Neuroleptic malignant syndrome

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Although a rare form of 'lethal' catatonia, involving high temperature and rigidity, was first described long before the advent of neuroleptic drugs, Delay's description of a *syndrome malin* in 1960 is usually regarded as the first recognition of this syndrome. Over the next 20 years the number of case reports grew and the appearance of reviews such as Caroff's in 1980 marked the birth of the neuroleptic malignant syndrome (NMS). Reports of its incidence give variation rates of up to fiftyfold, possibly due to differences in diagnostic criteria, and mortality reports are similarly variable. Although it is debatable whether it is a rare, severe idiosyncrasy or one of many neuromuscular side-effects of dopamine antagonists (Levinson & Simpson, 1986), most clinicians nowadays regard it as a serious but recognisable risk of neuroleptic treatment which merits further attention.

Epidemiology

Incidence and mortality

The reported incidence of NMS has varied widely, between 0.07% and 3%. Some of the highest incidences have resulted from retrospective surveys in which the precision of diagnosis is suspect. Large scale prospective studies on neuroleptic treated in-patients using clearly defined criteria suggest that the true incidence is at the lower end of this range. Thus Keck *et al* (1991) suggest an incidence of four out of 2695 patients (0.15%), Modestin *et al* (1992) found no cases in 335 patients, Deng *et al* (1990) 12 out of 9792 (0.12%) and Gelenberg *et al* (1991) one out of 1450 (0.07%).

However, some prospective studies show higher rates, e.g. that of Hermesh *et al* (1992) who found five cases in 223 and Naganuma & Fuji (1994) who found 10 cases in 564 patients. In both cases the diagnostic criteria seem rigorous (although the second study weights creatine phosphokinase (CPK) elevation to an extent greater than recommended in DSM–IV; APA, 1994) and it is difficult to reconcile these findings with those quoted above except by observing that their smaller size makes them statistically more suspect. We would support Caroff & Mann (1993) who give a pooled incidence rate of about 0.2% while acknowledging that local variations in both neuroleptic usage and awareness of the syndrome may contribute to some variation in the incidence.

As well as a decrease in the incidence there has been a decrease in the reported mortality. In the earliest studies it was quoted as up to 30%, in studies quoted after 1984 it was 11% and in most recent studies it has the status of a rare event. This is probably due to the earlier recognition of the syndrome and prompt recourse to corrective measures.

Risk factors

Psychiatric diagnosis

NMS occurs in neuroleptic treated patients from all psychiatric diagnostic groups. More than one study of NMS sufferers has found a preponderance of patients with a diagnosis of bipolar disorder, but many studies fail to confirm this. It is possible that mania may promote agitation (see below), a more reputable risk factor. Rosebush & Stewart (1989) reported 24 cases of NMS of which 43% had CT brain scan abnormalities, a much higher than expected proportion in psychiatric disorder.

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The link with established central nervous system compromise is strengthened by reports of NMS in Parkinson's disease after withdrawal of dopamine agonists, and in Huntington's disease after starting tetrabenazine. There have also been case reports of NMS in sufferers from severe mental subnormality or quadriplegia when treated with neuroleptics, although prospective studies on these groups have not been carried out.

Drug treatment

NMS has been described in association with all neuroleptics in current usage. This includes the selective D2 blockers, like sulpiride and remoxipride, as well as risperidone with its mild extrapyramidal side-effects. It is also reported in drugs such as perphenazine and metoclopramide when used as antiemetics. Lithium has also been reported to cause NMS both alone and in combination with neuroleptics, as have tricyclics (trimipramine and amoxapine) and SSRIs (fluoxetine). But reports of NMS in the latter two groups are rare and in the case of the SSRI may have been the serotonin syndrome (see below). Haloperidol and fluphenazine decanoate have been cited in some of the larger studies as being especially associated with the onset of the disorder, but this may reflect their widespread usage.

Clozapine has been suggested by some authors to be free from the potential to cause NMS and even advocated as the treatment of choice for those who have suffered the syndrome. However, there are reports of an NMS-like syndrome in association with clozapine (Thornberg & Ereshefsky, 1993), although several of the cases described were 'atypical' and clozapine has been described as producing a benign hyperthermia in the absence of other symptoms.

Most authors conclude that the first two weeks after starting or changing a neuroleptic drug regime are the most risky, but NMS has been reported to occur several months after starting drugs. There has been one case report of the development of severe NMS after cessation of long-term depot medication (Cape, 1994) and we know of a case where presentation occurred several days after the last dose of oral medication. It is worth drawing attention to the fact that risks from neuroleptic drugs may exist over a longer timespan than their half-lives in the peripheral circulation.

Circumstantial factors

These seem to be the most consistently associated with the genesis of NMS, both in epidemiological and case-control studies (Box 1). In particular, dehydration, agitation or overactivity in the patient

and the use of intramuscular preparations are found to predispose to NMS (Keck *et al*, 1989). Higher doses are also implicated. Keck *et al* (1989) found that the average dose of neuroleptic in cases was nearly twice that of controls (671 mg of chlorpromazine versus 388mg) but the association is not simple. Many of these factors, such as overactivity and dehydration or agitation and intramuscular injection, may be covariables. There is no evidence that hot weather or high ambient temperature are predisposing factors.

Demographic factors

NMS occurs more frequently in men than women and in the young than the old. However, it is possible that these findings represent patterns of neuroleptic usage such as the more frequent use of high dose or intramuscular preparations in young males. There is no evidence of ethnic or demographic predisposition.

Heredity

Unlike malignant hyperthermia (MH), NMS carries little or no familial risk and case reports showing more than one family member affected are rare. NMS sufferers show negative results on the halothane-caffeine test which is used to diagnose susceptibility to MH in probands' relatives.

Biochemical variables

While dehydration is a likely risk factor, it is difficult to ascertain whether any of the other metabolic disturbances associated with actual NMS are cause or effect. However, one abnormality that has attracted increasing attention is the finding of low serum iron in sufferers from NMS (Rosebush & Mazurek, 1991). It has been suggested that low serum iron may reduce the number of functional dopamine receptors, while also leading to the restlessness that is described as a risk factor. However evidence for the presence and relevance of low serum iron in NMS is inconclusive.

Box 1. Risk factors for NMS

History: previous NMS, known cerebral compromise
Mental state: agitation, overactivity, catatonia
Physical state: dehydration
Treatment: IM therapy, 'rapid neuroleptisation', high doses, high potency neuroleptics

Previous NMS

Recrudescence of NMS has been commonly described after early rechallenge with neuroleptics and one series suggests that as many as 17% of NMS sufferers have had previous episodes (Caroff & Mann, 1993).

Diagnosis

Symptoms

For practical purposes there are four symptom types; fever, rigidity, autonomic disturbance and alteration in consciousness.

According to Velamoor *et al* (1994), the earliest symptom is usually alteration in consciousness. This is likely to be missed, especially if persistent drowsiness is ascribed to the sedative effect of neuroleptics. Autonomic instability may produce variations in blood pressure, tachycardia, diaphoresis, salivation or incontinence. Some of these symptoms may be also be ascribed to direct drug side-effects unless especial vigilance is maintained. Hypertension should raise suspicion, as should urinary incontinence (the latter may easily be ascribed to 'behavioural' problems in a disturbed individual).

Rigidity may take the form of cogwheel or lead pipe rigidity. It tends to be impervious to treatment with anticholinergics. In most cases it involves the limbs but has been occasionally described as localised to head and neck. Other specific movement disorders such as opisthotonus, myoclonus, dysphagia or dysarthria sometimes occur. Fever is present in 98% of cases and in the majority rises above 38°C. In a small minority, hyperpyrexia (temperature > 41°C) occurs. This is associated with a high rate of mortality, as are the complications of severe rigidity, such as myoglobinuria and renal failure.

Laboratory investigations

There are no changes that are pathognomonic of NMS. Creatine kinase (CK) is frequently elevated and often exceeds 1000 units/litre. The upper limit of most reference ranges is 200 units/litre. CK is widely distributed in body tissue and has three isoenzymes. Most laboratories will measure the whole enzyme and also the MB isoenzyme (as part of their cardiac enzyme assay). In NMS, the pooled enzyme level is generally highly elevated with only a small amount of elevation in the myocardial (CK–MB) isoenzyme. However CK is sensitive to disruption by many factors including intramuscular injections, muscular injuries and exertion. It is also liable to be raised in those treated with neuroleptics who become febrile for other reasons (O'Dwyer & Sheppard, 1993). Hence it is not a very reliable diagnostic test. Serial estimations in documented cases indicate that rises and falls tend to correspond to fluctuations in the clinical state, so it may be considered a reasonably good marker for clinical progression of the syndrome.

A leucocytosis is found in the majority of cases and less commonly, mild elevation of enzymes such as lactic dehydrogenase, alkaline phosphatase and transaminases. Other biochemical findings may be hypo or hypernatraemia or metabolic acidosis. In severe cases there may be uraemia. Reports of darkening of urine should raise suspicion of myoglobinuria.

CT scanning reveals no abnormality or non-specific findings, nor does lumbar puncture. MRI findings in one case were said to resemble those of hypertensive encephalopathy.

Post-mortem findings

As fatal cases generally involve hyperpyrexia, coagulopathies, renal failure or other serious systemic complications it is difficult to tease out the effects of these from the effects of NMS *per se*. Cerebellar degeneration and anterior hypothalamic infarction have been reported, as have 'non-specific changes'.

Differential diagnosis

Although many drugs and toxins may cause hyperthermia and NMS-like symptoms may occur as part of generalised cerebral disorder, the important differentials for a psychiatrist to consider are as follows:

Heat exhaustion: Sufferers from heat exhaustion have been exposed to high ambient temperature and may have hyperpyrexia and agitation. Muscle rigidity is unlikely as are the autonomic disturbances of NMS, especially diaphoresis.

Atropinism: Anticholinergics are commonly used in psychoses and in high doses may cause pyrexia and confusion. They are unlikely to be associated with diaphoresis or autonomic instability. Improvement with physostigmine should distinguish atropinism from NMS.

Serotonin syndrome: This can resemble NMS (Ames & Wirshing, 1993) with fever and

fluctuating blood pressure being prominent symptoms together with diaphoresis, changes in mental state and tremor. Serotonin syndrome typically occurs with the use of drugs increasing the availability of serotonin, such as combinations of MAOIs and tricyclics, SSRIs and tryptophan etc. In cases where SSRIs and dopamine blocking agents are used together it should be considered. In the initial stages, management would consist of supportive measures and withdrawal of medication similar to the course of action in NMS.

Extrapyramidal symptoms with intercurrent fever: This is probably the most important differential, both because it is the commonest and because stoppage of neuroleptics is not indicated. One study suggests that up to a third of cases provisionally diagnosed as NMS may have intercurrent infections causing the fever (Sewell & Jeste, 1992). It has been shown that consumption of neuroleptics in the presence of a febrile illness can lead to rises in serum CK. Chest or urinary tract infections are the most common sources.

Catatonia: There is some overlap of the symptoms of NMS with catatonia and some authors consider them to be variants of the same syndrome (White, 1992). Circumstantial evidence to support the relationship between NMS and catatonia comes from the usefulness of ECT in both catatonia and NMS. While the resemblance is very strong for the 'lethal' variant of catatonia, where pyrexia and rigidity are the rule, there is no evidence to suggest that every case of acute catatonia becomes 'lethal', nor that every case of NMS is associated with catatonic symptoms. It is probably reasonable to assume that full blown NMS and 'lethal' catatonia are an identical final common pathway and that catatonia is a significant risk factor (White & Robins, 1991; Raja *et al*, 1994) for the development of this final common pathway. For this reason caution in the use of neuroleptics in the treatment of catatonia is urged.

Partial NMS (Forme Fruste NMS, EPS with fever etc): Several authors describe cases of neurotoxicity following neuroleptic treatment which fall short of the criteria of NMS as indicated in DSM–IV. As already mentioned, diagnostic criteria of NMS have varied widely (Guerrera *et al*, 1992) and inclusion of milder syndromes may have accounted for some of the larger estimates of its incidence. There is some debate about the wisdom of including such cases under the rubric of NMS (Adityanjee, 1991), but whatever the conceptual argument, the clinician needs to be aware that such phenomena occur and are probably more common than full-blown NMS.

Other disorders: Rare disorders that may mimic NMS include thyrotoxic crises, phaeochromocytoma and cerebral disorders such as encephalitides, lupus or tumours. Collateral evidence for these disorders is usually available.

Clinical course

NMS usually appears within a week of starting or changing the dose of neuroleptic drugs. If drugs are withdrawn and supportive measures instituted symptoms persist for an average of one week, although there is wide variation either side of this figure. The mortality rate as indicated, has decreased since the syndrome was first identified. Persistent morbidity is rare although there have been case reports of persisting neurological sequelae and even dementia following severe cases.

Management

General measures

It is generally agreed that on diagnosis or strong suspicion of NMS neuroleptics should be stopped immediately. It is probably also advisable to stop lithium given its association with NMS and other forms of neurotoxicity. The role of antidepressants in the causation of NMS is more doubtful but since tricyclics affect the autonomic nervous system and some SSRIs are thought to have dopamine blocking potential (and may cause a similar syndrome to NMS) their use may be considered hazardous. Benzodiazepines may be used for sedation and ECT is considered safe for the treatment of severe psychosis. Carbamazepine is also reportedly safe.

Supportive measures are of great importance especially rehydration and cooling. Advice from physicians should be sought early as there are reports of established cases deteriorating rapidly, even over hours. In most cases transfer to a medical ward is desirable (see Box 2).

Specific measures – bromocriptine and dantrolene

Because NMS is a rare and sporadic condition treatment tends to be empirical. Two measures that have achieved some degree of popularity are the use of the dopamine agonist bromocryptine, given in divided doses orally or parenterally in amounts up to 60mg per day, and the muscle relaxant

dantrolene. Although the aetiology of NMS is unknown, both measures have intuitive backing. One study (Rosenberg & Green, 1989), retrospectively compared cases where these agents have been used with cases where supportive measures alone were used and suggested that the time to symptom resolution is hastened. This view is debatable and Rosebush & Stewart (1989), using a similar method, have suggested that the use of these agents is actually associated with greater morbidity. One caveat to this view is that the more serious cases are less likely to be treated with supportive measures alone, leading to selection bias.

Until this debate is resolved, a sensible approach would be to use the agents selectively; thus dantrolene would be indicated where rigidity was severe and bromocryptine where other symptoms such as hyperthermia and autonomic instability are more salient. However, this is the physician's concern and we would not encourage psychiatrists to manage the established syndrome themselves.

Neuroleptic rechallenge

An important question facing the clinician when treating a psychotic patient who has had NMS is when and how to reintroduce neuroleptics. It is suggested (Rosebush *et al*, 1989) that the risk of recrudescence is appreciably lower if a gap of about 2 weeks is left between recovery from NMS and the reintroduction of neuroleptics. One study suggests that large doses and intramuscular and depot preparations be avoided. It is also considered wise to avoid high potency drugs with extrapyramidal side-effects such as the butyrophenones and thioxanthines.

Box 2. Management of NMS

Measure WCC, E&U, liver functions and CK
Correct dehydration and pyrexia
Withdraw neuroleptics, lithium and antidepressants
ECT and benzodiazepines not contraindicated
Specific remedies (bromocryptine, dantrolene) are probably useful
Refer to medical team

Management of milder forms of neuroleptic toxicity

Unfortunately little is known about the natural history of these milder reactions. Addonizio *et al* (1986) describes them as 'abating without cessation of neuroleptic treatment' but their outcome is difficult to predict in advance. Some clinicians have suggested an algorithm for the management of neuroleptic toxicity (Gratz *et al*, 1992), whereby different symptoms are treated in different ways and stopping medication is not advised until a certain threshold of severity is crossed. Although the consequences of stopping neuroleptics in a psychotic patient may be far-reaching, we would recommend that clinicians are cautious about neuroleptic usage in equivocal cases until NMS can be definitely ruled out.

Aetiology

Despite its superficial resemblance to malignant hyperthermia, it is likely that NMS is a central disturbance of dopamine metabolism. The evidence for this is manifold. Firstly, all the drugs involved with NMS have dopamine blockade in common, especially D2 blockade. This includes drugs such as tetrabenazine, which is not strictly a neuroleptic. The incidence of NMS with cessation of dopamine agonists in Parkinsonism also points to dopaminergic transmission. Further evidence comes from studies of dopamine metabolites in NMS sufferers. In several cases, the dopamine metabolite HVA has been found to be reduced in the CSF suggesting central depletion of dopamine.

Osman & Khurasani (1994) have recently proposed a 'dopamine shut-down' hypothesis for NMS suggesting that neuroleptic blockade in sufferers leads to massive central depletion of dopamine with adverse effects on temperature regulation in the hypothalamus. Drawing attention to the similarity between NMS and catatonia, he suggests that lethal catatonia is a spontaneous depletion of central dopamine often preceded by a period of intense dopaminergic overactivity and perhaps caused by a phase of presynaptic inhibition. NMS is seen as an iatrogenic version of this.

However obvious the connection with dopaminergic transmission, the rarity of NMS suggests that other factors may be involved. The relationship of dopamine to other neurotransmitter activity has come under scrutiny with suggestions

that serotonin, acetylcholine or NMDA- type glutamate receptors may be crucially involved in destabilising dopaminergic activity. Some studies have found noradrenaline metabolites to be increased in the body fluids of those suffering NMS and a link has been made between dopamine blockade and noradrenergic overactivity. It has been suggested that several of the symptoms of NMS could represent noradrenergic overactivity (hypertension, tachycardia, leucocytosis). Alternatively these phenomena and that of noradrenergic overactivity could be an effect of the profound physiological disruption caused by impaired thermoregulation rather than a cause.

Conclusions

Neuroleptic malignant syndrome is a severe and acute dysregulation of vegetative processes such as thermoregulation and control of the autonomic nervous system associated with blockade of dopaminergic synapses either by the use of antagonists or the sudden withdrawal of agonists. The aetiology is unclear but NMS is associated with high and/or frequently administered doses of neuroleptics. It is probably historically related to so-called 'lethal' catatonia and there are suggestions that catatonia is a risk factor or prodromal stage of the condition. Its sporadic nature makes it hard to draw definitive conclusions about treatment but there are suggestions that bromocriptine and dantrolene might be useful in hastening resolution.

It is important to draw attention to NMS because although mortality rates have declined it is a potentially lethal illness and may cause rapid multisystem failure. Its early stages may be missed on psychiatric wards because of lack of attention to physical observations such as temperature and the misattribution of equivocal signs, such as drowsiness or incontinence, to other causes.

The relation of NMS to milder forms of neuroleptic toxicity awaits elucidation but caution is recommended in each case until NMS is excluded. Creatine kinase is not useful in the diagnosis of NMS because of its oversensitivity but its fluctuations may be useful in measuring the progress of an established case.

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Multiple choice questions

1. Symptoms that may denote onset of NMS after neuroleptic ingestion include:
   a Fluctuating blood pressure
   b Persistent change in level of consciousness
   c Urinary incontinence
   d Maculopapular rash
   e Clasp-knife rigidity.

2. Medication implicated in the genesis of NMS includes:
   a Clozapine
   b Metoclopramide
   c Tetrabenazine
   d Lithium
   e Cessation of L-dopa.

3. The following is true of NMS:
   a CPK rise of above 800 units/litre is specific to the diagnosis
   b Routine CSF examination usually shows abnormalities
   c Leucocytosis is almost invariably present
   d Never occurs in psychiatric out-patients
   e Always occurs in the early stages of neuroleptic treatment.

4. In the case of an individual with established NMS:
   a A general medical opinion is mandatory
   b Neuroleptics should be withdrawn immediately
   c ECT is contraindicated
   d Observations of pulse temperature and blood pressure can be discontinued once the diagnosis is made
   e Benzodiazepines may be given for agitation.

5. Neuroleptic rechallenge in a patient with documented NMS:
   a Should be done as soon as vital signs have returned to normal
   b Should only involve depot preparations
   c Should only involve specific DA-2 blockers
   d Recrudescence risk decreases if a two week gap is left
   e Should be started on low dose low potency oral medication and cautiously increased.

MCQ answers				
1	2	3	4	5
a T	a T	a F	a T	a F
b T	b T	b F	b T	b F
c T	c T	c T	c F	c F
d F	d T	d F	d F	d T
e F	e T	e F	e T	e T