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Short report

Neuroleptic malignant syndrome: a case report with post-mortem brain and muscle pathology

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SUMMARY The neuroleptic malignant syndrome is a rare but dangerous complication of treatment with neuroleptics. The aetiology and pathophysiology of the syndrome are reviewed, and a fatal case is presented where both brain and muscle pathology are described. Striking myopathic changes in this case, accompanied by only minimal and non-specific brain abnormalities, support a peripheral rather than central mechanism for the hyperthermia.

The term *neuroleptic malignant syndrome* was introduced into English medical literature by Delay and Deniker[1] in 1968, and since an article by Caroff[2] in 1980 interest in the syndrome has flourished.[3–7] It is a rare[8–10] but potentially fatal hypersensitivity response in certain patients exposed to neuroleptic medication. The core features are a diffuse muscular rigidity (often with extrapyramidal or catatonic signs), hyperthemia, autonomic instability, and altered consciousness; typically these develop days or weeks after starting neuroleptic treatment and progress over 24–72 hours. Associated findings include a leucocytosis, elevated serum potassium, and elevated serum creatine phosphokinase (CPK), the latter reflecting skeletal muscle necrosis. Mortality is about 20%[2] and is particularly associated with long acting (depot) neuroleptics, a diagnosis of schizophrenia, and organic brain disease.[6]

The syndrome has been reported to occur in a wide range of psychiatric disorders apart from schizophrenia,[3 8 9 12 16] and indeed has occurred in well patients as a complication of pre-operative medication.[11] Some cases have occurred in the absence of a history of neuroleptic treatment, for example due to dopamine depleting drugs such as tetrabenazine and alpha-methyltyrosine in Huntington's chorea,[13] and withdrawal of dopamine agonists such as levodopa and amantadine in Parkinson's disease.[3 12 14 15] Combinations of tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) in overdose have also been implicated.[6] Some authors have suggested that concurrent treatment with lithium increases vulnerability to the syndrome.[3 9]

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Case report

A 70 year old widow suffering chronic depression had been an inpatient on a longstay psychiatric ward for 2 years when she became suddenly distressed and unwell, with dyspnoea, tachycardia of 150, diffuse muscular rigidity, and a pyrexia of 39·4°C. Within 1 hour she became cyanosed, hypotensive (BP 80/30 mmHg), and deeply comatose, with generalised rigidity and marked hyperreflexia. Her treatment at this time included a MAOI (isocarboxazid 10 mg od) and a neuroleptic (chlorpromazine 25 mg tds).

After initial resuscitative measures, the patient was transferred to a general hospital, where she had a grand mal fit. Investigations revealed a mild neutrophil leucocytosis, elevated serum potassium (6 mmol/l) and CPK (3,300 IU/l) and a sinus tachycardia on ECG. Chest radiograph, blood glucose, lumbar puncture, serial blood cultures and CT of the head were normal.

Combining the clinical picture and the results of the initial investigations, a diagnosis of neuroleptic malignant syndrome was made. Treatment comprised discontinuation of all psychotropic drugs, cooling, intravenous fluids and anticonvulsants. Within 24 hours the patient's clinical state improved considerably; her muscle rigidity and pyrexia resolved, and she regained full consciousness. However, as a result of widespread rhabdomyolysis she developed acute renal failure from which she died some days later.

It is of interest that throughout the previous two years of inpatient care, the patient had developed an unexplained toxic confusional state on six occasions. During this period she had received neuroleptics intermittently. These episodes were characterised by acute confusion with restlessness and

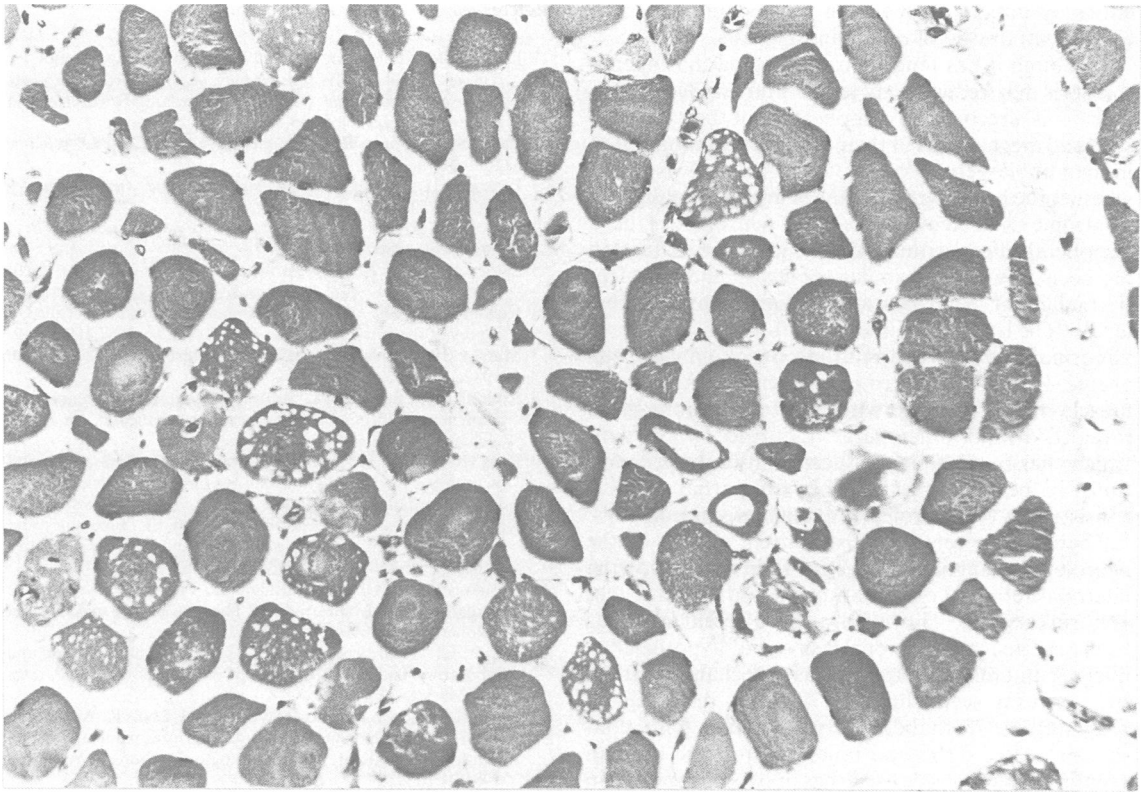

Fig *Section of psoas muscle showing myopathic features.*

bizarre posturing, brief loss of consciousness (on four occasions), and Parkinsonian rigidity (with trismus on one occasion); some were accompanied by a mild pyrexia of 37·5°C, hypertension, and urinary instability (both incontinence and retention). Repeated investigations including haematology, biochemistry, infection screen, chest radiography, ECG, and CT of the head were normal. EEG showed generalised excess fast activity on two occasions. Serum CPK had not been estimated.

Post-mortem examination

Post-mortem examination, performed 6 hours after death, showed scattered petechial subarachnoid haemorrhages over the brain, which was otherwise macroscopically normal, and further petechiae over the surfaces of the kidneys. Sections of muscle taken from psoas showed an increase in muscle fibre size, which was myopathic in appearance, and an acute disseminated segmental necrosis with regeneration. Occasional fibres showed distinct multiple vacuolation (fig). There was no fibrosis or increase in internal nucleation. Cerebral sections showed a number of tiny foci of acute ischaemic change in the lateral corpus callosum, internal capsule and globus pallidus, together with some recent extravasation of blood in the subarachnoid space. The hypothalamus showed a number of similar tiny parenchymal and perivascular haemorrhages, but no areas of necrosis. Further similar changes were present in the hindbrain. Microscopic examination of the kidney showed acute tubular necrosis.

Discussion

The clinical features and results of investigations in this patient's terminal illness are typical of the neuroleptic malignant syndrome.[2] Her age and sex are unusual, as the syndrome appears to have a predelection for young males.[2] The neuroleptic malignant syndrome can reoccur in the same patient, sometimes pursuing a milder chronic course before relapsing into an acute fulminant picture.[8 17–20] It therefore seems probable that this patient's earlier confusional states represented a prodromal phase of the actual syndrome.

There has been considerable interest in the pathophysiology of the neuroleptic malignant syndrome,[3 4 21–23] and in particular in the role of dopamine imbalance in the central nervous system. It has been postulated that the trigger is a sudden decrease of activity at central dopamine receptors, produced

either by dopamine depleting or blocking drugs, or abrupt withdrawal of dopamine agonists.

Although it has long been established that phenothiazines may reduce body temperature (indeed hypothermia is a recognised complication of their use), the sites and mechanisms of their thermoregulating action in man are largely unknown. Controversy exists over whether the hyperpyrexia in the neuroleptic malignant syndrome is a central effect of neuroleptics or a peripheral effect within skeletal muscle.[24] Attention has been drawn to the similarity between the neuroleptic malignant syndrome and malignant hyperpyrexia.[2 24–27] The latter is an inherited liability to develop an abnormal muscle reaction in response to anaesthetic agents. However, in vitro experiments on samples of muscle from patients with both conditions have revealed distinct differences.[24 28] Further, whilst dantrolene has been employed successfully in both conditions, its benefits appear to be only partial and less consistent in the neuroleptic malignant syndrome.[29]

There have been few post-mortem studies of the neuroleptic malignant syndrome. Four cases involving neuropathological examination showed no consistent abnormality.[25 30 31] However, a more recent case has been reported showing focal necrosis of hypothalamic nuclei,[32] and this was proposed as a mechanism for the hyperpyrexia seen clinically. Despite the frequent presentation of rhabdomyolysis in life, with consequent raised CPK and renal failure, post-mortem examination of muscle tissue has only been reported in one case.[33] An absence of muscle glycogen and neutral lipid were noted, and it was suggested that a primary biochemical abnormality, such as uncoupled muscle phosphorylation, might be responsible for the hyperpyrexia.

This is the first reported case of the neuroleptic malignant syndrome including both brain and muscle post-mortem histology. Examination of the brain failed to confirm the finding of hypothalamic necrosis reported in a previous case.[32] The abnormalities found in the brain of this case were acute, minimal, nonspecific, possibly agonal and of uncertain significance. The muscle pathology, however, was striking, and presented a picture of toxic myopathy. The observed changes in muscle were similar to those described in malignant hyperpyrexia,[34] where the myopathic changes are believed to be secondary to a primary biochemical defect in muscle membrane.[34]

The post-mortem findings reported here support the possibility that a common mechanism underlies both the neuroleptic malignant syndrome and malignant hyperpyrexia, and suggest that the primary defect is in muscle rather than brain.

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References

1 Delay J, Deniker P. Drug-induced extrapyramidal syndromes. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology. Diseases of the Basal Ganglia*. Amsterdam: North Holland Publishing Co., 1968;**6**:248–66.

2 Caroff SN. The neuroleptic malignant syndrome. *J Clin Psychiatry* 1980;**41**:79–83.

3 Levenson JL. Neuroleptic malignant syndrome. *Am J Psychiatry* 1985;**142**:1137–45.

4 Abbot RJ, Loizou LA. Neurolpetic malignant syndrome. *Br J Psychiatry* 1986;**148**:47–51.

5 Shalev A, Munitz H. The neuroleptic malignant syndrome: agent host interaction. *Acta Psychiatr Scand* 1986;**73**:337–47.

6 Kellam AMP. The neuroleptic malignant syndrome, so-called, a survey of the world literature. *Br J Psychiatry* 1987;**150**:752–9.

7 Murray JB. Neuroleptic malignant syndrome. *J Gen Psychol* 1987;**114**:39–46.

8 Addonizio G, Susman VL, Roth SD. Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. *Am J Psychiatry* 1986;**143**:1587–90.

9 Pope HG, Keck PE, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. *Am J Psychiatry* 1986;**143**:1227–33.

10 Keck PE, Harrison G, Pope HG, McElroy SL. Frequency and presentation of neuroleptic malignant syndrome: a prospective study. *Am J Psychiatry* 1987;**144**:1334–6.

11 Konikoff F, Kuritzky A. Jerushalmi Y, Theodor E. Neuroleptic malignant syndrome induced by a single injection of haloperidol. *Br Med J* 1984;**289**:1228–9.

12 Harsch HH. Neuroleptic malignant syndrome: physiological and laboratory findings in a series of nine cases. *J Clin Psychol* 1987;**48**:328–33.

13 Burke RE, Fahn S, Mayeux R, Weinberg H, Louis K, Willner JH. Neuroleptic malignant syndrome caused by dopamine depleting drugs in a patient with Huntington's chorea. *Neurology* 1981;**31**:1022–6.

14 Simpson DM, Davis GC. Case report of neuroleptic malignant syndrome associated with withdrawal of amantadine. *Am J Psychiatry* 1984;**141**:796–7.

15 Friedman JH, Feinberg SS, Feldman RG. A neuroleptic malignant-like syndrome due to levodopa therapy withdrawal. *JAMA* 1985;**254**:2792–5.

16 Blum A. Patients at risk of developing severe side-effects from depot fluphenazine treatment. *Am J Psychiatry* 1980;**137**:254–5.

17 Aizberg D, Shalev A, Munitz H. The aftercare of the patient with neuroleptic malignant syndrome. *Br J Psychiatry* 1985;**146**: 317–8.

18 Bhugra DK, Low NC. Neuroleptic malignant syndrome. *Br J Clin Practice* 1986;**40**:445–6.

19 Adityanjee. Recurrence, hyponatraemia, and neuroleptic malignant syndrome (letter). *J Neurol, Neurosurg Psychiatry* 1987;**50**:504–5.

20 McCarthy A, Bourke S, Fahy J, Binchy I, Fitzgerald MX. Fatal recurrence of neuroleptic malignant syndrome. *Br J Psychiatry* 1988;**152**:558–9.

21 Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenic role for dopamine receptor blockade. *Neurology* 1981;**31**:132–7.

22 Allsop P, Twigley AJ. The neuroleptic malignant syndrome: case report with a review of the literature. *Anaesthesia* 1987;**42**:49–53.

23 Harpe C, Stoudemire A. Aetiology and treatment of neuroleptic malignant syndrome. *Med Toxicol* 1987;**2**:166–76.

24 Caroff SN, Rosenberg H, Gerber JC. Neuroleptic malignant syndrome and malignant hyperthermia. *Lancet* 1983;**1**:234.

25 Itoh H, Ohtsuka N, Ogita K. Malignant neuroleptic syndrome—its present status in Japan and clinical problems. *Folia Psychiatrica Neurologica (Japan)* 1977;**31**:565–76.

26 Smego RA, Durack DT. The neuroleptic malignant syndrome.

Arch Intern Med 1982;**142**:1183–5.
27 Denborough MA, Collins SP, Hopkinson FC. Rhabdomyolysis and malignant hyperpyrexia. *Br Med J* 1984;**1**:1878.
28 Tollefson G. A case of neuroleptic malignant syndrome: in vitro muscle comparison with malignant hyperthemia. *J Clin Psychopharmacol* 1982;**2**:266–70.
29 Goulon M, Rohan-Charbot P, Elkharrat D, Gajdos P, Bismith G, Conso F. Beneficial effects of dantrolene in the treatment of neuroleptic malignant syndrome. A report of two cases. *Neurology* 1983;**33**:516–8.
30 Henry P, Barat M, Bourgeois M. Syndrome malinmortel succédant á une injection d'emblée d'oenanthate de fluphénazine. *Presse Med* 1971;**79**:1350.
31 Aubert C. Les hyperthermies dues aux neuroleptiques; essai d'interpretation physiopathologique. *Encephale* 1973;**62**: 126–59.
32 Horn E, Lach B, Lapierre Y, Hrdina P. Hypothalamic pathology in the neuroleptic malignant syndrome. *Am J Psychiatry* 1988; **145**:617–20.
33 Martin D, Swash M. Muscle pathology in the neuroleptic malignant syndrome. *J Neurol* 1987;**235**:120–1.
34 Harriman D. The pathology of malignant hyperpyrexia. In: Mastaglia F, Walton J, eds. *Skeletal Muscle Pathology*. U.K.: Churchill Livingstone, 1982.

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Notes