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Neuroleptic Malignant Syndrome

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The neuroleptic malignant syndrome (NMS) occurs as a hypersensitivity response in certain patients exposed to neuroleptics. It is a relatively rare, but potentially lethal complication, the incidence of which may have been underestimated. Recent interest in NMS has arisen due to the recognition that specific therapy may now be available. This review summarises the clinical features and discusses recent ideas regarding aetiology and treatment.

Neuroleptics were first used in the treatment of psychiatric disorders in the 1950s and their side-effects are generally well recognised (Marsden & Jenner, 1980). Preston (1959) first described the clinical features of an uncommon hypersensitivity reaction to neuroleptics, which subsequently became known as the neuroleptic malignant syndrome (NMS). This term was first introduced into the English literature by Delay & Deniker (1968), although a similar syndrome, the syndrome "Neurovegatif malin" was at that time well recognised in France (Delay *et al*, 1969). Sporadic reports have since occurred from other countries (Itoh *et al*, 1977; Singh, 1981) and considerable interest in this disorder arose in America following a major review by Caroff in 1980. Reference to NMS in the UK literature is sparse, although two recent editorials (Lancet, 1984; Szabadi, 1984) indicate an increasing awareness of its importance. Allan & White (1972) described hypothalamic side-effects of phenothiazines in 1972, but the first case report which recognised NMS did not appear until 1983 (Cope & Gregg, 1983). Clough (1983) subsequently described a further case, and suggested that the disorder was more common than has generally been accepted. Until recently, no specific treatment was available for NMS, which carries a mortality of about 20%.

Incidence

The incidence of NMS is unknown, since no major series has been described, but in a review of 60 cases in the world literature, Caroff (1980) quoted an age-range of 3 to 61, with 80% under the age of 40, and a male to female ratio of 2:1. He regarded this condition as a "neglected clinical problem of major proportions", which "may be unrecognised and underdiagnosed." Delay & Deniker (1968) estimated the incidence to be 0.5 to 1% in patients taking neuroleptics. On the other hand, Baastrup *et al* (1976) described 425 patients taking a combination of haloperidol and lithium, none of whom developed NMS. Singh (1981) treated 1,500 patients over a six-year period with neuroleptics, and observed three cases—an incidence of 0.2%, while Itoh *et al* (1977) collected the largest series yet reported, 14 cases in five years. Of these patients, the majority developed symptoms shortly after the initiation or alteration of neuroleptic therapy.

Aetiology

NMS appears to be an idiosyncratic reaction to a therapeutic dose of the neuroleptic, and it has been suggested that its appearance relates to a critical level of the drug in a predisposed patient (Caroff, 1980). The symptoms may develop at a variable interval, from a few days to a number of weeks, following introduction of therapy, and clinical features usually progress over a period of 24–72 hours after onset. They tend to subside 5–10 days later, when related to oral preparations, and 10–21 days after long-acting phenothiazines (Smego & Durack, 1982). Allan & White (1972) reported that the reduction in clinical signs coincided with a fall in the urinary concentration of fluphenazine breakdown products. Re-exposure of the patient to the same neuroleptic, following recovery, may or may not result in recurrence of symptoms, suggesting that variables other than the neuroleptic drug alone may be involved (Smego & Durack, 1982).

NMS has been reported following the use of a large number of different neuroleptics, used alone or in combination with other agents such as lithium and tricyclic antidepressants (Smego & Durack, 1982). It has also been described after dopamine-depleting drugs, such as tetrabenazine and alpha-methyltyrosine (Burke *et al*, 1981). It is not specific to patients treated for psychiatric disorders since it has also occurred in Huntington's disease (Burke *et al*, 1981), pre-induction anaesthesia (Haberman, 1978), hypnotic withdrawal (Greenblatt *et al*, 1978) and in a non-psychotic child (Shields & Bray, 1976). NMS may also occur following withdrawal of drugs such as levodopa and amantadine, whose effects

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enhance central dopaminergic neurotransmission (Toru *et al*, 1977; Simpson & Davis, 1984).

Caroff (1980) suggested that organic brain disease might be a predisposing factor, since 11 out of 60 patients with NMS had either brain damage or a history of alcohol or drug abuse prior to neuroleptic exposure. The potential of a phenothiazine for producing the syndrome appears to parallel the antidopaminergic potency of the drug administered (Itoh *et al*, 1977).

Clinical features

The cardinal clinical features of NMS are the development of hyperthermia, muscle rigidity, and autonomic instability in a patient exposed to neuroleptics; this can best be described by reference to a patient seen recently. A 26-year-old female presented with a four-day history of acute psychiatric disturbance, which developed on a background of normal personality, except for a short period of panic attacks three years previously. In the four days prior to her admission, she had initially become withdrawn, then restless and agitated, did not sleep, developed visual and auditory hallucinations, and became suspicious of her relatives. On admission to the psychiatric unit, she was noted to be disorientated in space and time, had no insight into her condition, and was uncooperative, with incoherent speech. There were no focal neurological signs and general examination was normal. There was no evidence of systemic disorder or alcoholic abuse to indicate a possible organic toxic confusional state, and the initial diagnosis was of a functional psychosis related to acute emotional stress. She was treated with lorazepam, 2.5 mgs, tds; temazepam, 20 mgs, nocte, and chlorpromazine, 100 mgs intramuscularly for three days. Following the third dose of chlorpromazine, she developed a temperature of 38°C and became drowsy. Tone in the limbs was normal at this stage. Investigations showed an ESR of 33 mm in the first hour, normal CT brain scan and CSF examination, but an abnormal EEG, with a diffuse mixture of fast and slow rhythms. The chlorpromazine was discontinued. Over the succeeding four days, the pyrexia increased to 39.5°C and she developed sweating, tachycardia (120 per minute), and tachypnoea. She became more unresponsive, requiring nasogastric-feeding and bladder catheterisation. Choreiform movements of the limbs and face became prominent, but there were no long-tract neurological signs. Catatonia due to a psychosis was considered and she was given two ECTs; following the second treatment, she was able to understand commands and to walk with help. Chlorpromazine, 100 mgs orally was then administered daily for three days and trifluoperazine, 10 mgs orally, daily for a further five days. She again deteriorated, becoming pyrexial, almost totally unrousable, and mute, with gross generalised rigidity, bilateral divergent squint, sluggish reflexes, and continuous choreiform movements of the limbs. A repeat CT scan and CSF examination were again normal, but the EEG remained diffusely abnormal. There was a neutrophil leucocytosis and elevation of hepatic transaminases. She was treated with procyclidine and cooling, and neuroleptics were stopped. Over the following four days, she showed profound bradykinesia and rigidity, involuntary choreiform movements, and subsequently catatonic posturing. However, her conscious level and responsiveness improved and the pyrexia resolved. She was then prompted to get up and walk, and within a week was fully recovered, except for having no recollection of the events of the six weeks of her illness. She remains well, 14 months later, on no medication.

This patient displayed the typical features of extrapyramidal rigidity of a plastic type, which occurs in NMS associated with bradykinesia and jerky involuntary movements, which are a frequent accompaniment in this condition. Catatonic features became prominent as the disorder developed, along with mutism and posturing, and the conscious level rapidly became depressed, though Smego & Durack (1982) have suggested that alertness and cooperation are often retained in the early stages of NMS. This patient at no stage developed the pulmonary congestion which was originally described as a cardinal feature of NMS (Delay & Deniker, 1968), but it now seems likely that this is a secondary complication.

The diagnosis of NMS is made on clinical grounds, since laboratory investigations show secondary or non-specific changes only. Thus, a neutrophil leucocytosis occurs without evidence of infection, and liver transaminases may be elevated. A rise in creatine phosphokinase (CPK) and serum potassium are indices of skeletal muscle necrosis. The EEG may show non-specific slow wave abnormalities, but CT brain scans and CSF examination are invariably negative. Postmortem studies (Morris *et al*, 1980; Cope & Gregg, 1983) have shown normal brain morphology and no site of systemic infection.

Differential diagnosis

Smego & Durack (1982) suggest that NMS should be included in the differential diagnosis of any febrile patient with a history of neuroleptic ingestion.

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Clearly, infections involving the central nervous system, such as encephalitis, meningitis, or tetanus, must be excluded, as must extrapyramidal disorders, such as severe Parkinson's disease and the rigid form of Huntington's chorea. Akinetic mutism, the 'locked in' syndrome, and other disorders involving higher centres or the brainstem should be excluded by a careful neurological examination. Other conditions which give rise to catatonia (Gelenberg, 1967) should also be considered.

More difficult to exclude are the less common disorders which produce hyperpyrexia with varying degrees of hypertonia. Heat stroke occurs in the presence of high ambient temperatures, and a number of fatalities have occurred in patients taking phenothiazines in such conditions (Ayd, 1956; Zelman & Guillan, 1970). Muscle rigidity is not usually a prominent feature of this condition, however.

Stauder's lethal catatonia (Stauder, 1934; Billing & Freeman, 1943) was described many years before neuroleptics were introduced, and is clinically indistinguishable from NMS, though the pathophysiological relationship between these two conditions is unclear. It is usually preceded by a prodromal phase lasting 1–2 weeks, following which the patient displays features of anxiety and restlessness; sudden clinical deterioration then occurs, the conscious level decreases, body temperature rises dramatically, and vasomotor collapse ensues. Postmortem studies have revealed small discrete haemorrhages in the hypothalamus and pituitary (Billing & Freeman, 1943).

Malignant hyperpyrexia is a hypersensitivity reaction which occurs in genetically predisposed individuals who are exposed to certain anaesthetics (Gronert, 1980). The underlying abnormality lies within skeletal muscle, and the condition is characterised by the development of intense muscle spasm and hyperpyrexia, within minutes of anaesthetic induction. There is often a positive family history, and it carries a 70% mortality. Although an association between malignant hyperpyrexia and NMS has not been definitively established, Caroff *et al* (1983) demonstrated that striated muscle from a patient who had recovered from NMS showed a response diagnostic of the susceptibility to malignant hyperpyrexia, when exposed to halothane *in vitro*.

Conversely, Denborough *et al* (1984) described the occurrence of NMS following treatment with fluphenazine in a patient with the muscle disorder which predisposes to malignant hyperpyrexia. In a clinical context, however, diagnostic confusion between these two disorders should not occur, since the pattern of clinical presentation of each is distinct.

Pathophysiology

It is widely recognised that phenothiazines may reduce body temperature and that hypothermia may be a complication of their use (Exton Smith, 1972). They have been used to treat life-threatening hyperpyrexia due to heat stroke (Hoagland & Bishop, 1961), yet the sites and mechanisms of their thermoregulating action in man are largely unknown. Animal experiments have demonstrated considerable variation in thermo-regulatory response to neuroleptics, depending upon the species studied and the site of drug administration. Thus, both rats (Hofmann & Zarrow, 1958) and monkeys (Chai *et al*, 1976) show a precipitous fall in body temperature when chlorpromazine is injected subcutaneously, whereas, when injected directly into the rostral hypothalamus or third ventricle of the rat, it produces prolonged *hyperthermia* (Rewerski & Jori, 1968). Further animal studies have demonstrated variation in thermo-regulatory response to phenothiazines, depending upon the age, sex, and social conditions of the animals (Barbelby & Loepfe Hinkaanen, 1979).

In man, it has been suggested that certain combinations of factors become operative in rendering an individual susceptible to NMS at any given time (Caroff, 1980); e.g. Itoh *et al* (1977) found that exhaustion and dehydration were commonly present at the initiation of phenothiazine therapy. Debate has arisen as to whether the muscle rigidity and hyperpyrexia originate from an effect of the central action of drugs, or are due to a peripheral effect within skeletal muscle. In malignant hyperpyrexia, where the primary disorder lies within the muscle tissue, the extreme spasm of the muscles is sufficient to generate a dramatic rise in body temperature, and a similar mechanism has been considered for NMS. The evidence for this belief was provided by *in vitro* studies on muscle biopsy specimens (Caroff *et al*, 1983; Denborough *et al*, 1984). Further evidence comes from the effect of dantrolene, a drug acting peripherally on skeletal muscle, which produced a rapid relaxation in muscle tone in a patient with NMS and a coincidental fall in body temperature from 42°C to normal (Goulon *et al*, 1983). Granato *et al* (1983) found that dantrolene normalised body temperature within 12 hours of administration and that the elevated CPK fell within 48 hours, but their patient remained rigid, tremulous, and stuporose until bromocriptine, a central acting dopamine receptor agonist, was given five days later.

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Morris *et al* (1980), in contrast, favoured a central mechanism for both the pyrexia and rigidity since curare—a neuromuscular blocker—produced complete flaccidity in a case of NMS, an effect not seen in malignant hyperpyrexia. The pyrexia improved slightly following muscle relaxation, but did not normalise for a further 19 days. In the patient described above, pyrexia was an early feature, in association with stupor and autonomic signs. Muscle rigidity only developed at a later stage, suggesting that at least in the early stages of this condition, the hyperpyrexia has a central origin, and probably arises from an effect upon the hypothalamic thermo-regulatory centres.

Treatment

Until recently, the management of established NMS has relied upon supportive therapy for the cardio-respiratory complications. It is clearly imperative that neuroleptics are stopped immediately the condition is suspected; strenuous attempts must be made to reduce the body temperature, respiratory support may be required via artificial ventilation, and secondary infections will require antibiotics. Renal dialysis has been described in a patient who developed acute renal failure secondary to widespread rhabdomyolysis (Samii *et al*, 1976), but is not effective in removing circulating neuroleptics, which are protein and lipid-bound (Caroff, 1980). More specific measures aimed at reducing muscle tone have included anticholinergics, but these drugs are generally regarded as ineffective (Itoh *et al*, 1977). ECT also was ineffective in two patients, one of whom had a cardiac arrest during the procedure (Regestein *et al*, 1977).

There are recent reports of two separate lines of treatment, which may be complementary. Since blockade of hypothalamic dopamine receptors by neuroleptics is the probable initiating mechanism, the effects of drugs which facilitate central dopaminergic mechanisms have been studied. Limited success was achieved with amantadine (McCarron *et al*, 1982; Gelenberg & Mandel, 1977) but more recently bromocriptine, in a daily dose of 60 mg, was shown effectively to reduce muscle tone and to improve conscious level (Granato *et al*, 1983; Mueller *et al*, 1983). The complementary use of dantrolene (10 mg/kg) to reduce muscle tone by a peripheral effect has been demonstrated on a number of occasions (Delacour *et al*, 1981; Boles *et al*, 1982; Coons *et al*, 1982; Goekopp & Carbaat, 1982; Goulon *et al*, 1983; Granato *et al*, 1983; May *et al*, 1983) and at present, the best drug treatment for NMS appears to be a combination of bromocriptine and dantrolene.

Conclusions

Much remains to be learned about the conditions which lead to the development of NMS, which, although a relatively rare complication of neuroleptic therapy, has perhaps been underestimated in incidence. There is a need for caution when using potent neuroleptics, and the combination of a greater awareness of this condition with the development of more specific forms of treatment may lead to future improvements in the prognosis. Delay & Deniker (1968) in their original description of this condition provide the most practical advice for the clinician: "should a fever commence and be recorded on two successive occasions one must stop medication immediately and completely, especially when there is no obvious infectious cause for the fever."

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