NEUROLEPTIC MALIGNANT SYNDROME

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The neuroleptic malignant syndrome (NMS) was first described by Delay et al[8] during early clinical trials of haloperidol. Other clinicians in France and Japan subsequently confirmed the existence of NMS, recognizing that it occurred during early phases of treatment with therapeutic doses of neuroleptics and that individual susceptibility was a significant factor in its development.[5, 23] Despite these early studies, NMS remained relatively unknown. After 1980, however, increasing recognition of NMS resulted in the publication of hundreds of case reports and numerous reviews.[3, 23] This literature is complicated by duplication of data, lack of controlled conditions, and selection biases inherent in cases chosen for publication. Nevertheless, the abundance of replicated clinical observations, including recent prospective studies of consecutive cases, has supported a more precise definition of NMS, clarified risk factors and treatment strategies, stimulated interest in related hypermetabolic disorders, and provided insights about pathogenesis.

EPIDEMIOLOGY

Incidence

Although NMS is rare, the widespread use of neuroleptic drugs suggests that the absolute number of cases is not insignificant. In a nationwide survey in Japan, two thirds of responding facilities reported experience with NMS.[47, 48] A total of 1666 cases was reported.

Estimates of the incidence of NMS have ranged from 0.02% to 3.23%,

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probably reflecting differences in diagnostic criteria, survey techniques, patient populations, clinical settings, and treatment practices.[23] The base number of neuroleptic-treated patients at risk is estimated in most studies and derived from retrospective chart reviews.

The degree of risk in the population studied may be an important factor that determines the incidence of NMS. For example, Gelenberg et al[12, 13] reported only one NMS case in 1470 patients (0.07%) monitored prospectively during 1 year, and no further cases among 1450 patients treated during a second year of observation. Gelenberg's group emphasized education of staff in recognizing and treating incipient cases of NMS, and use of conservative neuroleptic dosing strategies. Similarly, Keck and colleagues[20, 21] found four cases of NMS among 2695 neuroleptic-treated patients (0.15%) in a prospective survey, a significant decline from an incidence of 1.1% obtained from an earlier survey at the same center. They attributed the decline to earlier recognition and reduction in potential risk factors. Pooling data from 16 studies of incidence of NMS in the literature yields 66 cases among 33,720 neuroleptic-treated patients, or an incidence of about 0.2%.[12, 13, 20, 21, 23]

Risk Factors

Age

Although NMS is found primarily among young and middle-aged adults, it has been reported in all age groups, in parallel with the use of neuroleptics.[4, 23] The mean age of patients with NMS has been estimated to be 40 years. In the survey from Japan, 186 of 210 cases (89%) occurred in patients between the ages of 20 and 59.[47] In one case-controlled study, age did not distinguish patients with NMS from controls.[19]

Sex

Neuroleptic malignant syndrome is reported either more commonly in men or about equally between the sexes.[9, 19, 23] The effect of sex on susceptibility may be confounded by differences in the way neuroleptics are used based on sex. Thus, sex, like age, is not a meaningful risk factor.

Environmental Conditions

Neuroleptic malignant syndrome occurs independent of climate and ambient conditions. Whereas patients' inability to maintain body temperature in extreme conditions was recognized early as a side effect of neuroleptic treatment, this does not explain the occurrence of NMS, which has been reported in cold climates and throughout the seasons.[4, 23] Although high temperatures and humidity may augment the risk of NMS, they need not be present for NMS to occur.

Neuropsychiatric Diagnosis

Neuroleptic malignant syndrome is not specific to any neuropsychiatric diagnosis.[4, 23] It has been reported in patients treated with neuroleptics for diverse psychiatric illnesses as well as in patients without evidence of neuropsychiatric pathology. Nevertheless, it is possible that certain disorders predispose patients to NMS. Various authors have proposed that patients with

disorders of mood,[23, 34] catatonia,[46] schizophrenia,[41, 48] or organic syndromes[3] may be at risk. Differences in diagnostic criteria, variability in the use of neuroleptics and adjunctive drugs, and lack of control data among investigators again limit conclusions.

Physiologic State

Apart from the underlying diagnosis, the physiologic state of the patient at the time neuroleptics are administered may be important. For example, preexisting abnormalities in the state of brain dopamine activity or receptor function may constitute a critical variable in the development of NMS.

Systemic risk factors have included exhaustion, psychomotor activity, and dehydration.[23] Keck et al[19] found that NMS patients were significantly more likely to be agitated prior to the onset of NMS. Rosebush and Stewart[34] found that agitation preceded onset in 18 of 24 NMS episodes (75%), and that most patients were dehydrated. However, they noted that it is difficult to distinguish between dehydration as a precipitating factor or as a result of the fluid losses associated with NMS. Patients with medical illnesses or drug-related conditions that compromise thermoregulation may also be at risk for NMS. Therefore, it is imperative to ensure adequate hydration and reduce psychomotor activity in acutely disturbed patients.

Heredity

There are only two reports of the familial occurrence of NMS. Deuschl et al[11] reported the occurrence of NMS in twin brothers with schizophrenia. Otani et al[31] reported the occurrence of NMS in a mother and two daughters, all of whom had catatonic schizophrenia, and speculated that this family shared a genetic vulnerability in central dopaminergic systems. These findings are also consistent with the familial occurrence of lethal catatonia, an NMS-like syndrome described by Stauder.[42] Finally, Lazarus et al[24] diagnosed NMS without rigidity in a retarded patient with an inverted duplication of chromosome 15.

Malignant hyperthermia, another NMS-like syndrome triggered by anesthetics, is a heterogeneous pharmacogenetic disorder involving a membrane-related defect in calcium sequestration in skeletal muscle.[23] Data from family studies[16] and in vitro testing[1] indicate that NMS patients do not share a genetic defect with malignant hyperthermia patients. In fact, malignant hyperthermia and NMS seem to result from different triggering mechanisms; patients with one of the disorders do not appear to be at risk for the other.

Pharmacologic Variables

About 17% of NMS patients experienced a similar episode during prior treatment with neuroleptics.[4, 47] Conversely, Caroff and Mann[4] found that about 30% developed subsequent episodes on rechallenge with neuroleptics. Rosebush et al[35] found that in 15 patients recovered from NMS, 5 (33%) developed at least one subsequent NMS episode on rechallenge. This implies that a history of prior NMS episodes is a significant risk factor.

Virtually all classes of D_2 dopamine receptor antagonists have been associated with NMS. This includes not only typical and atypical neuroleptics used in the treatment of psychosis, but also neuroleptic drugs such as prochlorperazine, droperidol, and promethazine, used as antiemetics, anesthetics, and sedatives. Haloperidol has been implicated in nearly half of the reported cases

and is the sole precipitating agent in 28% of cases.[4, 47] This may reflect the frequency with which this drug is prescribed, or the relatively high dosages and rates of administration commonly employed. Low-potency agents such as chlorpromazine have also been implicated. Clozapine, an atypical neuroleptic, may have reduced potential to cause NMS, although recent reports of NMS in patients treated with clozapine suggest otherwise.

Data on dosage indicate that NMS is not a result of overdosage, and usually occurs with dosages within the therapeutic range.[4, 23] Studies of recurrence of NMS on rechallenge have been inconsistent as to whether potency or dosage correlate with NMS. Caroff and Mann[4] and Shalev and Munitz[41] found that high-potency agents increased the risk, whereas in a prospective study Rosebush et al[35] found no relationship between potency or dosage and recurrence of NMS.

Shalev and Munitz[41] further proposed that the loading rate of neuroleptics in treating psychosis, rather than total dosage, is a key factor. This was supported by the study of Keck et al[19] in which patients with NMS received significantly higher doses of neuroleptics at greater rates of increase and more intramuscular injections than controls. Although this was contradicted by Rosebush and Stewart[34] who found no correlation with changes in dosage, the decline in incidence of NMS achieved in some centers[12, 21] supports the advantages of conservative dosing practices and the hazards of rapid neuroleptization in psychotic patients.

Deng et al[9] compared treatment data on 12 NMS patients and 102 control patients. Although no differences were found between groups in the mean dosages of neuroleptics used, they found that NMS patients treated with intramuscular fluphenazine decanoate, a long-acting neuroleptic, had 3 times the rate of NMS rising to 10 times the rate if fluphenazine decanoate was administered without antiparkinsonian agents. This effect was not observed by Keck et al.[19]

Concomitant treatment with adjunctive psychotropic drugs has been proposed as another potential risk factor. More than half of reported cases of NMS involve concomitant administration of other drugs, including lithium carbonate, tricyclic- and monoamine oxidase–inhibiting antidepressants, antiparkinsonian agents, and benzodiazepines.[4, 23] However, Keck et al[19] and Deng et al[9] found no significant differences in the use of these drugs between small groups of NMS patients and neuroleptic-treated controls.

In summary, there are no proven reliable risk factors that outweigh the benefits of neuroleptic therapy in a given patient. Evidence is accumulating, however, to support psychomotor agitation, dehydration, previous episodes of NMS, the rate of increase of neuroleptic dosage, and the use of parenteral medication as potential risk factors. It is difficult to demonstrate the significance of specific variables because the numbers of patients are small in any one study, control data are often lacking, and the variables may be interrelated or act synergistically.

Nevertheless, rational guidelines have been proposed to reduce the risk of NMS. A careful drug history, physical examination, and laboratory evaluation should be obtained prior to neuroleptic administration. Patients should be sedated and monitored to prevent agitation, exhaustion, and dehydration. Indications for neuroleptics should be clear and increases in dosages made judiciously based on symptom response, with alternative methods, such as physical restraint, benzodiazepines, or interpersonal interventions used to optimize sedation and behavioral control.

CLINICAL CHARACTERISTICS

Prodromal Signs

In addition to patient and treatment variables that could predict risk of NMS, the identification of reliable prodromal signs would be useful in aborting episodes. At times NMS may progress within hours and thus preclude identification of early signs, but usually NMS is preceded by insidious neurologic and autonomic signs that defy diagnosis and prove refractory to conventional treatment. Signs that may precede NMS include unexpected changes in mental status, particularly obtundation or new-onset catatonia; episodic tachycardia, tachypnea, or hypertension; dysarthria, dysphagia, diaphoresis, sialorrhea, incontinence, low-grade temperature elevations, rigidity, myoclonus, tremor or other extrapyramidal signs unresponsive to antiparkinsonian agents; and unexplained elevations in serum creatine phosphokinase.[5] However, these signs are nonspecific, do not necessarily progress to NMS, and do not invariably precede the syndrome.

Clinical Signs

As a clinical syndrome, NMS has been diagnosed consistently on the basis of hyperthermia, muscle rigidity, mental status changes, and autonomic instability. Although there is a general consensus on these features, some investigators have noted the heterogeneity among reported cases[26] or have emphasized the blurred demarcation between mild cases of NMS and the spectrum of more benign extrapyramidal effects of neuroleptics. Whether and how NMS differs in pathogenesis from less profound side effects remains unclear.

Neuroleptic malignant syndrome is best defined as a form of drug-induced hyperthermia. It is the product of neuroleptic-induced disruption of regulatory mechanisms in the hypothalamus and basal ganglia that results in the failure to compensate for an increased rate of endogenous metabolic activity and heat production. Both the increased peripheral metabolic activity and central thermoregulatory failure are dopamine dependent and therefore affected by neuroleptic treatment.

Hyperthermia associated with profuse sweating occurs in 98% of reported NMS cases, exceeding 38°C in 87% and 40°C in 40%.[4, 5] Extreme hyperthermia may predispose to complications, including irreversible cerebellar or other brain damage, if not reduced immediately.

Generalized rigidity, described as "lead-pipe" in its most severe form, is reported in 97% of NMS cases and is associated with myonecrosis.[4, 5] Cogwheeling may or may not be present. Coarse tremors and myoclonus are reported frequently; other extrapyramidal and bulbar signs, including focal dystonias, sialorrhea, dysphagia and dysarthria, opisthotonus, oculogyric crisis, and dyskinesias are reported less commonly.

Changes in mental status have been reported in 97% of cases.[4, 5] Manifestations include clouding of consciousness that varies from stupor to coma, delirium, and the development of catatonic features. The classic NMS patient is alert but appears dazed and mute. Some patients continue to have periods of agitation during NMS, requiring sedation with benzodiazepines or physical restraints. Finally, autonomic activation and instability, manifested by sinus tachycardia (88%) or oscillations of blood pressure (61%), have been reported in 95% of cases.[4, 5] Moderate to severe respiratory distress and tachypnea which

may result from metabolic acidosis, hyperthermia, chest-wall restriction, aspiration pneumonia, or pulmonary emboli may be observed in 31% of cases[47, 48] and may lead to respiratory arrest.

Laboratory Findings

Although several laboratory findings have been reported consistently, none are specific or pathognomonic for NMS. Nevertheless, a complete laboratory evaluation is essential in excluding other causes of the syndrome and identifying complications. Elevations in serum creatine phosphokinase from skeletal muscle have been reported in 95% of NMS cases, and myoglobinuria was found in 67% of cases in which urine was tested.[5] This supports the frequent occurrence of muscle necrosis in NMS, which stems from rigidity, hyperthermia, and ischemia, and may result in acute renal failure. Other factors such as agitation or intramuscular injections may contribute to elevations in creatine phosphokinase, so the diagnostic value of serum enzymes has been questioned. However, measurement of creatine phosphokinase remains important as a measure of severity and the risk of renal failure. Other serum enzymes such as lactic acid dehydrogenase, transaminases, and aldolase may be elevated as well and probably derive from myonecrosis. Bilirubin and alkaline phosphatase are usually normal.

Other common findings include a nonspecific leukocytosis with or without a left shift in 98% of cases, and metabolic acidosis or hypoxia on blood-gas analysis in 75% of cases examined.[4, 5] Nonfocal, generalized slowing on electroencephalography has been reported in 54% of cases.[4, 5] Less consistent findings include hyponatremia, hypernatremia, dehydration, low serum iron,[33] elevations in serum catecholamines, and coagulopathies.[23]

Viewed as a diagnosis of exclusion, NMS can be supported only when other disorders are ruled out. In the literature, 95% of computed tomographic scans of the head have been negative, with the remainder showing nonspecific or pre-existing pathology.[4, 5] Similarly, cerebrospinal examination has been negative in 95% of reported cases. Evaluation for primary infectious causes of the syndrome was negative in virtually all reported NMS cases reviewed before 1987.[5] However, it may be difficult to distinguish primary from secondary infections, and patients with pre-existing infections such as encephalitis may be at risk for NMS.[5, 34]

Diagnostic Criteria

The consistent clinical and laboratory features reported in hundreds of cases diagnosed as NMS have enabled several groups to propose standardized diagnostic criteria.[5, 15, 23] In criteria proposed by our group[5] (Table 1), we require the presence of muscle rigidity and hyperthermia. Other associated signs must be present but are considered less critical, less frequent, more variable, difficult to distinguish from pre-NMS findings, or more likely a secondary result of hypermetabolism. Diagnostic criteria must specify neuroleptic treatment and underscore that NMS is considered when other neuropsychiatric, systemic, and drug-induced hypermetabolic disorders have been excluded. Continued comparison of the validity, reliability, sensitivity, and specificity of diagnostic criteria would be valuable in refining the diagnosis of NMS.

Table 1. DIAGNOSTIC CRITERIA FOR NEUROLEPTIC MALIGNANT SYNDROME*

1. Treatment with neuroleptics within 7 days of onset (2 to 4 weeks for depot neuroleptics)
2. Hyperthermia (≥38°C)
3. Muscle rigidity
4. Five of the following:
   - Change in mental status
   - Tachycardia
   - Hypertension or hypotension
   - Tachypnea or hypoxia
   - Diaphoresis or sialorrhea
   - Tremor
   - Incontinence
   - Creatine phosphokinase elevation or myoglobinuria
   - Leukocytosis
   - Metabolic acidosis
5. Exclusion of other drug-induced, systemic, or neuropsychiatric illnesses

*All five items required concurrently.

Adapted from Caroff SN, Mann SC, Lazarus A, et al: Neuroleptic malignant syndrome: Diagnostic issues. Psychiatric Annals 21:130–147, 1991; with permission.

Clinical Course

The factors involved in the relationship between drug exposure and the onset of NMS appear complex. In the review by Caroff and Mann,[4] 16% of patients developed signs of NMS within 24 hours of initiating neuroleptic treatment, 66% by 1 week, and 96% within 30 days. Neuroleptic malignant syndrome is less likely to occur after 30 days, but this did happen in 4% of cases.

Once neuroleptics are stopped, NMS is self-limited barring complications. Among 65 reported cases involving oral neuroleptics, untreated by dopaminergic agonists or muscle relaxants, the mean recovery time was 9.6 ± 9.1 days.[4] Twenty-three percent recovered in 48 hours, 63% by the end of 1 week, and 97% by the end of 1 month. Other estimates of the mean duration of NMS range from 6.8 to 10.6 days.[9, 36, 37] Patients receiving long-acting depot neuroleptics may have NMS episodes nearly twice as long.[3, 9, 23]

Outcome

Despite therapeutic effects, 25 (10%) of 256 cases of NMS reported in the literature between 1980 and 1987 ended in death.[4] This represented a decline compared to cases reported before 1980. Shalev et al[40] confirmed these findings, showing a decline in mortality from 25% to 11.6% before and after 1984. In Japan, the mortality rate was 28% before 1986.[47, 48] Due to biases in reporting, more accurate estimates of mortality derive from series of cases studied at individual centers. Such reports support an apparent decline in deaths from nearly 30% to no fatalities in recent series.[9, 19, 35] Presumably, this decline reflects greater awareness of the syndrome, early diagnosis, rapid drug discontinuation, institution of supportive care, or use of specific pharmacotherapy.

Death results from cardiac or respiratory arrest that may occur suddenly or follow cardiac failure, infarction or arrhythmias, aspiration pneumonia, pulmonary emboli, myoglobinuric renal failure, or disseminated intravascular

coagulation. Shalev et al[40] found increased mortality associated with prior organic brain syndromes (38.5%) and the development of renal failure (50%). Apart from this review, predictors of outcome are not well established. Autopsy findings in NMS have been nonspecific and variable, depending on complications. Neuropathologic findings are usually negative or consistent with the effects of hyperthermia and hypoxia.

Persistent, long-term clinical sequelae of NMS are rare.[23] Deficits are related to complications or severity of the syndrome, particularly hypoxia or hyperthermia. There have been reports of persistent organic amnestic syndromes and extrapyramidal or cerebellar disorders that may persist for weeks, months, or indefinitely.[34, 36, 44] Severe peripheral neuropathy, muscle weakness, and contractures have also been described.[2, 18, 35] Neurologic complications may be increased if lithium toxicity accompanies NMS.[23]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of NMS encompasses a broad range of disorders presenting with fever, necessitating a thorough medical and neurologic evaluation (Table 2).[5] The differential is narrowed by the associated features of rigidity, mental status changes, and autonomic dysfunction. Even so, despite careful investigation, the cause of the syndrome in some patients may remain elusive or reflect multiple determinants.

Primary Brain Disorders

Infections

Viral encephalitis or postinfectious encephalomyelitis can be difficult to distinguish from NMS, particularly when the presenting signs are behavioral.

Table 2. DIFFERENTIAL DIAGNOSIS OF NEUROLEPTIC MALIGNANT SYNDROME

Primary Central Nervous System Disorders
Infections (viral encephalitis, human immunodeficiency virus, postinfectious encephalomyelitis)
Tumors
Cerebrovascular accidents
Trauma
Seizures
Major psychoses (lethal catatonia)
Systemic Disorders
Infections
Metabolic conditions
Endocrinopathies (thyroid storm, pheochromocytoma)
Autoimmune disease (systemic lupus erythematosus)
Heatstroke
Toxins (carbon monoxide, phenols, tetanus, strychnine)
Drugs (salicylates, dopamine inhibitors and antagonists, stimulants, psychedelics, monoamine oxidase–inhibitors, anesthetics, anticholinergics, alcohol or sedative withdrawal)

Adapted from Caroff SN, Mann SC, Lazarus A, et al: Neuroleptic malignant syndrome: Diagnostic issues. Psychiatric Annals 21:130–147, 1991; with permission.

Pre-existing viral illness, headaches, meningeal signs, seizures, focal signs, and positive cerebrospinal fluid examination or brain imaging suggest a viral etiology. Several cases of NMS have been reported in patients infected with human immunodeficiency virus who also received neuroleptics. In these cases, it may be difficult to distinguish drug effects from viral illness, although discontinuation of neuroleptics may be wise regardless. The predilection of human immunodeficiency virus and other viruses to infect midbrain structures may increase the risk of severe extrapyramidal reactions, including NMS, among infected patients treated with neuroleptics.

Structural Pathology

Anatomic lesions resulting from tumors, abscesses, stroke, or trauma should be evaluated by history, neurologic examination, and brain imaging. In particular, damage to the anterior cingulate gyri, the mamillary bodies, periventricular nuclei in the hypothalamus, or brain stem areas may produce akinetic mutism resembling NMS, possibly due to damage to dopamine tracts passing through these regions.[23, 29] In contrast to these cases with diagnosable brain lesions, brain imaging and postmortem examination of NMS patients have revealed no consistent or specific pattern of brain pathology.

Seizures

Rarely, cases of status epilepticus resembling NMS may be encountered. Confusion may arise from the observation of fever and elevations of creatine phosphokinase after convulsive activity. However, seizures are not commonly observed in NMS and should prompt a search for metabolic or structural causes.

Major Psychoses (Lethal Catatonia)

The potentially lethal progression of catatonic states in psychotic disorders has been well described for over a century. In these cases, unchecked hyperactivity can lead to exhaustion, stupor, hyperthermia, and death.[28, 42] Sometimes, a uniformly stuporous course with rigidity indistinguishable from NMS may occur. With the advent of modern medical and psychiatric interventions, the incidence of lethal catatonia may have decreased. Nevertheless, this must be considered when hyperthermia develops in an agitated and untreated psychotic patient. Differentiation from NMS in a neuroleptic-treated stuporous patient is more difficult. In either case, however, discontinuation of neuroleptics may be indicated; in most NMS cases symptoms should resolve in 1 to 2 weeks, and in lethal catatonia neuroleptics appear to be ineffective and may further compromise thermoregulation.[27] In fact, open trials suggest that electroconvulsive therapy is the treatment of choice in lethal catatonia.[27]

Systemic Disorders

Extrapyramidal Symptoms with Fever

Intercurrent fever caused by infections or metabolic disorders may develop in patients who also have parkinsonism or catatonia related to neuroleptic treatment.[5, 26] The importance of excluding common causes of fever in these patients before diagnosing NMS can hardly be overstated. Negative medical, laboratory, and postmortem evidence of infectious processes is the rule in the

majority of NMS cases. Although NMS is a form of drug-induced hyperthermia apart from extrapyramidal symptoms with fever, this distinction can present a difficult diagnostic challenge.

Endocrinopathies

Extreme hyperthermia may be observed in thyrotoxicosis and pheochromocytoma.[5] Hyperthyroid patients may manifest tremor, tachycardia, diaphoresis, and elevated temperatures reminiscent of prodromal signs of NMS. Thyroid storm has been mistaken for malignant hyperthermia during surgery, although unlike malignant hyperthermia and NMS, muscle rigidity and rhabdomyolysis are not usually observed. Diagnosis is further complicated by the fact that hyperthyroidism may predispose patients to develop severe rigidity on neuroleptics, and neuroleptics may precipitate thyroid storm.

In patients with pheochromocytoma, an acute crisis that may be precipitated by psychotropic drugs may resemble NMS. Although rigidity is not known to occur, significant rhabdomyolysis contributing to renal failure has been reported. It may be difficult to diagnose pheochromocytoma on the basis of plasma or urinary catecholamines because these values may be strikingly elevated in NMS as well.[4, 5]

Autoimmune Disorders

Systemic lupus erythematosus or mixed connective tissue diseases may present with fever, meningitis, and mental status and movement disorders, and may be confused with NMS if neuroleptics are prescribed for behavioral manifestations or steroid psychosis.

Heatstroke

During hot weather, agitated patients are at risk for exertional heatstroke characterized by sweating, hypotension, high temperatures, acidosis, and rhabdomyolysis that may progress to renal failure, disseminated intravascular coagulation, and death.[23] Administration of neuroleptics increases the risk of heatstroke, although most cases of heatstroke associated with neuroleptics resemble classic rather than exertional heatstroke. The classic form is not related to exertion and is characterized by anhidrosis and respiratory alkalosis. Unlike NMS, neither form of heatstroke is typically associated with muscle rigidity. Although clinicians should be aware that neuroleptics increase the risk of heatstroke in hot weather, NMS may occur in patients at rest independent of ambient temperature.[23]

Toxins and Drugs

Hyperthermia has been reported with occupational exposure to phenolic compounds, and with muscle rigidity has also followed carbon monoxide poisoning and L-asparaginase toxicity.[5, 23] Other toxins to consider are fluoride and iron salts, strychnine, methylphenyltetrahydropyridine, and tetanus or staphylococcal toxins.

Several drugs can cause NMS-like states through peripheral or central actions.[5, 23] By uncoupling oxidative phosphorylation, salicylates may induce hyperthermia after acute intoxication or chronic usage. Malignant hyperthermia, associated with the use of anesthetic gases and succinylcholine, is another drug-induced hypermetabolic disorder indistinguishable from NMS that results from the effects of triggering drugs on skeletal muscle.[23] Malignant hyperthermia is a consideration in the differential diagnosis of NMS only in the perioperative setting where both anesthetics and neuroleptics may be used.

Centrally active drugs may also produce an NMS-like picture. Antidopaminergic drugs, such as metoclopramide, amoxapine, tetrabenazine, and reserpine have been associated with NMS. Similarly, withdrawal of levodopa or "freezing" episodes associated with treatment of Parkinson's disease have resulted in an NMS-like picture.[5, 23] These non-neuroleptic drug reactions share the common element of acute reduction in brain dopamine activity, thereby confirming the causal connection between the dopamine antagonist properties of neuroleptics and the clinical signs of NMS.

Other drugs to consider include lithium, which by itself is an unlikely cause of hyperthermia but in combination with neuroleptics may increase the risk of NMS.[5, 23] Amphetamines and cocaine may produce hyperthermia as a result of agitation, seizures, or rigidity compounded by impaired heat loss due to vasoconstriction. Psychedelic drugs also cause hyperthermia, with rigidity and rhabdomyolysis frequently associated with phencyclidine intoxication. Tricyclic antidepressants are rarely associated with hyperthermia, but monoamine oxidase–inhibitors have caused an NMS-like syndrome when taken in overdose or prescribed in combinations with serotonergic tricylics, stimulants, tryptophan, narcotics, or tyramine-containing foods.[5, 23]

Hyperthermia associated with anticholinergic toxicity is also a consideration in the diagnosis of NMS but may be distinguished by the absence of rigidity, presence of atropinic signs, and response to physostigmine. Withdrawal from alcohol or sedative–hypnotics may be confused with NMS due to mental status changes, autonomic dysfunction, and elevated temperatures in both conditions. Rigidity is not associated with delirium tremens, although rhabdomyolysis may be found in alcoholic patients. The diagnosis may be obscured if neuroleptics are administered during withdrawal. Withdrawal also may increase the risk of NMS. In view of this, as well as their tendency to lower the seizure threshold, neuroleptics should be used cautiously in these patients.

TREATMENT

Prevention/Supportive Care

The basis of treatment of NMS remains reduction of risk factors, early recognition, cessation of neuroleptic medication, and institution of intensive medical care focusing on fluid replacement, reduction of temperature, and support of cardiac, respiratory, and renal functions. Careful monitoring for complications, particularly aspiration pneumonia, thromboembolism, and renal failure is essential. The favorable outcomes obtained in recent prospective studies provide support for this fundamental approach.[9, 12, 21, 34]

Pharmacotherapy

The role of specific pharmacotherapy in the treatment of NMS is less clear due to the lack of controlled, prospective data. Most studies of pharmacotherapy have relied on retrospective analyses of the literature or anecdotal experience. Employing retrospective data, Rosenberg and Green[37] found that both dantro-

lene and bromocriptine significantly reduced the time to clinical response and resolution of symptoms. Sakkas et al[38, 39] failed to find an effect of drug treatment on duration of NMS, but demonstrated a highly significant effect on the mortality rate, which declined from 21.0% in patients receiving only supportive therapy to 9.7% in patients receiving specific drug treatment. Shalev et al[40] similarly reported that mortality for patients treated with dantrolene, amantadine, or bromocriptine was significantly reduced, but noted that this effect was negated when controlled for the overall reduction in mortality since 1984.

In contrast, Deng et al[9] were unimpressed by the effect of bromocriptine on patients in their series. Moreover, Rosebush et al,[36] in an open, nonrandomized study, found that eight patients who received either dantrolene, bromocriptine, or both drugs had a significantly longer duration of symptoms and a higher rate of complications and morbidity (75%) compared to the duration and sequelae in supportively treated patients. However, patients receiving drug therapy also had a higher incidence of underlying medical illnesses.

Dopamine Agonists

Dopamine agonists are presumed to act by reversing D_2 dopamine receptor blockade due to neuroleptics. Bromocriptine, a direct dopamine receptor agonist, is given by mouth or nasogastric tube in divided doses ranging from 7.5 to 60 mg daily. Side effects, including nausea, hypotension, and delirium require careful monitoring, as does exacerbation of the underlying psychotic illness and recrudescence of NMS symptoms if the drug is discontinued prematurely. Rosenberg and Green[37] reported that bromocriptine significantly shortened the time to recovery compared to supportive treatment alone. Sakkas et al[38, 39] found that bromocriptine significantly reduced mortality from 21% to 10.1% when combined with other drugs, and to 7.8% when used alone. In the Japanese survey, 81.8% of patients had a positive response to bromocriptine.[47, 48] Similarly, Sakkas et al[38, 39] found that amantadine significantly reduced the death rate to less than 6% when used alone or with other drugs. Although few NMS patients have received levodopa, it was effective in about half of the reported cases. Overall, dopamine agonists were reported to significantly reduce mortality from 21 to 9.2%.[38, 39]

Dantrolene

Dantrolene is a hydantoin derivative used as a muscle relaxant in treating spasticity and malignant hyperthermia of anesthesia. It acts by inhibiting the excitation–contraction mechanism in skeletal muscle through the sequestration of calcium in the sarcoplasmic reticulum. Dantrolene has been administered to NMS patients to reduce rigidity, muscle metabolism, and heat generation. It is available in an oral and parenteral form. Initial intravenous doses of 1 to 2 mg/kg body weight are recommended for malignant hyperthermia, and up to 10 mg/kg daily may be required in four divided doses. Once temperature control and relaxation have been achieved, an oral dose can be substituted. The major side effect is hepatotoxicity at high or prolonged doses, although excessive muscle relaxation or cardiorespiratory arrest, when it is combined with calcium channel blockers, may occur. As for the dopamine agonists, Rosenberg and Green[37] and Sakkas et al[38, 39] found comparable and significant effects on recovery time and mortality in NMS patients treated with dantrolene. Yamawaki et al[47, 48] reported positive effects in 74.5% of cases treated in Japan.

It is intuitively appealing to combine dopamine agonists and dantrolene to treat neuroleptic effects on both central neuroregulation and peripheral hypermetabolic processes in skeletal muscle. Although this has been tried in numerous cases, Sakkas et al[38, 39] were unable to demonstrate any significant advantage of the combination over either drug alone.

Miscellaneous Pharmacotherapy

Other drugs to consider include benzodiazepines, which may be useful in controlling agitation or reversing catatonia although enduring responses have not been achieved.[23] Anticholinergics do not appear to either prevent or reverse the syndrome, and may contribute to hyperthermia and delirium. Other drugs found to be effective in isolated reports include lisuride, nitroprusside, other muscle relaxants, and calcium channel blockers.[23]

To summarize, use of dopamine agonists or dantrolene or both appears promising based on anecdotal evidence, and further investigation is certainly warranted. However, the lack of prospective, controlled data using standardized dosing protocols and the self-limited course of NMS make it difficult to evaluate the relative efficacy of pharmacotherapy in NMS compared to supportive treatment alone. It may be more practical to develop guidelines for use based on relative indications that consider severity of symptoms; the age, stamina, and health of the affected patient; involvement of long-acting neuroleptics; and the duration or failure to progress of symptoms.

Electroconvulsive Therapy

Despite the lack of controlled trials, data from studies of lethal catatonia suggest a life-saving effect of electroconvulsive therapy when administered early in the course of this disorder.[27, 28] Because of similarities between lethal catatonia and NMS, electroconvulsive therapy has also been used in NMS patients. In reviewing the literature, Mann et al[27] found 27 cases of NMS treated with electroconvulsive therapy, with 20 patients (74%) responding favorably. Davis et al[7] reported favorable responses to electroconvulsive therapy in 24 of 29 (83%) cases reported in the literature. The five nonresponders received concomitant neuroleptic treatment. Davis et al also showed that mortality of electroconvulsive therapy–treated NMS patients was reduced, albeit not to a statistically significant degree, to 10.3% from 21% in a control group. Davis et al showed that the majority of patients who received electroconvulsive therapy during or after resolution of NMS also showed improvement in their underlying psychiatric disorders.

Although Davis et al underscore the efficacy and safety of electroconvulsive therapy, provided neuroleptics are discontinued, the occurrence of two cases of atrial arrhythmias and one case of cardiac arrest and the development of ventricular fibrillation in another NMS patient during electroconvulsive therapy suggests closer scrutiny of this usually well-tolerated procedure. In the context of NMS, patients may be at greater risk for cardiac arrythmias during electroconvulsive therapy.

It may be premature to draw firm conclusions on the relative indications and safety of electroconvulsive therapy in NMS versus pharmacotherapy or supportive therapy alone. In diagnostically ambiguous cases where lethal catatonia may play a role, in NMS cases that fail to respond to supportive or pharmacologic therapy, and certainly for psychiatric illness in patients recovered from NMS, electroconvulsive therapy may be a viable treatment alternative.

Rechallenge and Recurrence

After recovery from NMS, patients may require treatment with neuroleptics for the re-emergence of psychotic disorders. In reviewing the literature, Shalev and Munitz[41] found recurrence of NMS with two fatalities in 50% of 24 patients rechallenged with neuroleptics. They recommended use of low potency drugs, because the recurrence rate dropped to 10% in cases treated with thioridazine. Similarly, Caroff and Mann[4] reported recurrence in 14 of 47 cases (30%), dropping to 15% when low-potency drugs were used. More recently, Gelenberg et al[12] treated six patients who had NMS previously, four of whom received thioridazine without recurrence, although one patient developed elevated temperature and creatine phosphokinase elevations when briefly treated with the more potent drug, loxapine.

Wells et al[45] reported that recurrence of symptoms doubled when neuroleptics were reintroduced within 5 days of recovery. Susman and Addonizio[43] found that 15 of 35 patients (43%) experienced recurrence. They noted that retreatment before 2 weeks elapsed after recovery increased the risk of recurrence. However, three of their own patients developed recurrences as late as 7 to 24 months after the initial episode. Rosebush et al[35] reported neuroleptic rechallenge in 15 patients over a 6-year period and found that 13 (87%) were eventually able to take neuroleptics safely. However, on initial rechallenge 5 of the 15 patients (33%) experienced partial or complete recurrence of NMS. Rosebush et al also found a significant effect of time from recovery but failed to demonstrate a clear relationship between recurrence and drug potency or dosage. However, the numbers of patients in these studies may be too small to separate parameters of drug use from the time of administration and other variables.

Pope et al[32] found only one possible recurrent episode of NMS during 16 years of subsequent neuroleptic exposure and 71 years of previous exposure in 20 patients studied after a single episode of NMS, and concluded that individual predisposition contributed only modestly to the risk of recurrence compared to state-related cofactors that remain unclear. However, compared to the risk of NMS in all neuroleptic treated patients (0.2% or less), the risk of recurrence, roughly 30% in some studies, suggests that certain patients may be inherently susceptible. The majority of patients can be safely treated with neuroleptics after NMS, provided certain guidelines to reduce the risk are followed. Previous episodes of NMS should be thoroughly reviewed for accuracy of diagnosis. After recovery, the indications for treatment with neuroleptics should be assessed and documented. Alternative treatments should be considered. Informed consent from the patient and family is advisable. Potential risk factors, such as dehydration, agitation, and concomitant medical illness should be minimized. At least 2 weeks should elapse after complete recovery from NMS before neuroleptics are administered. Although data on neuroleptic potency are inconclusive, gradual titration of low doses of low potency drugs may be safest. Patients should be monitored in the hospital for incipient signs of NMS. Some authors have advocated prophylactic treatment with dantrolene or dopamine agonists, although there is no evidence that this offers advantages over conservative management. Development of newer antipsychotics, such as clozapine, may offer even safer alternatives.

PATHOGENESIS

There are several lines of evidence providing support for the involvement of dopamine in the pathogenesis of NMS.[23, 29] All neuroleptics implicated in

NMS share the property of D_2 dopamine receptor antagonism. Although it has been difficult to conclusively demonstrate a correlation between NMS and drug dosage or potency, evidence from studies of incidence,[12, 21] rate and route of drug administration,[19] and recurrences[4, 35] support a positive correlation. Other drugs such as metoclopramide and amoxapine that are dopamine antagonists but not used as antipsychotics have been known to cause NMS. Most importantly, patients treated with dopamine agonists for idiopathic Parkinson's disease have developed NMS-like states when drugs were withdrawn or lost effectiveness. Finally, dopamine agonists appear to be effective in treating NMS and may contribute to recrudescence of symptoms if withdrawn prematurely.[38, 39]

Mann et al[23, 29] reviewed anatomic correlates of NMS. Neuroleptic malignant syndrome–like disorders have been reported in patients with lesions involving the anterior cingulate gyri, the mamillary bodies, periventricular nuclei in the hypothalamus, or brain stem areas, perhaps as a result of interruption of dopaminergic tracts passing through these regions. Recent evidence increasingly suggests a role for dopamine in heat-loss pathways involving hypothalamic neurons that project to the medial anterior hypothalamic preoptic area, the central thermoregulatory site. Similarly, Mann et al have suggested that dysfunction of dopamine in the nigrostriatal tract, mesocortical pathway, and hypothalamic nuclei could give rise to the rigidity, mental status changes, hyperthermia and autonomic dysfunction characteristic of NMS.

There are scattered, inconclusive data on neuroanatomic or neurochemical findings in patients with NMS. Postmortem findings have not revealed specific or consistent patterns of neuropathology in the brains of NMS patients. Autopsy findings have included cerebellar degeneration,[22, 25] necrosis of hypothalamic nuclei,[17] cell loss in the nucleus basalis (in lethal catatonia treated with neuroleptics),[22] ischemic/anoxic changes,[40] or no changes at all.[19] Kish et al[22] found normal levels of hypothalamic and striatal dopamine and D_2 dopamine receptor binding in the brains of three patients with fatal hyperthermic syndromes, but noted that the reduced level of homovanillic acid in two of the patients suggested reduced capacity of the dopamine system to compensate for stress or neuroleptic-induced receptor blockade. In this study, a profound reduction in choline acetyltransferase in the cortex and limbic system was found, in addition to marked reduction in hypothalamic noradrenaline, prompting Kish et al to speculate that striatal dopamine dysfunction and cholinergic hypoactivity predispose to NMS, whereas noradrenaline depletion may result secondarily from stress and hyperthermia. Gertz and Schmidt[14] suggested dopamine hypoactivity in one case of NMS in which they noted a striking loss of melanin as a breakdown product in the substantia nigra. Finally, DeReuck et al[10] performed positron emission tomography in three NMS patients and found increased metabolism in the striatum, cerebellum, and occipital cortex in two patients, which they interpreted as implicating neurotransmitter systems in addition to dopamine in the pathogenesis of the syndrome.

Consistent with the findings of Kish et al,[22] Nisijima and Ishiguro[30] found significant reductions in homovanillic acid in the cerebrospinal fluid of eight patients with NMS as compared with controls. This reduction persisted after recovery and was also associated with a persistent reduction in 5-hydroxyindoleacetic acid, a metabolite of serotonin, leading the authors to propose that decreased metabolism of dopamine and serotonin may be involved in the pathogenesis of NMS. Metabolites of noradrenaline were elevated and attributed to stress and sympathetic arousal. Several other reports of neurotransmitter metabolites in NMS patients have not yielded consistent patterns, with the

effect of psychotropic drug treatment and the patients' underlying psychiatric status representing major confounding variables.[23]

The view that NMS results from dopamine blockade may be simplistic, as it fails to account for the rare occurrence of the syndrome and its unpredictable onset even in patients with previous episodes. Obviously, other cofactors are necessary to trigger an episode.[5, 23, 29] Cofactors may include the physiologic state, underlying psychiatric illness, or genetic factors that increase vulnerability by altering baseline function of dopamine, dopamine receptors, or postsynaptic second messenger systems. Alternatively, reports of NMS-like episodes in animal models and patients on serotonin-enhancing drugs suggest that the balance between dopamine and serotonin, or other neurotransmitters, may be critical in the onset of hyperthermic reactions.

One or a combination of several peripheral cofactors may be important as well. For example, dehydration, exhaustion, medical illness, or hot weather may impair thermoregulation. Direct neuroleptic effects on neuromuscular function and calcium homeostasis in skeletal muscle may also increase susceptibility to hypermetabolism in NMS.[6]

Further investigations of pathogenesis may be impeded by the difficulties inherent in designing controlled experiments of patients with NMS. The development of relevant animal models or in vitro pharmacologic studies may be helpful. In this regard, the successful use of animal models in the study of malignant hyperthermia and reports of an NMS- and malignant hyperthermia–like hypermetabolic stress syndrome in several mammalian species may be instructive.[5, 6, 23]

SUMMARY

Neuroleptic malignant syndrome is a rare but potentially fatal reaction associated with neuroleptic drugs. It occurs in about 0.2% of patients treated with neuroleptics. Risk factors include previous episodes, dehydration, agitation, and the rate and route of neuroleptic administration. Although NMS has been reported in patients with diverse psychiatric diagnoses, as well as in normal subjects, patients with organic brain disorders or mood disorders, particularly when receiving lithium, may be at increased risk.

Standardized criteria for the diagnosis of NMS have been developed and emphasize the classic findings of hyperthermia, muscle rigidity, mental status changes, and autonomic dysfunction. The syndrome lasts 7 to 10 days in uncomplicated cases receiving oral neuroleptics. Treatment consists primarily of early recognition, discontinuation of triggering drugs, management of fluid balance, temperature reduction, and monitoring for complications. Use of dopamine agonists or dantrolene or both should be considered and may be indicated in more severe, prolonged, or refractory cases. Electroconvulsive therapy has been used successfully in some cases and is particularly useful in the post-NMS patient. As a result of these measures, mortality from NMS has declined in recent years although fatalities still occur. Neuroleptics may be safely reintroduced in the management of the majority of patients recovered from an NMS episode, although a significant risk of recurrence does exist, dependent in part on time elapsed since recovery and dose or potency of neuroleptics used.

Data drawn from clinical observations and basic studies support the primary role of an acute reduction in brain dopamine activity in the development of NMS. Additional studies of facilitating cofactors may lead to innovative risk-reduction strategies and the development of safer neuroleptic drugs.

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