NEUROLEPTIC MALIGNANT SYNDROME WITH RENAL AND RESPIRATORY COMPLICATIONS – A CASE REPORT

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ABSTRACT

The neuroleptic malignant syndrome is an idiosyncratic reaction to neuroleptic therapy which sometimes can be fatal because of the various associated complications. We describe a schizophrenic patient who, after commencement of haloperidol, developed this reaction which was complicated by acute oliguric renal failure and aspiration pneumonia. It is mandatory that the patient is treated in a medical intensive care unit once the syndrome is recognised. The management of the neuroleptic malignant syndrome and its complications is discussed.

Keywords: Aspiration pneumonia, idiosyncratic, renal failure.

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INTRODUCTION

The neuroleptic malignant syndrome, characterised by a diffuse muscular rigidity with extrapyramidal signs, hyperpyrexia, an alteration of consciousness as an idiosyncratic reaction to neuroleptic therapy. It carries a mortality of 20% (1) which is attributed to the complications that arise during the course of the syndrome. These include dehydration and electrolyte imbalance, acute renal failure, aspiration pneumonia, thromboembolism, cardiovascular collapse and hypoventilation from decreased chest wall compliance. This report describes a case of neuroleptic malignant syndrome complicated by acute renal failure and aspiration pneumonia which are successfully treated.

CASE REPORT

KN is a Malay lady who first presented to University Hospital, Kuala Lumpur in 1980 with a two week history of restlessness, aggressive behaviour, withdrawal, neglect of personal hygiene, auditory hallucination and poor insight. She was diagnosed to have schizophrenia and antipsychotic therapy was started with haloperidol 1.5 mg tid. plus benzhexol 2 mg tid. The dose of haloperidol was doubled after three days. She was discharged when her psychotic symptoms were under control. At follow-up in the psychiatric clinic, University Hospital, Kuala Lumpur a month later, she was found to have stiffness of her body and akathisia and her neuroleptic therapy was changed to chlorpromazine 50 mg tid. Her psychosis was fairly well-controlled and she was able to function quite well at home. She was on regular follow-up and maintenance of chlorpromazine until November 1987 when she subsequently defaulted treatment and was seen again in the psychiatric clinic on 19 April 1988 for relapse schizophrenia with symptoms of withdrawal, neglect of self-care and auditory hallucination. She refused hospitalisation and haloperidol was commenced at 3 mg tid, plus trihexphenidyl 2 mg tid. She was not given any intramuscular injection.

Four days later she started to develop generalised muscle stiffness, hand tremors, inability to walk, high fever, increased sweating and urinary incontinence. She was brought to hospital and on admission to the medical intensive care ward, she was found to have a temperature of 40.5°C, profuse sweating, clinical dehydration, blood pressure of 110/50 mmHg, tachycardia of 150/min, regular and respiratory rate of 25/min. Her lungs were clear on auscultation and abdominal examination revealed no abnormality. She was conscious but mute, with generalised muscular stiffness and severe extrapyramidal signs which consisted of cogwheel rigidity of her upper limbs, hand tremors and akinesia. The tendon reflexes were symmetrically brisk and plantar responses downgoing. Fundoscopy was normal and there was no obvious focus of infection. Her urine was not discoloured.

A diagnosis of neuroleptic malignant syndome was made based on the presence of severe extrapyramidal signs, hyperpyrexia and autonomic abnormalities like profuse diaphoresis and tachycardia which were out of proportion to the degree of fever. The recent neuroleptic therapy with haloperidol had brought on the syndrome.

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Initial laboratory investigations revealed a haemoglobin of 18g/dl and a high haematocrit of 50% due to dehydration as these values returned to normal after rehydration. A marked leucocytosis of 19200/µl with 80 per cent neutrophils was present. Blood film was negative for malaria parasites. Serum creatinine was 438 µmol/L (normal 60-130 µmol/L) and blood urea was 30.6 mmol/L (normal 2.3 – 6.8 mmol/L). The serum sodium was 154 mmol/L and serum potassium was 4.0 mmol/L. The serum creatine phosphokinase level was 19,520 IU/L (normal range 25-170 IU/L). Urine microscopy did not reveal any increased number of cells and there were no reddish-gold pigmented granular casts of myglobinuria. Myoglobin was not detected in the serum or urine by electrophoresis. The radioimmunoassay method which is more sensitive for detection of myoglobin was not available at the University Hospital, Kuala Lumpur. A 12-lead electrocardiogram showed sinus tachycardia without any infarct changes. Chest X-ray showed clear lung fields. Cerebrospinal fluid examination was normal. Blood, urine and cerebrospinal fluid cultures were negative. An electroencephalogram showed non-specific diffuse slow wave abnormalities.

Haloperidol and benzhexol were discontinued when the diagnosis of neuroleptic malignant syndrome was made. Bromocriptine was commenced at 2.5 mg tid. Intravenous midazolam infusion was also started at 2 mg per hour for relaxation of muscles. For the pyrexia she was given paracetamol 1 gm every six hours via a nasogastric Ryle's tube as she was unable to swallow. Tepid sponging was also carried out. The dehydration was corrected by intravenous fluids with central venous pressure monitoring. Peritoneal dialysis was carried out on the third and fourth hospital days because she developed acute oliguric renal failure with rapidly rising serum creatinine and blood urea plus worsening metabolic acidosis. Her temperature subsided dramatically after commencement of bromocriptine, paracetamol and rehydration. By the 4th hospital day her temperature was normal. The sinus tachycardia showed a similar trend of improvement with the heart rate slowing down to around 80/min on the 4th hospital day. There was also significant reduction of sweating. The hand tremors disappeared completely by the 3rd hospital day. However, the generalised muscular rigidity though much reduced, did not disappear completely. The serum creatine prosphokinase level which was highest on the day of admission at 19,520 IU/L had fallen down to within normal range by the 5th hospital day.

On the 5th hospital day, she developed a fever with clinical and radiological signs of right lower lobe consolidation which was thought to be due to aspiration pneumonia. Ceftazidime and metronidazole were commenced after blood cultures had been taken. Chest physiotherapy and postural drainage were carried out. The blood cultures failed to isolate any organism. Despite supplemental oxygen therapy delivered via a face mask, hypoxaemia due to the aspiration pneumonia and mechanical hypoventilation due to respiratory muscle rigidity failed to improve. She required mechanical ventilatory support for 10 days. During this time the pneumonia gradually resolved and a tracheostomy was performed to wean her off the respirator, to protect her airway from further aspirations and to facilitate endotracheal suctioning of airway secretions until the extrapyramidal signs improved and until the respiratory muscles regained their strength. The tracheostomy tube was eventually removed on the 60th hospital day.

Following the peritoneal dialysis her renal function gradually improved. On the 64th hospital day antipsychotic therapy was cautiously reinstituted with a different neuroleptic drug – thioridazine, plus trihexphenidyl. The dose of thioridazine was gradually increased. After 70 days in hospital she was discharged fully ambulant and able to take care of herself. During follow-up at the psychiatric clinic her psychosis was under control and she did not have excessive extrapyramidal side-effects.

DISCUSSION

Unlike the more common extrapyramidal syndromes that occur in patients treated with neuroleptics, neuroleptic malignant syndrome is a relatively uncommon but potentially lethal consequence of neuroleptic therapy. It is because of its sometimes fatal outcome that Delay and Deniker (2) who first described the syndrome in the English Literature in 1968, characterised it as "malignant". The neuroleptic malignant syndrome is an idiosyncratic reaction to neuroleptic treatment that occurs after therapeutic rather than toxic doses of neuroleptic drugs (3). This is illustrated in the present case by the relatively low dose of haloperidol used and by the fact that the patient had previously been exposed to the same dose of the drug without developing a similar severe reaction. This time she developed the syndrome 4 days after commencement of the drug. Its occurrence is unrelated to the duration of therapy for it can occur soon after the first dose of drug or after weeks of treatment. In most cases, extrapyramidal signs appeared early in the course of neuroleptic treatment or soon after a change to a new drug, with fever appearing usually one to five fays after commencement of treatment or change of treatment (4).

Although most cases have been described following haloperidol or fluphenazine administration, a few cases have occurred after chlorpromazine, thioridazine, trifluoperazine and prochlorperazine therapy (3). The term neuroleptic malignant syndrome is a misnomer as the offending agent need not be a neuroleptic drug as the syndrome has also been seen after discontinuation of levodopa and carbidopa in the treatment of Parkinsonism (5) and following administration of monoamine oxidase inhibitors and tricyclic antidepressants. Psychiatric illness is not a prerequisite for the development of neuroleptic malignant syndrome because psychiatrically normal people have had the syndrome after neuroleptic drugs were given for preinduction anaesthesia or sedative-hypnotic withdrawal (3). It has also occurred in Huntington's disease following dopamine depleting drug therapy. (6)

As fever is a prominent feature of the syndrome, it is imperative to exclude a coexisting infective process before attributing pyrexia to NMS. Elevation of serum creatine phosphokinase level is due to skeletal muscle necrosis secondary to ischaemia of muscles as a result of sustained muscular contraction. A marked neutrophil leucocytosis is a well described feature of the syndrome and electroencephalograms usually show nonspecific slow waves consistent with an encephalopathy although no specific anatomical lesions have been found in postmortem studies on the brains of patients who had died from the syndrome (3).

Once a diagnosis of neuroleptic malignant syndrome is made the offending neuroleptic drug should be promptly discontinued. Bromocriptine, which is a direct-acting dopamine (DA-2 receptor) agonist, should be commenced to restore dopamine neurotransmission as the proposed mechanism for the development of the syndrome is related to neuroleptic-induced dopamine-receptor blockade in the basal ganglia and the hypothalamic thermoregulatory centres (3). Doses of bromocriptine which have been used in cases reported in the literature range from 7.5 mg to 60 mg/day (4) but according to Mueller (7) at least 5 mg t.d.s. is the minimum starting dose and for some patients the dose may be rapidly increased to as high as 20 mg t.d.s. or q.i.d. (8). Following clinical improvement, treatment with bromocriptine should be continued for at least 10 days (9). The disadvantage of using bromocriptine is that no parenteral form of the drug is available and nasogastric tube administration of bromocriptine as in nasogastric tube feeding risks aspiration particularly in the presence of a poor protective cough mechanism. In a situation where bromocriptine cannot be given orally, intravenous dantrolene sodium which ony has a peripheal effect in reducing muscle tone may be used until oral bromocriptine can be given (10). Anticholinergic drugs and benzodiazepines are usually ineffective in reducing muscle rigidity in NMS (11). In fact anticholinergic agents may worsen hyperpyrexia (10).

The neuroleptic malignant syndrome carries an estimated mortality of 20% (1). Morbidity and mortality are mainly due to complications that arise during the course of the syndrome. It needs to be emphasised that supportive treatment in a medical intensive care unit is mandatory with early treatment of complications as they arise. Our patient was dehydrated because of poor oral intake due to immobilisation from severe muscular rigidity, compounded by increased insensible water loss from the fever and profuse diaphoresis. The hypernatraemia had resulted from excessive water loss in the sweat which is hypotonic.

Acute renal failure due to myoglobinuria resulting from rhabdomyolysis is well described in this syndrome (12). The mechanisms for the renal failure in our patient included dehydration and possibly myglobinuria in view of the high serum creatine phosphokinase level reflecting extensive muscle necrosis. Dehydration itself also predisposes to acute tubular necrosis due to myoglobinuria. As a prophylaxis against acute renal failure in the presence of myoglobinuria forced saline, mannitol and frusemide diuresis should be instituted with concurrent urinary alkalinisation with intravenous sodium bicarbonate once diuresis is established. However, institution of forced alkaline diuresis is often too late to be effective when acute renal failure is already established at presentation (13).

Dialysis is necessary to correct the biochemical derangement that accompanies acute renal failure but is ineffective in removing the offending drug from the circulation as most neuroleptics are bound to serum lipids or proteins (3).

The predisposing factors for aspiration pneumonia in our patient included hypertonic involvement of her pharyngeal muscles (3) which impaired swallowing and a poor protective cough mechanism due to reduced chest wall compliance resulting from respiratory muscle rigidity.

Recovery from the neuroleptic malignant syndrome occurs in 5 to 7 days for most of the neuroleptic drugs but takes 10 to 21 days for long-acting depot preparations like fluphenazine (3). If neuroleptics are still indicated after recovery from NMS, they should be recommenced cautiously with appropriate antiparkinsonian medication (4). Rechallenging patients with an offending drug after recovery from the acute episode may or may not result in recurrence of symptoms (3). However it is advisable to use a different neuroleptic.

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