SHALEV, A., HERMESH, H. & MUNITZ, H. (1989) Mortality from neuroleptic malignant syndrome. *Journal of Clinical Psychiatry*, 50, 18–25.
SPIESS-KIEFER, C., GROHAMANN, R., SCHMIDT, L. G., *et al* (1988) Severe and life threatening adverse reactions to psychotropic drugs. *Pharmacopsychiatry*, 21, 290–292.

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Neuroleptic Malignant Syndrome Presenting as Hyperosmolar Non-ketotic Diabetic Coma

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A 50-year-old man presented with hyperosmolar non-ketotic diabetic coma associated with the neuroleptic malignant syndrome (NMS) after intramuscular treatment with haloperidol. It is suggested that NMS may occur as a complication of uncontrolled diabetes mellitus with dehydration. Conversely, NMS might precipitate diabetic coma in patients with previously well controlled blood glucose.

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Case report

A 50-year-old white man in diabetic coma was transferred to a general medical hospital from a psychiatric unit. Over the previous 15 years he had suffered from recurrent episodes of depression with psychotic features. He did not have any other medical problems and was unaware of his glucose intolerance. Ten days earlier he had been admitted to the psychiatric hospital with retarded depression and was treated with tricyclic antidepressants and trifluoperazine, 1 mg twice daily. This treatment had been given on three other separate occasions with consequent improvement.

Over three days, the patient developed catatonia and was treated with haloperidol 5 mg intramuscularly every six hours. Electroconvulsive therapy was performed on two occasions with only slight improvement. The attending anaesthetist recorded wide fluctuations in blood pressure with readings varying from 160/100 to 190/130 mmHg (mean 170/110 mmHg). Two days before his transfer, moderate muscle rigidity and a fine Parkinsonian tremor were noted. There were no dyskinetic movements. In view of his deteriorating general condition, increasing rigidity, and progressive unresponsiveness, he was referred to a general medical hospital for intensive supportive care.

In the emergency room he was comatose. His respiratory rate was 24 per minute, regular both in frequency and in amplitude. He was grossly dehydrated, had a small volume pulse of 120 beats/min, a blood pressure of 100/60 mmHg and a rectal temperature of 40 °C. Blood tests showed: glucose 45 mmol/l, haemoglobin 16 g/dl, white cell count 23 000/mm^3, urea 23.8 mmol/l, creatinine 200 μmol/l, Na^+ 145 mmol/l, K^+ 4.5 mmol/l, pH 7.34, HCO^{3-} 20.2 mmol/l, pO_2 120 mmHg, creatinine phosphokinase (CPK) 840 U/l (normal 0–100 U/l), plasma osmolality 368 mosm/kg. The chest X-ray and the electrocardiogram were unremarkable. Urine analysis showed heavy glucosuria, no ketonuria or indeed any other abnormality.

Three litres of fluid were rapidly infused. Central venous pressure measured in the intensive care unit was 2 cm water and a further three litres of fluid were infused. An insulin infusion was started at eight units per hour. Treatment with ice-packs and rectal paracetamol had little effect on his body temperature. He was also treated with intravenous cefuroxime and low-dose subcutaneous heparin.

Twelve hours after admission, his fluid deficit and high blood glucose had been corrected. His general condition improved, but consciousness remained clouded. There was extreme muscle rigidity, tremors of all four limbs, and at times opisthotonus and trismus. Computerised tomography of the brain did not show any cerebral oedema or any other abnormality. Blood and urine cultures taken before and after the start of antibiotic therapy were repeatedly negative.

He was treated with intravenous dantrolene 60 mg every six hours. There was a slight decrease in muscle rigidity, but overall there was no clear improvement. Twenty-four hours after admission he became extremely tachypnoeic (50–60 min). Arterial blood gases on 50% oxygen showed a pO_2 of 73 mmHg and pCO_2 of 32.9 mmHg. An intravenous infusion of heparin at a dose of 1500 U/h was started.

Up to day nine, his general condition remained unchanged, with temperature persistently above 38.5 °C (Fig. 1), continuous unstable tachypnoea of around 40/min, and unabating muscle rigidity. His CPK was persistently

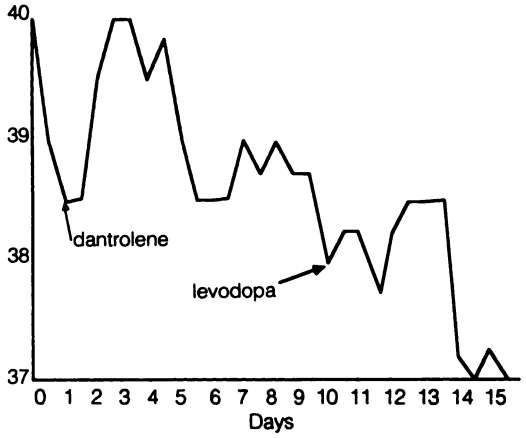

Fig. 1 Body temperature days 1 to 15.

above 350 U/ml and the white cell count remained above 15 000/mm³. On day 10, treatment with oral levodopa with carbidopa was started and gradually increased to 220 mg every six hours. Dantrolene was stopped.

By day 15, consciousness was clear, his body temperature had returned to normal and the respiratory rate became stable at 24/min. Muscle rigidity persisted and was particularly severe in the lower limbs. Creatinine phosphokinase at this stage was normal. By day 25 his muscle rigidity had gradually diminished and he was able to walk unaided. Levodopa was reduced and stopped while his diabetes mellitus was controlled with a total daily dose of 40 IU of insulin.

Discussion

Pope's criteria for the diagnosis of NMS (Pope *et al*, 1986; Keck *et al*, 1989) were fulfilled. Hyperthermia, severe extrapyramidal rigidity and autonomic instability were present long after the correction of the metabolic upset.

Dantrolene did not seem to affect the course of the illness despite 10 days of therapy. Pyrexia gradually resolved during treatment with levodopa and this was followed by an improvement in autonomic instability and by a decrease in muscular rigidity. As NMS usually resolves over a period of 10–15 days, this response to levodopa could have been coincidental.

The suggested pathogenesis of NMS is that rapid central dopaminergic receptor blockade predisposes to generalised muscle contraction leading to a hypermetabolic state (Smego & Durack, 1982). Dehydration and physical exhaustion have been suggested as precipitating factors (Itoh *et al*, 1977; Caroff, 1980; Harsh, 1987; Keck *et al*, 1989). The possible mechanism is that dehydration impairs heat dissipation by causing vasomotor constriction (Harsh, 1987).

Uncontrolled diabetes mellitus together with dehydration may precipitate NMS in diabetic patients on neuroleptics. The hypermetabolic state in NMS may cause ketotic or non-ketotic diabetic coma in patients with previously well controlled blood glucose, making the recognition of the syndrome more difficult. It is logical to suppose that the severity of dehydration and the rate of thrombotic complications will be increased in diabetic patients with NMS. Further studies and more attention to blood glucose levels in reported cases of NMS are needed to support these conclusions.

References

CAROFF, S. N. (1980) The neuroleptic malignant syndrome. *Journal of Clinical Psychiatry*, **41**, 79–83.

HARSH, H. H. (1987) Neuroleptic malignant syndrome. Physiological and laboratory findings in a series of 9 cases. *Journal of Clinical Psychology*, **48**, 328–333.

ITOH, H., OHTSUKA, N., OGITA, K., *et al* (1977) Malignant neuroleptic syndrome, its present status in Japan and clinical problems. *Folia Psychiatrica et Neurologica Japan*, **31**, 567–576.

KECK, P. E., JR, POPE, H. G., COHEN, B. M., *et al* (1989) Risk factors in neuroleptic malignant syndrome. *Archives of General Psychiatry*, **46**, 914–918.

POPE, H. G., KECK, P. E., JR, MCELROY, S. L., *et al* (1986) Frequency and prevention of neuroleptic malignant syndrome in a large psychiatric hospital. *American Journal of Psychiatry*, **143**, 1227–1233.

SMEGO, R. A. & DURACK, D. T. (1982) The neuroleptic malignant syndrome. *Archives of Internal Medicine*, **142**, 1183–1185.

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