NEUROLEPTIC MALIGNANT SYNDROME — REPORT OF A CASE

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SYNOPSIS

A case of neuroleptic malignant syndrome is described in a 23 year old female suffering from manic-depressive psychosis. She developed the syndrome after receiving the following drugs: fluphenazine, chlorpromazine, lithium, benzhexol and diazepam. Her main symptoms were fever, clouding of consciousness, extrapyramidal rigidity, dysphagia and incontinence. The diagnosis was confirmed by a markedly raised serum creatine phosphokinase (1351 u/1), and a leukocytosis (WBC 18,830/ul). She was treated with benztropine, benzhexol and bromocriptine. She recovered after one week when she started to show signs of mania. This was treated with chlorpromazine and lithium carbonate. The major manifestations of this syndrome are fever, rigidity and elevated creatine phosphokinase which are all found in this case. The main complications are rhabdomyolysis (26%) and acute renal failure (19%). The mortality rate is 15–20%.

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INTRODUCTION

Neuroleptic malignant syndrome is a rare but potentially fatal idiosyncratic reaction to neuroleptic medication. It was first described by Delay and Deniker (1) in the 1960s and since then approximately 160 cases have been reported in the World literature (2). Its rate was estimated to be 0.5%–1.0%, but higher rates of 1.4% and 2.4% had been reported recently by Pope et al (1986) (2), and Addonizio et al (1986) (3) respectively. The frequency of this syndrome had been underestimated in the past because many cases were missed and not diagnosed. Recent studies have suggested that the syndrome is not a unitary condition but a spectrum disorder with milder variants which are often not diagnosed (3,4).

A case of neuroleptic malignant syndrome occuring in a female patient is reported here to emphasize the importance of early recognition of this rare syndrome and the need for prompt treatment.

CASE REPORT

Ms FB, a 23-year old Pakistani woman was first admitted in August 1986 to a hospital in Jeddah where she was treated for depression for 2 weeks and subsequently sent back to Singapore.

In September 1986, she was noted by her family members to be sleeping poorly, talkative, irritable, quarrelsome and spending money excessively. On 30 Nov 1986, she was admitted to a psychiatric hospital and treated for mania with chlorpromazine 200 mg tds, benzhexol 2 mg tds, haloperidol 1.5 mg tds and diazepam 10 mg nocte. Her condition improved and she was discharged on 23 Dec 86.

She was readmitted to the psychiatric hospital from 30 Dec 86 to 23 Jan 87 for a relapse of her mania and was treated with chlorpromazine 125 mg bd, lithium carbonate 300 mg tds, benzhexol 2 mg bd and diazepam 10 mg nocte. She was also given i/m fluphenazine decanoate 12.5 mg on 31 Dec 86 and 18.75 mg on 9 Jan 87.

On 18th Jan 87 she was noted to have a fever of 38°C and was treated symptomatically with paracetamol. Her mood and behaviour improved and she was discharged on 23 Jan 87 at the insistence of her relatives. She was told to continue the medication as an outpatient.

She was noted by her relatives to be lethargic, unsteady in her gait, slurred in her speech and eating poorly at home. She became progressively worse till 2 weeks later, when she was unable to talk and walk. She could hardly swallow any food and had incontinence of urine and faeces. Three days prior to admission, she developed fever and chills.

On 9 Feb 87, she was admitted to National University Hospital in a stuporous state. She had signs of Parkinsonism — mask like face and stiffness. Her temperature was 37.6°C, pulse rate 105 per minute, and blood pressure of 130/90. She had tachypnoea and galactorrhoea. She was initially diagnosed as stupor caused by organic brain disease, depression or drug overdose. She was transferred to the psychiatric ward and a diagnosis of neuroleptic malignant syndrome was made after a period of observation.

The patient was taken off all psychotropic medications, given supportive nursing care, and investigated and treated for neuroleptic malignant syndrome. On 10 Feb 87, she was treated with injection benztropine 2 mg followed by benzhexol 2 mg tds. On 12 Feb 87, when the diagnosis was more certain, she was also treated with bromocriptine 1.25 mg tds which was withdrawn 4 days later after she developed a rash and her condition improved. Over the next one week, her condition continued to improve. She gradually became more alert and less rigid, and started to take solid food. At the end of one week she was able to walk and take a full diet.

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INVESTIGATIONS

The following investigations were carried out:

Investigations	9.2.87	17.2.87
Haemoglobin	12.1 g%	12.1 g%
White blood cells	14,200/ul*	18,830/ul*
Polymorphs	78%*	90%*
Lymphocytes	16%	5%
Erthrocyte sedimentation rate	34 mm/hr*	34 mm/hr*
Serum sodium	145.00 mmol/l	140.0 mmol/l
Serum chloride	107 mmol/l	95 mmol/l
Serum potassium	4.60 mmol/l	4.10 mmol/l
Blood urea	11.0 mmol/l	3.60 mmd/1
Creatinine	147.0 umol/l*	88.0 umol/l
Serum creatine phosphokinase	1351.0 U/l*	115.0 U/l*
Total bilirubin	11.0 umol/l	6.0 umol
Bilirubin (direct)	1.00 umol/l	0.0 umol/l
Serum protein	82.0 g/l	79.0 g/l
Albumin	40.0 g/l	40.0 g/l
Alanine amino-transferase	16.0 U/l	16.0 U/l
Serum alkaline phosphatase	128.0 U/1*	137.0 U/l*
Gamma glutaryl transferase	20.0 U/l	23.0 U/l
Aspartate amino-transferease	29.0 U/l	33.0 U/l
Lactate dehydro-genase	216 U/l*	175 U/l*

* abnormal values

The results of other investigations were serum calcium 2.66 mmol/l, phosphate 1.26 mmol/l, magnesium 1.16 mmol/l. Thyroid functions tests results were: thyroxine 109 mmol/l, tri-iodothyronine uptake 1.01, and free thyroxine index 108. Urinary examination showed red blood cells 7 per high power field, white blood cells 1–2 per high power field and urine myoglobin negative.

Chest X-Ray showed no abnormalities. Her cerebral spinal fluid was normal, but her electro-encephalogram (EEG) showed mixed background of 6–7 Hz theta and 8–9 Hz alpha rhythm with intermittent and frequent 3–4 Hz delta waves, non-lateralized sharp waves and some triphasic waves. This indicated an abnormal EEG suggestive of some form of encephalopathy or encephalities compatible with an idiosyncratic drug induced encephalitis.

DISCUSSION

Neuroleptic malignant syndrome is an uncommon but potentially fatal side effect of neuroleptic medication. It is characterized by (1) hyperpyrexia, (2) severe extrapyramidal symptoms such as rigidity, trismus, choreiform movements and opisthotonus, and (3) signs of autonomic lability such as tachycardia, labile hypertension, diaphoresis and incontinence.

All patients treated with neuroleptics are at risk. According to Sternberg (1986) (5), the syndrome is associated with the conditions below:

(1) young patients (80% of cases occur in those under 40 years old.
(2) males (twice as frequent as in females)
(3) non schizophrenic psychiatric illness
(4) those on high potency anti-psychotic drugs
(5) medically ill patients with concomitant neurological illness
(6) dehydration, exhaustion and malnutrition
(7) patients receiving lithium

Neuroleptic malignant syndrome should be differentiated from:

(1) severe dystonic reaction and Parkinson's disease
(2) catatonia
(3) intracranial infections including meningoencephalitis and post encephalitic states
(4) toxic encephalopathies including lithium toxicity
(5) allergic drug reactions
(6) hyperthyroidism, hypocalcemic or hypomagnesemic tetany
(7) heat stroke

The case described in this paper manifested most of the signs and symptoms of neuroleptic malignant syndrome. It also fulfils the criteria proposed by Levenson 1985(6) for the diagnosis of this syndrome. Her symptoms included: fever, severe extra-pyramidal side effects — rigidity, hypersalivation, dysphagia and mutism; autonomic lability — mild hypertension which became normal after recovery, clouding of consciousness and incontinence. The manifestations can be divided into major or minor as shown in table 1.

TABLE 1
CRITERIA FOR DIAGNOSIS OF NEUROLEPTIC MALIGNANT SYNDROME

Major Manifestation	Minor Manifestation
Fever	Tachycardia
Rigidity	Abnormal blood pressure
Elevated creatine phosphokinase	Tachypnoea
	Altered consciousness
	Diaphoresis
	Leukocytosis

The presence of all three major, or two major and four minor manifestations indicate a high probability of neuroleptic malignant syndrome.

adapted from Levinson JL (4)

The laboratory investigations which supported the diagnosis included: (1) leukocytosis reaching as high as 18,830/ul in the absence of any systemic infections, (2) markedly elevated creatine phosphokinase of 1351.0 u/l (20–240), (3) mildly elevated hepatic enzymes, (4) mild elevation of serum urea and creatinine levels and (5) non specific EEG changes compatible with a drug induced idiosyncratic reactions.

Inspite of her clinical picture, there was initial reluctance in making a diagnosis of neuroleptic malignant syndrome because of the rarity and severity of the syndrome. However the increase of serum creatine phosphokinase and the absence of other causes to account for the fever and leukocytosis confirmed the diagnosis.

The management of the patient includes: (1) immediate discontinuation of all neuroleptics, (2) intensive nursing care, hydration, nutrition and coma nursing (3) specific drug treatment which includes (a) anticholinergics, (b) bromocriptine and (c) dantrolene.

Levenson (1985) (6), in a review of 53 cases showed that anticholinergics were generally not helpful. However this patient showed improvement with anticholinergics. Burke et al (7) suggest that the syndrome is caused by neuroleptic-induced dopamine depletion or blockade resulting in derangement of central thermoregulation and muscle tone. On the basis of this hypothesis, the dopamine agonist bromocriptine has been recommended and successfully used for the treatment of the syndrome (2,4,5,6). Bromocriptine was commenced in this patient in doses lower than that generally recommended and it was stopped after 1 week of treatment after she developed a rash. May et al (8) who documented elevated oxygen consumption in skeletal muscle which decreased with treatment and improvement, concluded that a hypermetabolic state in muscle was the fundamental cause of the syndrome. On this basis, dantrolene, a direct acting muscle relaxant has been used successfully in the treatment of the syndrome (2,4,5,6).

Following resolution of the neuroleptic malignant syndrome the patient still required treatment of her primary psychiatric condition. Neuroleptic was reintroduced carefully at low doses. There was no recurrence of the syndrome. The review by Shalev et al (9) of 25 cases suggest that challenge with low potency neuroleptics may be wisest choice.

Early recognition and treatment of the syndrome is vital because of high risk of morbidity and mortality. Levenson (6) in his review of 53 cases found the following complications (1) rhabdomyolysis (26%), (2) acute renal failure (19%), (3) acute respiratory failure (4) myocardial infarction, (5) hepatic failure, (6) disseminated intravascular coagulation and (7) E coli fascitis. The mortality rate is reported to be as high as 15% (6) and 20% (10).

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