Postgraduate Medical Journal (1989) **65**, 653 - 655

Missed Diagnosis

Neuroleptic malignant syndrome: another medical cause of acute abdomen

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Summary: We present a patient with neuroleptic malignant syndrome and intestinal pseudo-obstruction misdiagnosed as being secondary to septicaemia. The management of the patient is discussed with emphasis on the role of creatine kinase and liver function tests.

Introduction

Neuroleptic malignant syndrome (NMS) is an occasional but potentially lethal idiosyncratic complication of neuroleptic drugs.[1,2] By February 1989 the Committee on Safety of Medicines had received reports of 99 cases. (Committee on Safety of Medicines, personal Communication). It is thought that the condition is underdiagnosed.[3,4] We report on a case of NMS of which the presenting features and therapeutic complications occurring during the course of the illness served to further our knowledge in this condition.

Case report

A 36 year old woman with a history of psychotic depression was admitted into the psychiatric unit with a relapse of her condition. Chlorpromazine 50 mg three times a day and flupenthixol decanoate 20 mg intramuscularly were given.

Twenty-four hours later, she developed a pyrexia of 38°C together with tachycardia up to 160/minute, excessive perspiration, vomiting and urinary incontinence. Her blood pressure was labile and fluctuated between 95/50 and 180/120 mmHg. Neurological examinations revealed no focal abnormality but generalized rigidity was present. Her conscious level also showed variation between being awake and mutism. On the third day after admission, she developed a distended abdomen which felt tense with minimum diffused tenderness but no guarding or rebound. Bowel sounds were absent. Investigations showed haemoglobin 11.2 g/dl, white cell count 17.9×10^9/l (92% neutrophils), serum sodium 130 mmol/l, potassium 5.1 mmol/l, urea 8.8 mmol/l, creatinine 79 μmol/l, bilirubin 15 μmol/l, alanine transaminase 837 IU/l (normal 7–45), aspartate transaminase 392 IU/l (normal 9–41), gamma glutamyl transferase 15 IU/l (normal <65), alkaline phosphatase 62 IU/l (normal 35–125). Serial electrocardiograms showed sinus tachycardia with no acute change. Abdominal X-ray revealed marked gaseous distension of small and large bowels with multiple fluid levels seen on decubitus films. A diagnosis of pseudo-obstruction secondary to septicaemia from urinary tract infection was made by the surgical team on call and treatment with intravenous gentamicin and amoxycillin together with naso-gastric suction was started.

She showed further deterioration in the conscious level together with progressive increase in generalized rigidity over the following 3 days. Her pyrexia, abdominal distension and absent bowel sounds persisted. At this stage, she was referred to the medical team and by then her pyrexia had reached 42°C. Based on the clinical signs and history of neuroleptic drugs usage, a clinical diagnosis of neuroleptic malignant syndrome was made that day. This was further reinforced by the finding of a markedly elevated creatine kinase > 40,000 IU/l (normal 24–195), the presence of myoglobinuria and a leucocytosis of 23×10^9/l with negative blood and urine cultures, and a normal chest X-ray.

She was transferred to the high dependency unit and the chlorpromazine was discontinued. She was rehydrated and dantrolene 140 mg intravenously (at 2 mg/kg body weight) was given over a period of 10 minutes. Respiratory arrest occurred 5 minutes later and she was intubated and ventilated. Her pyrexia responded dramatically to dantrolene and within 8 hours, it had settled to 38°C. Further episodes of pyrexia (over

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Accepted:13 March 1989

39°C) occurred over the following 5 days, all of which were successfullly treated with intravenous dantrolene.

Her condition improved gradually. By the eleventh day after admission, her pyrexia remained below 38°C, the abdominal distension had resolved and the bowel sounds were normal. She remained conscious but her generalized rigidity was unchanged. She was, therefore, started on Sinemet (levodopa plus carbidopa) 110 mg three times a day and bromocriptine 5 mg twice a day, both orally. Dantrolene was also given orally for 6 days until her pyrexia had completely settled.

She was eventually weaned off the ventilator when her generalized rigidity resolved and the level of serum creatine kinase, alanine transaminase and aspartate transaminase returned to normal on the twenty-ninth day after admission. She was discharged 51 days after admission on no medication.

A review of psychiatric notes suggested a similar episode 2 years previously with development of a pyrexial illness and an acutely distended abdomen 2 days after an injection of flupenthixol decanoate 20 mg i.m. depot. Laparotomy was performed then and no abnormality was found although a normal appendix was removed. Her pyrexia continued for 3 weeks post-operatively despite antibiotics. No source of infection was identified. Unfortunately, no record was made of her conscious level, muscular tone and serum creatine kinase.

Discussion

The term neuroleptic malignant syndrome (NMS) was first coined by Delay and Deniker.[5] The combination of hyperpyrexia, altered consciousness, muscular rigidity and autonomic dysfunctions in neuroleptic drug-treated patients should alert one's awareness of NMS. The presence of leucocytosis, elevated creatine kinase and myoglobinuria should be looked for to further substantiate the diagnosis.[6,7] However, despite all the generally accepted clinical manifestations and laboratory abnormalities of the syndrome, there is still no accepted agreement or conclusion regarding the role of any particular drug (singly or in combination) which might be responsible, or which patient is most at risk. Its actual pathogenesis has not been identified though it is widely believed to be related to dopamine receptor blockage in the basal ganglia and the hypothalamus.[8-10]

Treatment is essentially supportive and consists of neuroleptic drug withdrawal, correction of dehydration and electrolyte imbalance, cooling of the patient and prevention of respiratory, cardiac and renal complications. Levodopa in combination with dopadecarboxylase inhibitor, bromocriptine[11] and amantidine[12] have all been tried because of their dopamine-agonist property. However, anticholinergic drugs have been reported to produce both beneficial and harmful response.[13] The effect of dantrolene lies in its ability to inhibit release of calcium ions from the sarcoplasmic reticulum. It therefore interferes with the excitation-contraction coupling in the skeletal muscle leading to a decrease in heat production.[14] However, the optimal dose, method of administration and the effectiveness of dantrolene have not been fully assessed.

Overall, our patient's illness serves to improve our knowledge of NMS. Firstly, NMS should be included in the differential diagnosis of acute abdomen in the form of pseudo-obstruction as illustrated in our case. All surgeons should be aware of this possibility when faced with patients on neuroleptic drug therapy. Gastrointestinal disturbances in NMS, consisting of sialorrhoea, dysphagia, constipation and faecal incontinence have been reported.[2,15] The sequestration of fluid into the dilated bowels together with excessive perspiration, vomiting, poor fluid intake and pyrexia may all lead to dehydration which is a well recognized risk factor for the development of NMS,[16] and unless corrected, will perpetuate the attack. The mechanism underlying the development of pseudo-obstruction in our patient remains speculative but undoubtedly it is multifactorial, and autonomic disturbances, hyperthermia, hypoxia and electrolyte imbalance are all contributory.[17,18]

Secondly, gradual reduction of serum creatine kinase appeared to correlate closely with clinical improvement in our patient. It has been shown that serum creatine kinase is markedly elevated in 92% of cases of NMS[13] but its maximum level is not related to the degree or duration of the clinically observed rigidity.[16] Serum creatine kinase returns to normal in those patients recovered from NMS but in fatal cases, it remains elevated and presumably it is due to persistent hyperthermia and muscular rigidity leading to continuous rhabdomyolysis.[6] There does not appear to be a published study on creatine kinase levels in acute abdomen or pseudo-obstruction. However, it has been shown that the gastrointestinal tract contains only a small amount of creatine kinase, mainly in the form of CK-BB isoenzymes.[19,20] Surgery involving the gastrointestinal tract does not increase serum creatine kinase level, nor is the CK-BB generally detected after such procedures.[21] We did not check the CK isoenzymes pattern in our patient but it is obvious that the contribution of pseudo-obstruction to the marked increase in creatine kinase level in this case was negligible. Serial measurement of serum creatine kinase but not any single isolated reading is therefore a good indicator for the progression of NMS and hence can be used as a guide for its management.

Thirdly, serial measurements of serum alanine tran-

saminase and aspartate transaminase levels in our patient showed gradual reduction in parallel with the decrease in serum creatine kinase level and clinical improvement. Hence, the abnormal 'liver' function tests observed in NMS were more indicative of muscle disease and may, therefore, serve to monitor progress and provide a clue to the correct diagnosis of NMS. We have reported this case to the Committee on Safety of Medicines and the pharmaceutical companies concerned.

Acknowledgement

We wish to express our thanks to the medical and nursing staffs in the High Dependency Unit who collaborated in this patient's care.

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