The neuroleptic malignant syndrome (NMS) is an uncommon but dangerous complication of treatment with neuroleptic drugs. First described by Delay and Deniker in 1968, the syndrome is characterized by hyperthermia, muscle rigidity, altered consciousness and autonomic disturbances during neuroleptic treatment. The pathogenesis of the syndrome is unknown. Central dopamine receptor blockade has been implicated both in the pathogenesis of neuroleptic malignant syndrome (Henderson and Wooten, 1981) and in its therapy (Mueller, Vester and Fermaglich, 1983). A primary defect in skeletal muscle has been suggested in view of similarities in the clinical presentations of neuroleptic malignant syndrome and anaesthetic-induced malignant hyperthermia (Andersson, 1972; Tollefson, 1982; Caroff, Rosenberg and Gerber, 1983; Downey, Rosenberg and Caroff, 1984). These similarities, including successful treatment with dantrolene (Delacour et al., 1981), suggest a common pathophysiology underlying both disorders.

In malignant hyperthermia, survivors of the crisis and susceptible family members can be identified by the increased sensitivity of muscle fibres to contracture induced by both caffeine and halothane (Britt et al., 1973; Ellis, Harriman and Currie, 1978). These in vitro contracture tests are, at present, the most reliable method of identifying individuals susceptible to malignant hyperthermia. The aim of this study was to define if a relationship exists between neuroleptic malignant syndrome and malignant hyperthermia susceptibility, by using the halothane and the caffeine contracture tests on survivors of the neuroleptic malignant syndrome.
NEUROLEPTIC MALIGNANT SYNDROME AND MALIGNANT HYPERTERMIA

Table I. Characteristics of the patients studied. CK = Creatine kinase concentration

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>(Psychotic illness/others)</th>
<th>Neuroleptic agent</th>
<th>Clinical features</th>
<th>CK (iu litre⁻¹)</th>
<th>Dantrolene sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>F</td>
<td>37</td>
<td>Schizophrenia</td>
<td>Levomepromazine</td>
<td>Hyperthermia (39 °C) Rigidity Fluctuating consciousness</td>
<td>12000</td>
<td>600 mg day⁻¹ by mouth</td>
</tr>
<tr>
<td>II</td>
<td>F</td>
<td>40</td>
<td>Psychosis</td>
<td>Levomepromazine</td>
<td>Hyperthermia</td>
<td>25000</td>
<td>1 mg kg⁻¹ day⁻¹ i.v.</td>
</tr>
<tr>
<td>III</td>
<td>M</td>
<td>54</td>
<td>Psychosis</td>
<td>Levomepromazine</td>
<td>Hyperthermia (39.9 °C)</td>
<td>18000</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
<td>M</td>
<td>73</td>
<td>Burn</td>
<td>Thiapride Haloperidol</td>
<td>Hyperthermia (38.5 °C)</td>
<td>10000</td>
<td>No</td>
</tr>
<tr>
<td>V</td>
<td>M</td>
<td>40</td>
<td>Alcoholism Delirium tremens</td>
<td>Trihexyphenidyle</td>
<td>Hyperthermia (39 °C) Rigidity Autonomic dysfunction Stupor Renal failure</td>
<td>56000</td>
<td>600 mg day⁻¹ by mouth</td>
</tr>
<tr>
<td>VI</td>
<td>F</td>
<td>58</td>
<td>Melancholia</td>
<td>Levomepromazine</td>
<td>Hyperthermia (39 °C)</td>
<td>11500</td>
<td>200 mg day⁻¹ by mouth</td>
</tr>
</tbody>
</table>

![Fig. 1. Diagnostic criteria. MHS implies a threshold (an increase in tension > 0.2 g) at 2% or less halothane and at 2 mmol litre⁻¹ or less caffeine. MHN implies no threshold at 2% or less halothane and 2 mmol litre⁻¹ or less caffeine. MHE implies a threshold to either halothane or caffeine at the above mentioned concentrations.](https://academic.oup.com/bja/article-abstract/59/12/1554/249140/fig1)

DISCUSSION

In malignant hyperthermia, a genetic defect in the sarcoplasmic reticulum accounts for a loss of control of intracellular ionized calcium in the sarcoplasmic reticulum.
presence of triggering agents, resulting in an increase in intracellular calcium concentration, muscle contracture, metabolic stimulation and changes in permeability. This is reflected in the lower concentrations of caffeine and halothane required to produce contractures in vitro in muscle biopsy specimens from susceptible patients. This provides the basis of a screening test which we have been using in our laboratory. The fact that none of the patients in our study was MHS suggests that there is no pharmacological abnormality in neuroleptic malignant syndrome similar to that found in malignant hyperthermia.

Few results of investigations using halothane and caffeine contracture tests in survivors of the neuroleptic malignant syndrome are to be found in the literature. Caroff, Rosenberg and Gerber (1983) and Downey, Rosenberg and Caroff (1984) studied contractility of muscles in a patient with neuroleptic malignant syndrome and found a contracture of 5.1 g tension on exposure to 1.2 % halothane—a response diagnostic, for those authors, of susceptibility to malignant hyperthermia. Denborough, Collins and Hopkinson (1985) reported the results of an in vitro test in a patient with neuroleptic malignant syndrome. The 1 %-halothane contracture was 0.45 g and the caffeine 2-mmol litre⁻¹ contracture 0.4 g. The patient’s brother also had positive contracture responses. Tollefson (1982) studied contractility of muscles in a patient with neuroleptic malignant syndrome. The tests were negative for both halothane and caffeine, and Tollefson concluded that there was no common peripheral pathophysiological link between neuroleptic malignant syndrome and malignant hyperthermia. It is possible that some of the variations in the results in different centres could be attributed to variations in laboratory procedures.

In the present study, the absence of pharmacological abnormalities in the muscle of patients susceptible to neuroleptic malignant syndrome, and the laboratory differences between neuroleptic malignant syndrome and malignant hyperthermia, suggest that factors other than a muscle defect may be more important for most patients with neuroleptic malignant syndrome.

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REFERENCES