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Classic diseases revisited

The neuroleptic malignant syndrome: a logical approach to the patient with temperature and rigidity

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Summary

The neuroleptic malignant syndrome is a rare, potentially fatal, adverse reaction to neuroleptic drugs characterised by severe rigidity, high temperature and autonomic dysfunction. In the light of the hypothesized pathophysiology of this condition, a rational approach to the management of patients presenting with temperature and rigidity is provided. The aims of this approach are threefold: to reduce the incidence of the condition, to be able to recognise it early so as to treat before life-threatening complications arise, and to be able to recognise early those conditions which mimic neuroleptic malignant syndrome, so as not to delay their specific treatment.

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In the early 1960s Delay described a clinical syndrome caused by neuroleptics, characterised by severe extrapyramidal rigidity, hyperthermia, and unstable respiration, pulse and blood pressure.[1] The incidence was about 1% of patients treated with neuroleptics while mortality was thought to be around 40%.[2 3] This was the neuroleptic malignant syndrome (NMS). Although hundreds of cases of NMS have now been reported in the literature, only a few prospective series are available[2 3] and treatment modalities have not been assessed in prospective randomised controlled trials. However, information available in the literature has led to development of rational approaches to the management of this condition.[4]

It is possible that a cautious rational use of neuroleptics can actually reduce the incidence of NMS.[5] Recognition of the early forms of neuroleptic-induced severe extrapyramidal rigidity (forme fruste NMS), with timely withdrawal of the offending drug can possibly abort the development of full-blown NMS.[4] Furthermore, the early institution of intensive supportive care in full blown cases of NMS, before life-threatening complications set in, can significantly improve outcome. In fact it appears that the mortality of this condition is also on the decrease.[6] The aim of this review is to provide a practical approach to the management of patients presenting with rigidity and temperature.

Pathophysiology and clinical features of NMS

Sudden and profound central dopaminergic blockade is the most favoured hypothesis for the pathogenesis of NMS.[7] Although this is probably a simplistic model, as serotonin and cholinergic systems also probably play a minor role,[8 9] it forms a good basis for the explanation of most of the clinical manifestations of the syndrome. Most physicians are familiar with drug-induced parkinsonism which accompanies neuroleptic use. However, NMS represents a sudden severe blockade, due either to an individual hypersensitivity to that particular dopamine antagonist,[10] or to the rapid, massive, parenteral use of potent neuroleptics such as haloperidol (box 1).[11]

However, why do only a minority of patients develop NMS? While genetic susceptibility is unproven,[4] a number of psychiatric states, namely catatonia,[12] or affective disorder,[13] or physical illness with dehydration, are thought to predispose.[11 14] Box 2 lists the suspected mechanisms.

Hyperthermia probably results from a large increase in heat production, when heat-dissipating mechanisms are overwhelmed.[15] It is unclear to what extent, central dopaminergic blockade impairs central autonomic homeostatic regulators, particularly thermoregulation (box 1).[16]

Hypertension and tachycardia can be explained by the hypermetabolic state caused by severe muscle rigidity and hyperthermia. Together with the consequent dehydration and hypoxia, this results in a massive secondary peripheral hyperadrenergic state.[9 14] Tachypnoea is the result of decreased chest wall compliance due to severe chest wall muscle rigidity. Tachypnoea of about 40–60 breaths/min, with very small tidal volumes can lead to respiratory failure as inhaled air reaches mostly up to the dead space, with consequent alveolar hypoventilation (box 1).

It is unclear whether the autonomic features are due to the central effects of neuroleptics, or to the peripheral hyperadrenergic state. This author has documented that sudden reversal of rigidity reverses virtually all of the autonomic features.[10] A close parallel between autonomic features and the degree of muscle rigidity has been observed in patients treated with the muscle relaxant dantrolene,[17] so that the second hypothesis seems more likely. The minute-by-minute instability of these patients is difficult to explain, although this could reflect subtle changes in muscle rigidity in these short time frames.

Pathophysiology of NMS

Cause

Profound central dopaminergic blockade and extreme extrapyramidal rigidity
- caused by potent dopamine blockers, ie, haloperidol, withdrawal of L-dopa in Parkinson's disease
- CSF metabolites of dopamine low in NMS
- dopaminergic drugs provide effective therapy

Consequential effects
- hyperthermia
- severe muscle rigidity increases heat production
- heat-dissipating mechanisms overwhelmed
- possible resetting of hypothalamic regulatory centre

Autonomic instability
- massive peripheral hyperadrenergic state documented
- hypertension
- tachycardia
- tachypnoea due to chest wall muscle rigidity resulting in decreased chest expansion
- tachypnoiec hypoventilation with respiratory failure can occur

Obtunded consciousness, diaphoresis, mutism
- possibly due to hyperthermia
- ? direct effect of central dopamine blockade
- inability to speak due to rigidity

Laboratory changes
- raised creatine kinase and raised white cell count due to prolonged muscle contraction and hyperthermia result in muscle trauma and inflammation

Box 1

Risk factors for NMS: why does massive dopaminergic blockade occur?

The patient
- idiopathic hypersensitivity to dopaminergic blockade (eg, metoclopropamide)
- underlying psychiatric diagnosis (possibly dopamine depleted): catatonia, manic excitement (?lithium therapy)
- physical illness (possibly impaired heat dissipation): dehydration, agitation, debilitating illness

The drug
- high potency of the antidopaminergic effect (eg, haloperidol)
- initial large dose
- rapid climb in dose
- parenteral use

Box 2

Spectrum concept

Drug-induced parkinsonism and NMS could represent two ends of a spectrum, with a number of moderately severe, possibly self-limiting prolonged extrapyramidal reactions in between. These intermediate or partial forms have been labelled by some authorities as formes frustes. This point of view is useful in clinical practice, although the concept is regarded as controversial.[18 19]

The challenge facing the practising physician is to recognise NMS, and forme fruste types early so as to be able to withdraw neuroleptic therapy, and administer supportive and dopaminergic therapy before irreversable complications set in.[20 21] In this context, it must be remembered that patients with mild extrapyramidal rigidity may have life-threatening medical conditions such as bacterial meningitis, encephalitis, pneumonia, urinary tract infection or limb venous thrombosis.[22] The coincidental occurrence of these medical conditions with extapyramidal neuroleptic-induced parkinsonism could lead to an erroneous diagnosis of NMS with disastrous consequences.[4] Furthermore, therapy with other drugs may cause similar syndromes, eg, the anticholinergic syndrome with excessive use of these drugs,[23] or the serotonin syndrome in patients on mono-amine oxidase inhibitors (MAOIs), or in patients abusing cocaine or ecstasy.[24 25]

Approach to a patient with temperature and rigidity

DEALING WITH NMS

The hallmark of NMS is the severe form of rigidity, resulting in a 'patient turned to stone' appearence. Extreme forms of rigidity with bizarre posturing such as opisthotonos are not uncommon. In such cases, malignant hyperthermia associated with anaesthesia and muscle relaxant use is the main differential diagnosis. This can usually be confidently excluded by history taking, and the absence of previous episodes or a family history of similar problems with anaesthesia.[16]

When there is a clear history of neuroleptic use, and the criteria for the diagnosis of NMS are fulfilled (box 3),[4 26 27] the patient should be transferred as early as possible to an intensive therapy unit and further neuroleptic therapy withheld. These two measures are indeed the most important and life-saving manoeuvres in this potentially 'malignant' syndrome.[4 13 28] After vigorous rehydration and the application of physical measures such as ice packs to control hyperthermia, infection must be carefully excluded, both clinically and by laboratory investigation, even if the diagnosis of NMS is a confident one. A computed tomography (CT) scan of the brain, and lumbar puncture should be high on the priority list. A chest X-ray to exclude pneumonia, and urinalysis to screen for urinary tract infection are necessary, and blood and urine cultures should be obtained.[4 16] As aspiration pneumonia is a common complication of NMS, the presence of consolidation on chest-X-ray does not exclude NMS.[22] A toxicology screen for neuroleptics, anticholinergic and serotinergic drugs is advisable.[23 24]

Severe tachypnoea, with consequent tachypnoeic hypoventilation, may result in respiratory failure. Mechanical ventilation with muscle relaxant use may be necessary in a minority of cases. It has now been shown that malignant hyperthermia is a totally separate condition from NMS and for this reason cross-reactivity between neuroleptics and muscle relaxants is unlikely to occur.[15]

Once the patient's condition is under control, being adequately monitored, and the diagnosis of NMS is a confident one, specific treatment can be given. Dopaminergic therapy with agents such as L-dopa, bromocriptine and amantadine by nasogastric tube are thought to speed up the reversal of this massive central dopaminergic blockade.[29–31] A progressive increase in dose, from 7.5 mg to 60 mg of bromocriptine daily, is widely used. Secondly, where muscle rigidity is severe, and body temperature difficult to control, dantrolene, a muscle relaxant which prevents calcium release in the sarcolemmal membrane can be used. The reduction in muscle rigidity is achieved by doses between 1–2 mg/kg and 10 mg/kg in four divided doses. Dantrolene decreases heat production and improves respiration by improving chest compliance, thus attenuating the peripheral hyperadrenergic state.[10 17] However, because no prospective randomised controlled trial has been carried out to date, whether the duration of NMS is shortened or not by this drug remains unestablished.[29–31]

A number of cases of apparent NMS have occurred in the absence of neuroleptic therapy, particularly in the context of catatonia progressing into malignant catatonia.[32] Electroconvulsive therapy (ECT) with full anaesthesia and muscle relaxation has been used with good results.[33] The role of ECT in NMS with neuroleptic use is controversial.[34] It should be reserved for cases of NMS that fail to respond to supportive and pharmacological therapy, and for psychiatric treatment of patients having recovered from NMS.[4] With the extreme

Criteria for diagnosis of NMS (from [27])

All three required*

Hyperthermia
- oral temperature of at least 38°C in the absence of another known cause

Severe extrapyramidal effects
Two or more of:
- lead pipe muscle rigidity
- trismus
- pronounced cogwheeling
- dysphagia
- sialorrhea
- choreiform movements
- oculogyric crisis
- dyskinetic movements
- retrocollis
- festinating gait
- opisthotonos
- flexor–extensor posturing

Autonomic dysfunction
Two or more of the following:
- hypertension (at least 20 mmHg in diastolic above baseline)
- tachycardia (at least 30 beats above baseline)
- tachypnoea (at least 25 respirations/min)
- prominent diaphoresis
- incontinence

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* If one of the three items is not specifically documented, two criteria must be clearly met plus one of the following:
- clouded consciousness, ie, delirium, mutism, stupor, or coma
- leucocytosis >15×10^9/l
- creatine kinase >1000 U/l

Box 3

degree of immobility in NMS it is no surprise that thromboembolism is a common complication,[35] frequently accounting for the observed mortality. For this reason full anticoagulation with heparin has been recommended in established cases.[36]

HYPERTHERMIA, LITTLE RIGIDITY

In a clinical context of hyperthermia with only mild muscle rigidity, NMS is much less likely. However, a careful drug history to exclude the anticholinergic syndrome, or the serotonin syndrome associated with MAOIs, cocaine or ecstasy should be obtained. In warm climates, heat stroke is another important possibility.[37] Supportive measures should be promptly instituted and a thorough screen for infection would be prudent. Specific therapy with cholinergics, and anti-serotinergics may be helpful.

MODERATE TEMPERATURE WITH MODERATE RIGIDITY

A common clinical problem is represented by the patient with moderate rigidity and temperature. The question in one's mind is: is this early NMS (forme fruste)[7] or is there an underlying co-incidental medical problem?[22] In this situation the infection screen takes precedence as the likelihood of NMS is not so high. Transfer to intensive care should depend on the the patient's clinical condition, however this is not as high a priority as in NMS. Ideally, neuroleptics should be stopped until the infection screen is completed, however a cautious reduction in dose or potency might be more practical, particularly in disturbed patients. Benzodiapezines might be preferable to control agitation.

If infection is indeed the cause of the temperature one must still be careful with neuroleptic dosage as medical illness predisposes to NMS.[11] When the infection screen is negative, and rigidity is on the increase, NMS is likely. Anticholinergics at this stage are unlikely to work and can actually aggravate the hyperthermia by impairing the body's ability to dissipate heat.[23] Early transfer to intensive care, vigorous supportive therapy, and total withdrawal of neuroleptics should be the mainstay of these early forms of NMS.[29]

Conclusion

Although clinical experience with this syndrome has greatly increased in the last 15 years, most treatment strategies are based on retrospective case reports. The

Logical approach to the patient with rigidity and temperature

Drug-induced parkinsonism

How to prevent NMS
- indication for neuroleptic clear
- prior history of NMS excluded
- use of small doses preferably oral
- small gradual increments in doses
- avoid in physical illness + dehydration
- treat agitation with physical restriction or benzodiazepines

Management options
- withdraw drug or decrease dose
- use less potent dopamine antagonist
- add anticholinergic

Forme fruste NMS*

Early signs of NMS
- unusually prolonged or severe rigidity
- partial or short-lived effect of anticholinergic drugs
- impaired consciousness or akinetic mutism
- temperature, no focus of infection
- persistent unexplained tachycardia
- unexplained fluctuations or increase in the blood pressure
- restlessness and akathisia

Management
- intensive search for infection source (CT brain, LP, CXR, urine+blood cultures)
- withdraw neuroleptic
- avoid anticholinergics
- vigorous rehydration
- transfer to intensive care early if clinical condition deteriorates
- toxicological screen

Full blown NMS

Diagnostic criteria, core features
- severe rigidity
- hyperthermia
- autonomic dysfunction
- laboratory data (WBC and CK)

Management
- immediate transfer to intensive care
- withdraw neuroleptic
- infection screen
- specific measures, eg, dopaminergic drugs or dantrolene
- toxicological screen

NMS+ complications

Complications of NMS
- respiratory failure (tachypnoeic hypoventilation)
- severe dehydration with hypovolaemic shock (renal shut down)
- rhabdomyalysis with acute renal failure
- venous thromboembolism
- aspiration pneumonia
- metabolic upset, eg, hyperglycaemia, hypernatraemia, acidosis

Management
- transfer to intensive care unit and aggressive supportive therapy of highest priority
- infection screen when stable
- specific measures for NMS
- specific measures for complications, eg, antibiotic, heparin, dialysis

*Could be self-limiting – can progress.

Box 4

lack of uniform diagnostic criteria makes interpretation difficult. There are only a handful of prospective studies in the literature, while proper prospective controlled randomised clinical trials are unlikely be conducted because of the life-threatening nature of the illness.

However, it appears that the incidence of this adverse reaction is on the decline,[5] mainly due to more prudent dosing of neuroleptics and the recognition of risk factors. The mortality rate also appears to be dropping to about 10–20% from around 40%.[38] This is probably because of earlier recognition of NMS, with consequent earlier referral to intensive care units. Whether specific therapies with dantrolene, dopaminergic drugs or heparin have had any impact is difficult to determine in this otherwise self-limiting illness.

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