation to place and person was present. He appeared confused, had dysarthria and dysphagia. Rigdity was present in all four limbs and temperature was 38° C. His blood pressure (BP) was 140 / 110 mm Hg. There was no evidence of focal neurological deficits, psychotic symptoms and mood change. There was no nausea, vomiting, diarrhoea, myoclonic jerks, hyper -reflexia or seizures. Blood tests revealed creatinine phosphokinase (CPK) value of 4930 units per litre (u /L) (normal range being 10 - 80 u / L) and white blood cell (WBC) count of 19,430 per cubic milli metre. Serum lithium was 0. 96 m Eq /L. Serum electrolytes, liver function tests and renal function tests were within normal limits.

The patient was put on intravenous fluids and other supportive measures. Oral bromocriptine 5mg per day was started. All other drugs were stopped. However, over the next few days, his condition worsened. His level of consciousness decreased, he became stuporous and the rigidity increased. There were fluctuations in his BP and he was sweating profusely. On the third day after admission, he lost consciousness and was transferred to the neurology intensive care unit. On that day, blood tests revealed CPK value of 1725 u / L. WBC count of 15,340 /mm and serum lithium as 0. 4.mEq/L. Oral bromocriptine was increased to 7.5mg per day. He developed secondary complications of syndrome of inappropriate anti - diuretic hormone secretion and pneumonia. However, his NMS symptoms improved over a period of three weeks and CPK value returned to normal limits.

Two weeks after his admission in the intensive care unit, he started developing hypomanic symptoms and so was transferred back to the psychiatry ward. The dose of bromocriptine was reduced to 2.5 mg per day and was stopped a week prior to discharge. Oral lorazepam 3mg per day was started to control the hypomania. He was discharged by mid-March 1994 . At the time of discharge he had no active symptoms of NMS. He had mild cognitive deficits characterised by mild recent memory and new learning impairment. Hypomanic symptoms were in parital remission.

DISCUSSION

Based on rigidity, alteration in consciousness, increased temperature, raised CPK value and autonomic changes, a diagnosis of NMS can be made in our patient. The aetiology and pathopysisology of NMS is not clearly known (Addonizio & Susman, 1991 ; Caroff & Mann, 1993). The use of high potency neuroleptics, concurrent use of lithium, diagnosis of mania and possible electolyte imbalance in our patient are all known risk factors for the development of NMS (Addonizio & Susman, 1991). For a period of 10 days after his intial discharge, our patient was maintaining the improvement. The symptoms of NMS were abrupt in onset and were temporally related to the stoppage of trihexyphenidyl. It is possible that sudden withdrawal of anticholinergics might have precipitated the development of NMS in our patient. Also, there are earlier reports of NMS occuring in patients on withdrawal of drugs with anticholinergic properties like thioridazine, amitriptyline, imipramine (Merriam, 1987; Corrigan & Coutter, 1988). This supports our suggestion that NMS in our patient might have occured due to the sudden stoppage of THP.

There are numerous reports of patients developing neurotoxicity on lithium and neuroleptic combination (Prakash et al, 1982). More recently , there is increasing attention on the enhanced risk of development of NMS on this combination (Addonizio et al, 1986; Keck et al, 1987). NMS often occurs on this combination of drugs when serum lithium is within therapeutic range (Addonizio & Susman, 1991). Though

neurotoxicity has been reported in patients taking lithium alone, even when the serum lithium is within therapeutic range (West and Meltzer 1979), it usually occurs when serum lithium is in the toxic range (Goodwin & Jamison 1990). Though relapse of NMS has been reported on lithium re - challenge (Susman & Addonizio, 1987), occurence of NMS for the first time on lithium alone when serum lithium is in the therapeutic range has not been reported. Since the serum lithium was within normal limits at the time of the patient's original discharge and re-admission with NMS symptoms, and the absence of other associated symptoms of lithium toxicity , it is unlikely that our patient had a primary lithium toxicity. However, the concurrent usage of lithium might have most likely increased the risk of developing NMS in our patient.

Cholinergic receptor supersensitivity can occur as a result of treatment with anticholinergics (Disalver et al, 1987). Sudden withdrawal of anticholinergics can produce a hypercholinergic state, which has been postulated to evoke a hypodopaminergic state increasing the risk of development of NMS (Corrigan & Coutter, 1988). Alternatively anticholinergic withdrawal may produce EPS which can result in dysphagia. This can produce an electrolyte imbalance and metabolic changes which have been implicated in increasing the risk for the genesis of NMS (Addonizio & Susman, 1991).

Most hypotheses regarding the pathophysiology of NMS revolve around a hypodopaminergic state in the central nervous system, especially in the striatum and hypothalamus (Addonizio, 1987). The occurrence of a NMS - like state in patients with Parkinson's disease suddenly, when dopaminergic agonists like levodopa and bromocroptine were stopped, has also been put forward to support the above hypotheses (Gibb & Griffith ,1986; Keyzer & Rodnizky, 1991). However, a careful analysis of the above literature reveals that most of these patients were on a variety of other drugs like anticholinergics, anthihistaminics and amantadine, which were also withdrawn. Hence it can be argued that the NMS in these patients may not be due to levodopa withdrawal alone.

Current models of NMS based on the hypodopaminergic state alone may be too simplistic and may not be able to explain the complex physiological changes and pharmacological responses in these patients. The role of other potential neurochemicals like acetylcholine, norepinephrine, gammaaminobutyric acid, serotonin and glutamic acid needs further exploration. It might be worthwhile to be on the lookout for NMS when anticholinergics are withdrawn, especially when patients have other risk factors for the development of NMS.

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