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The presentation of the patient with altered mentation and muscular irritability represents a significant challenge to the emergency physician. Urgent, therapeutic decisions must be made as the patient is being resuscitated and general supportive therapy is administered. The differential diagnosis should prompt consideration of a number of potentially lethal illnesses, including neuroleptic malignant syndrome, malignant hyperthermia, lethal catatonia, heatstroke, thyroid storm, serotonin syndrome, dystonias, various ingestions, substance withdrawal states, central nervous system infection or hemorrhage, tetanus, rabies, hypoglycemia, and hypocalcemia. (See Table 1.) Early resuscitation is guided by the patient's condition in the emergency department (ED), whereas additional therapeutic measures require a more definitive diagnosis. For example, the patient with fever, altered mental status, and muscular rigidity who presents in the summer season during periods of high ambient temperature may be experiencing CNS infection, heatstroke, or neuroleptic malignant syndrome. Although body cooling is necessary, each condition will require additional therapy or diagnostic evaluation. These may include antibiotic administration, antipyretic agents, serum electrolytes and glucose levels, or cranial computed tomography. The purpose of this two-part series is to help ED physicians identify the range of clinical syndromes associated with altered mental status and muscular rigidity. Approaches to diagnosis and management strategies are highlighted.

—The Editor

Life-Threatening Syndromes Presenting with Altered Mentation and Muscular Rigidity

Part I: Neuroleptic Malignant Syndrome, Hyperthermia, Thyrotoxicosis, and Malignant Catatonia

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Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), a disease process that typically presents in patients on neuroleptic medication, is characterized by altered mental status, muscular rigidity, hyperpyrexia, and autonomic instability. The pathogenesis is as yet unknown, but may involve reduced dopaminergic activity in the central nervous system (CNS).[1] Laboratory findings suggestive of the diagnosis include leukocytosis, electrolyte abnormalities, and, perhaps most importantly, increased serum creatinine phosphokinase (CPK). NMS is a clinical diagnosis supported by the finding of fever and muscle rigidity in a person exposed to neuroleptics or other dopamine antagonists. Treatment of NMS is largely supportive, although several medications may

halt the progression of the illness, thereby limiting morbidity and mortality.

General Features. The incidence of NMS ranges from 0.5% to 1.0% of all patients exposed to neuroleptic agents;[1,2] the actual incidence of NMS depends upon which set of diagnostic criteria is used for diagnosis.[3] Men are affected twice as often as women, with a mean age of 40 years at syndrome onset. NMS, however, may affect people of any age, from the young child to the extreme elderly. The syndrome is generally precipitated by exposure to dopamine antagonist agents, most commonly antipsychotic medications, including butyrophenones, phenothiazines, and thioxanthenes.[1,2,4] It should be stressed, however, that patients who have received dopamine antagonists—among them, antiemetics, sedatives, or analgesics—also may develop NMS. Moreover, patients with idiopathic parkinsonism who undergo either a rapid reduction in or cessation of their dopaminergic therapy may develop NMS.[1,5]

With respect to risk factors, neither the dosage of neuroleptic medication used nor the duration of therapy appear to be important. Specific agents, however, are associated with a higher risk. For example, neuroleptic agents with more potent dopamine antagonistic properties are encountered more often in the NMS patient and, therefore, they are felt to increase the risk of inducing the illness. In addition, depot forms of these drugs seem to increase the risk of developing NMS, as compared to oral or parenteral forms. Other factors also appear to impart additional risk toward syndrome development, including Japanese heritage, dehydration, malnutrition, weight loss of greater than 1 kg per week, physical exhaustion, lithium therapy, organic brain disease, and periods of intense psychomotor excitement.[6]

Pathogenesis. While the exact pathogenesis of NMS remains unclear, it is suspected that reduced dopaminergic activity in the CNS plays a major role.[1,4] The role of dopamine in NMS is supported by the following observations: 1) NMS occurs when either dopamine antagonists are administered or when dopamine agonists are suddenly withdrawn; and 2) NMS responds to replacement therapy with L-dopa treatment.[1] Dopamine is involved in the control of body temperature, both centrally and peripherally at the muscular level. Neuroleptic agents block dopaminergic receptors in the hypothalamus; such receptor antagonism may produce elevations in body temperature and, if unchecked, may produce hyperthermia. Acute dopamine depletion also may lead to development of extrapyramidal symptoms, including muscular rigidity, which can contribute to increased heat production and further heat stress. Dopamine depletion may also increase body temperature as a result of interactions at the corpus striatum and spinal cord structures, producing muscle contraction, vasomotor abnormalities, and sympathetic discharge, additional features that exacerbate the body's "heat burden."

Clinical Course. NMS usually develops rapidly over 24-72 hours.[2,5] Symptoms typically begin with mental status changes, followed sequentially by muscular rigidity, hyperthermia, and autonomic dysfunction. *(See part A of Table 2.)* One large study reviewing 340 clinical reports of NMS in the literature identified this progression of symptoms in a majority of cases (70% of patients).[7] The mental status is almost always impaired and ranges from agitation and rage to stupor and coma. Muscular findings are described as "lead pipe" rigidity, similar to that seen in patients with severe Parkinson's disease. Muscular rigidity in that region of the thorax may lead to constrictive hypoventilation requiring ventilatory support. In some cases, pronounced muscle contraction may produce rhabdomyolysis with myoglobinuria, leading to acute renal failure. Other motor abnormalities include akinesia, cogwheeling, fluctuating tremors, and involuntary movements.[8] Fever as high as 41°C generally follows onset of muscular findings. Autonomic changes are manifested by alterations in blood pressure and heart rate. Dehydration, which most often is secondary to the patient's increased metabolic demand, coupled with a reduction in oral intake, is frequently present and clinically significant. Babinski's sign, seizures, opisthotonos, trismus, and oculogyric crisis may be seen in some patients. One retrospective study of 34 patients suggested that patients with NMS had an

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increased incidence of dehydration, cogwheeling, disorientation, drooling, dysphagia, and diastolic blood hypertension compared to non-NMS patients with altered mentation and muscular rigidity.[8]

Diagnostic Evaluation. Although most laboratory studies are either normal or nonspecific, several investigations may assist in establishing the diagnosis of NMS. Serum levels of muscle enzymes, especially CPK, are often elevated and result from myonecrosis associated with sustained muscle contractions.[2] At least one study, however, has suggested that CPK elevation in febrile, neuroleptic-treated patients is a non-specific finding; its presence in this setting as a diagnostic criterion may lead to an over diagnosis of NMS.[9] Other enzyme elevations—transaminases, alkaline phosphatase, and lactate dehydrogenase—may also be present. Electrolyte abnormalities generally will reflect underlying complications of the syndrome, including rhabdomyolysis, dehydration, and acute renal failure. Hypocalcemia, hyperkalemia, and hyperphosphotemia are also common findings. Analysis of the cerebrospinal fluid (CSF), as well as the results of the CT and EEG, are often normal or nonspecifically abnormal; these studies assist in ruling out life-threatening syndromes with similar presentations. It is important to realize that the aforementioned laboratory abnormalities are not universally present in NMS patients and that they are not diagnostic in and of themselves.[8]

A number of diagnostic criteria for NMS have been proposed. The most widely accepted (Levenson) diagnostic criteria include major and minor features. Major criteria include fever, muscular rigidity, and elevated CPK. Minor criteria include tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis. This scheme suggests that the presence of all three major criteria indicates a high probability of NMS; alternatively, two major criteria and four minor criteria also are predictive of the diagnosis.[10] *(See part B of Table 2).* Although additional criteria have been proposed by other investigators,[11,12] these do not produce a significant increase in diagnostic accuracy. One study noted that the application of these three different sets of criteria to 64 possible NMS episodes produced markedly different rates of syndrome diagnosis.[13] Some experts argue that NMS is a syndrome of parkinsonism and hyperpyrexia, and propose that the only clinical features that are absolutely necessary for diagnosis are rigidity and fever in a patient who has received dopamine antagonists.[1] As mentioned, NMS may be complicated by rhabdomyolysis, which leads to acute renal failure. Other complications include intravascular thrombosis and pulmonary embolism, cardiovascular collapse, arrhythmia, myocardial infarction, aspiration with pneumonia, and acute respiratory failure.

Treatment. Treatment of NMS principally involves supportive measures coupled with simultaneous removal of the offending agent. *(See Table 3.)* In the ED, rapid temperature reduction with the application of aerosolized tepid water/fanning method is recommended. Intravenous fluid hydration and ventilatory support may also be required. All neuroleptic agents should be discontinued. The patient should be admitted to an intensive care unit (ICU) and managed with a multidisciplinary team approach. Other causes of fever and rigidity, especially CNS hemorrhagic and infectious etiologies, should be ruled out. In particular, bacterial meningitis should be suspected and empirically treated while the CT scan of the brain rules out CNS bleed. Treatment of patients with rhabdomyolysis begins with isotonic fluid administration. Saline (0.9%) loading by intravenous route is the mainstay of therapy in that it restores intravascular volume and induces a solute diuresis. All patients should have a urinary catheter to adequately monitor fluid output. Diuresis, which may convert oliguric to non-oliguric acute renal failure, can be accomplished using an osmotic agent (mannitol) or a loop diuretic (furosemide). Sodium bicarbonate may protect the kidneys from the effects of myoglobinuria by rapidly increasing urinary pH, provided that the development of frank metabolic alkalosis is avoided. The use of sodium bicarbonate is based on the theoretical advantage of inhibiting the formation of the nephrotoxin ferrihemate. Hyperkalemia is treated in the usual manner, with infusion of insulin, glucose, and calcium gluconate, inhalation of a nebulized beta-agonist agent, administration of oral and rectal exchange resins, electrocardiographic monitoring, and elimination of potassium intake. Dialysis may be required to correct electrolyte abnormalities or to treat oliguric renal failure.

A number of pharmacotherapeutic approaches have been used to treat patients with NMS. Dantrolene, which has been very successful in treating malignant hyperthermia, has been effective for shortening the duration of illness.[14] Dosages range from 0.8 to 3.0 mg/kg IVq 6 h to 10 mg/kg/d. Certain authorities recommend initial bolus doses of 2 mg/kg IV be repeated twice to reduce muscular spasm. It is important to note that dantrolene is hepatotoxic at levels above 10 mg/kg/d. Accordingly, patients should be started at lower drug dosages, then gradually advanced as needed. Dantrolene appears to offer the most benefit in patients with pronounced muscular rigidity. The second most widely used agent in NMS, bromocriptine mesylate, is a dopamine agonist that has been administered alone, or in combination with dantrolene.

Table 1. Syndromes Presenting with Altered Mentation and Muscular Rigidity—The Differential Diagnosis of a Life-Threatening Presentation

Neuroleptic malignant syndrome
Malignant hyperthermia
Lethal catatonia
Heatstroke
Thyroid storm
Serotonin syndrome
Dystonias
Various ingestions (anticholinergic/sympathomimetic)
Withdrawal states (ethanol)
Central nervous system infection/hemorrhage
Tetanus
Rabies
Hypoglycemia
Hypocalcemia

Table 2. Findings and Diagnostic Criteria in the Patient with Neuroleptic Malignant Syndrome[10]

A. Mental status changes
Muscular rigidity
Hyperthermia
Autonomic dysfunction
Elevations in CPK
Leukocytosis

B. Major criteria* — fever, muscular rigidity, elevated CPK
Minor criteria* — tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, leukocytosis

* Presence of all three major criteria, or the combination of two major criteria and four minor criteria also reliably suggests the diagnosis.[10]

Table 3. Treatment of Neuroleptic Malignant Syndrome

DANTROLENE	
Initial dose	Mild—25-75 mg po Moderate to severe—1.0 mg/kg IV
Repeat dose	Mild—25-75 mg po tid Moderate-to-severe—1.0 mg/kg IV every 3-5 minutes PRN to maximum
End points	Complete resolution of muscular rigidity or total dose 10 mg/kg/24 h Therapy for 3-5 days after complete relief of symptoms
BROMOCRIPTINE	
Initial dose	2.5-10 mg po (or NG tube)
Repeat dose	2.5-10 mg po tid
End points	Complete resolution of muscular rigidity then for 3-5 days
LORAZEPAM OR ALTERNATIVE BENZODIAZEPINE	
Initial dose	2 mg IV
Repeat dose	1-2 mg IV PRN
End points	Signs of clinical toxicity Relief of symptoms
INTRAVENOUS FLUID (0.9% SALINE) WITH SODIUM BICARBONATE TO MAINTAIN ADEQUATE URINE OUTPUT	
COOLING MEASURES AS APPROPRIATE	
DISCONTINUE EXPOSURE TO PRECIPITATING AGENT(S)	

Dosage ranges from 2.5 to 7.5 mg po (or via nasogastric tube) q 8 h. Other dopamine agonists have also been used to treat patients with NMS, including amantadine, levodopa, and carbidopa-levodopa. Some authors have suggested using anticholinergic and antihistaminic agents as the first line of therapy in patients with a fever of less than 38.5°C. Other recommended drugs include benztropine (2-8 mg/d), trihexyphenidyl (2-10 mg/d), and diphenhydramine (50-250 mg/d).[14,15]

The most prudent and targeted approach to therapeutic decisions in the NMS patient centers on treatment linked to the patient's major clinical problem(s). For example, a patient with pronounced hyperthermia may fare better with bromocriptine or another centrally acting agent, while a patient who presents with significant muscle rigidity may be more appropriately treated with a non-specific muscle relaxant such as dantrolene. Combination therapy may be necessary in refractory or difficult cases.[4]

Malignant Hyperthermia

Malignant hyperthermia (MH) is a medical emergency. This disease of the skeletal muscle is precipitated by exposure to inhalational anesthetic agents (halothane) or depolarizing muscle relaxants (succinylcholine). The disorder, which was initially described in 1960, is characterized by abrupt onset of muscular rigidity, hyperthermia, altered mentation, metabolic acidosis, hypermetabolism, and rhabdomyolysis; these findings appear soon after administration of the triggering agent(s). Within the ED setting, MH may be encountered if the patient develops MH after administration of succinylcholine in the setting of rapid sequence-aided endotracheal intubation. Alternatively, the patient may develop the initial syndrome in the outpatient surgical suite and require transfer to the ED for stabilization, additional therapy, and diagnostic evaluation. MH is rare, occurring in only 0.001-1.0% of patients exposed to anesthesia; however, the disorder is more common in younger patients, with approximately one-half of all cases appearing before age 15.

Risk for developing MH is associated with an autosomal dominant trait.[16] The mortality is approximately 10%; recent developments in the therapy, as well as increased physician awareness of the entity and at-risk patient identification, have reduced the death rate markedly over the past two decades. Patients who acquire MH frequently are found to have had a subclinical myopathy prior to exposure to the triggering medication; the often dramatic appearance of MH during a medical procedure is usually the initial manifestation of the underlying skeletal muscle abnormality. Unfortunately, severe forms of the disorder are encountered in patients even after minimally invasive procedures—an event which may initially confuse the health care team. The risk of developing MH appears to be greater for the depolarizing muscle relaxants compared to the volatile anesthetic gases.[16] Other risk factors that increase a patient's chance of developing MH include: 1) history of an MH episode during surgery; 2) first-degree relative on a patient with MH; 3) non-first-degree relative family member of a larger clan with multiple episodes of MH; 4) history of neuromuscular disease, such as Duchenne muscular dystrophy; 5) high basal serum CPK level; and 6) a history of NMS or heatstroke.[17,18] An objective test, the caffeine-halothane contracture test, which is not appropriate for either the ED or the emergent airway control situation, will confirm functional susceptibility to the muscular abnormality.

Presentation. The pathophysiology of MH is reasonably

Table 4. Findings in the Patient with Malignant Hyperthermia

Muscular rigidity
Hyperthermia
Altered mentation
Metabolic acidosis
Hypermetabolism
Elevated CPK with rhabdomyolysis
Abrupt onset with rapid progression

Table 5. Treatment of Malignant Hyperthermia[19]

- Discontinue exposure to precipitating agent(s)
- Dantrolene administration, bolus doses of 2 mg/kg IV up to maximum of 10 mg/kg/24 h
- Saline infusions with sodium bicarbonate to maintain adequate urine output
- Surveillance for/management of cardiac arrhythmia (avoid calcium antagonist agents)
- Cooling measures as appropriate
- Management of hyperkalemia in standard fashion with unexpected cardiac arrest in children managed with such therapy

well understood, at least at the genetic and cellular levels. Genetically, the tendency for development of the disease is passed via an autosomal dominant gene; the pattern of inheritance is characterized by both variable expression and incomplete penetrance. Consequently, at-risk patients may never manifest the disorder despite numerous anesthetic exposures, while other patients develop the illness either at the initial administration or only after multiple applications. On the cellular level, exposure to a triggering agent causes a rapid accumulation of calcium within the cytoplasm of skeletal muscle. An increased intracellular calcium concentration results in muscular contraction which, if sustained, leads to excessive heat production and cellular dysfunction. Cellular dysfunction ultimately produces a depletion of intracellular high-energy phosphate compounds, culminating in myocyte death and rhabdomyolysis. The release of intracellular contents, including calcium, only hastens the process for adjacent, viable myocytes.

Acute MH occurs soon after administration of the precipitating agent; less often, it occurs during the procedure or in the post-anesthesia care unit. Some individuals will experience a recurrence of the syndrome within 48 hours after initial therapy reverses the process; the recurrent form is usually less severe. Early signs which foretell development of MH include masseter muscle spasm and a rise in the end-tidal carbon dioxide after succinylcholine infusion. The clinical characteristics of MH include sudden onset of muscular contraction coupled with a rapid development of hyperthermia, tachycardia, altered mentation (if the patient's alertness is not already altered by the administered medications), and cyanosis. *(See Table 4.)* The temperature elevation is usually impressive, both in terms of absolute magnitude and the rate of development; patients with a core temperature of 105°F commonly are encountered. The muscular rigidity is usually diffuse, affecting all muscle skeletal groups. Tachycardia, usually a "reactive" sinus tachycardia, is seen; on occasion, malignant ventricular arrhythmia will be encountered. Laboratory abnormalities seen in MH include elevated CPK values with myoglobinuria, metabolic acidosis, hyperkalemia, and hypoxemia.

Management. Treatment of MH requires rapid recognition of the syndrome. In the ED environment, sudden development of muscular rigidity and hyperthermia in a patient recently intubated should suggest the diagnosis. The antidote for MH is dantrolene, administered in dosages similar to those used in the patient with NMS. The Malignant Hyperthermia Association of the United States has published set treatment recommendations.[19] These include, but are not limited to, the following maneuvers *(See Table 5)*:

- discontinue exposure to precipitating agent(s);
- dantrolene administration—bolus doses of 2 mg/kg IV up to a 24 hour maximum of 10 mg/kg/24 h;
- saline infusions with sodium bicarbonate to maintain an adequate urine output;
- surveillance for/management of cardiac arrhythmia (avoid calcium antagonist agents);
- cooling measures as appropriate; and
- management of hyperkalemia in standard fashion with unexpected cardiac arrest in children managed with such therapy.

Patients should be admitted to the hospital, and initially managed in a critical care setting for continued therapy and/or observation.

The emergency physician should avoid use of depolarizing muscle relaxants (i.e., succinylcholine) in patients with known or suspected risk factors; in these patients, nondepolarizing agents represent safer alternatives, although MH has been anecdotally reported after their use. Agents such as vecuronium or pancuronium are acceptable. Other medications that are considered safe for use in the patient with known past MH or who is at risk for the illness include etomidate, propofol, opiates, barbiturates, and benzodiazepines.

Malignant (Lethal) Catatonia

Malignant catatonia (MC) is a syndrome that includes motor abnormalities, psychosocial withdrawal or excitement, and bizarre repetitive behaviors. This neuropsychiatric disorder occurs when hyperthermia or autonomic instability develops in the setting of catatonia, and can be life-threatening. MC develops twice as often in females as males, with an average age at onset of 33 years (recall that NMS occurs more frequently in middle-aged men). MC can occur at almost any age, and the mortality rate can be as high as 60%.[20]

This syndrome has multiple etiologies, including medical, psychiatric, and medication-related events. Unlike NMS, it can and often does develop in patients with psychiatric disorders who have *not* been managed with anti-psychotic agents. MC arises in the setting of psychiatric disease in approximately 88% of cases. Schizophrenia is the most common associated psychiatric disease, occurring in 117 of 256 cases of MC that

Table 6. Findings in the Patient with Lethal (Malignant) Catatonia

Prodromal phase—Labile mood, anorexia, insomnia
Mental status change—Lethargy to coma
Muscular rigidity
Hyperthermia
Unrelenting motor agitation
Disorganized thought process
Pressured speech
Hallucinations (auditory/visual)
Delusions
Stuporous exhaustion
Cardiovascular collapse
Rhabdomyolysis

were felt to be associated with a psychiatric condition. MC may also more commonly be seen in patients with affective disorders; however, the incidences of MC in these patients is not known. In approximately one-third of cases, no specific psychiatric diagnosis can be established.[20] MC can also occur in the setting of other medical conditions, including infections, metabolic disorders, and neurological syndromes. In one review, 12% were associated with an organic illness.[20] Most common among these are infections, including viral encephalitis and bacterial septicemia. Toxic and metabolic disorders, such as uremia and hyperthyroidism, also are associated with the development of MC.[20]

Clinical Presentation. The pathogenesis of MC has not been precisely characterized. Multiple neurochemical changes have been demonstrated in the CNS of patients who have succumbed to MC-related complications. The diencephalon appears to be a major site of disease involvement while dopamine antagonism or depletion plays a major pathophysiologic role.[20-22] Dopamine plays a dual role in mediating temperature control in the hypothalamus—by aiding in core temperature reduction as well as by interacting with serotonergic receptors to control hyperthermia.[21] Disordered dopaminergic transmission in a major hypothalamic heat loss pathway may account for the hyperthermia seen in MC.[20] Nigrostriatal inhibition of the GABA-nergic neurons in the thalamo-prefrontal motor pathway is also mediated by dopamine—reduced inhibition of this pathway can lead to muscular rigidity. Moreover, central dopaminergic blockade causes increased sympathetic discharge and recruitment of peripheral dopamine receptors. In the presence of hypodopaminergia, these receptors can produce sympathetic discharge and autonomic instability.

The clinical course of MC frequently begins with a prodromal phase involving labile mood, anorexia, and insomnia, which then progresses to mental status changes and muscular rigidity that usually persist for an average of 2 weeks. *(See Table 6.)* This phase then progresses to unrelenting motor agitation, including bizarre, repetitive behaviors such as mannerisms, stereotypy, and echophenomena; in extreme cases, these manifestations may be associated with unprovoked physical violence and bizarre suicide attempts. Refusal of food or drink, coupled with a clouding of consciousness, is characteristic. The patient's thought process may become disorganized, speech becomes pressured, and hallucinations (auditory/visual) may be accompanied by delusions. Psychosis is a universal finding in all patients and usually is associated with motor signs, including rigidity and waxy flexibility. Psychosocial withdrawal or excitement may be manifested by negativism, mutism, stupor, impulsivity, and combativeness. Autonomic instability is manifested by profuse diaphoresis, tachycardia, bradycardia, and labile blood pressure. Hyperthermia rapidly occurs during this stage, and may reach 43°C.[20,22] This phase may last for a period of hours to weeks, and generally persists for an average of eight days.[20,21]

Subsequently, patients develop a stuporous exhaustion, with simultaneous muscular rigidity and pronounced hyperthermia. If untreated, these patients will then develop coma, cardiovascular collapse, rhabdomyolysis, and death.[20-22] The development of hyperthermia and autonomic instability generally signal the onset of a severe, rapidly progressive deterioration to multisystem organ failure and death. Complications associated with MC are numerous, representing both processes that develop due to the physiologic stress of the illness as well as those events that occur due to MC itself. These complications include, but are not limited to, trauma, rhabdomyolysis, acute renal failure, aspiration pneumonia, acute respiratory failure, adult respiratory distress syndrome, myocardial infarction, arrhythmia, seizure, disseminated intravascular coagulation, deep venous thrombosis, and pulmonary embolism.[20,23,24]

As with NMS, no specific laboratory finding or imaging result will confirm the diagnosis of MC. Many investigations are performed to rule out syndromes with similar presentations and to look for complications noted above. Although most patients will have an elevated CPK at some point in their illness, this abnormality is not present in all patients, and when it is present, it is a non-specific finding. Radiographic imaging, such as CT scanning of the head, may reveal frontal atrophy in some patients, while other individuals will have normal scans.

Management. Successful management of patients with MC depends on early diagnosis and prompt initiation of supportive therapy. In the early stage of MC, patients should be adequately fed, hydrated, and kept mobilized. If MC progresses, patients will generally require parenteral fluid and nutritional support as well as aggressive airway management. The patient should be admitted to ICU. Other causes of fever and altered mental status should be ruled out.

When MC is caused by a reversible organic disorder, the condition should be treated. The physician should be aware of the wide range of potential complications associated with MC and should manage each aggressively. When autonomic instability and/or hyperthermia develop, management should include: discontinuation of any neuroleptic or other drug that may have contributed to development of MC (or reinstituting any DOPA agonist that may have recently been withdrawn); initiating supportive measures to prevent medical complications; and frequent reevaluation of the patient's condition to rule out the development of new medical complications.

Dopamine agonists, most notably bromocriptine and amantadine, and muscle relaxants, including dantrolene and paralyzing agents, have occasionally been used to treat MC associated with psychiatric disorders; these agents are routinely used to treat MC

Table 7. Findings in the Patient with Thyroid Storm

Usual features of hyperthyroidism (exaggerated)—Exophthalmos, widened pulse pressure, goiter
Decompensation of one or more organ systems
Fever
Tachycardia
Diaphoresis
Emotional liability
Altered mentation (agitation, lethargy, obtundation, coma)
Myopathy (proximal muscles)
Arrhythmias
Acute congestive heart failure
Gastrointestinal symptoms (n/v/d, abdominal pain, jaundice)
Liver dysfunction

Table 8. Treatment of Thyroid Storm

INHIBITION OF FURTHER THYROID SYNTHESIS

Propylthiouracil (PTU) 900-1200 mg po followed by 30-60 mg daily for 3-6 weeks; alternative methimazole

BLOCKADE OF RELEASE OF PREFORMED THYROID HORMONE

Potassium iodide 5 drops po every 6 hours or Lugol's solution 30 drops po q d in 4 divided doses (1 hour after starting PTU [or MMI]); alternative lithium carbonate

BLOCKADE OF THE PERIPHERAL THYROID HORMONE EFFECTS (MAINSTAY OF THERAPY)

Beta-adrenergic blocking agents (propranolol 1 mg/min IV with incremental increases of 1 mg every 15 minutes to a total of 10 mg as needed or esmolol infusion titrated to end-organ effect)

SUPPORTIVE CARE

Intravenous fluids
Correction of electrolyte imbalances
Antipyretics and additional cooling measures for hyperthermia
Administration of sedatives with caution (mental status is a useful marker of therapy response)
Treatment of cardiac arrhythmias
Glucocorticoids
Search for and treat the precipitating event

associated with neuroleptic agents. Several studies generated different conclusions about the efficacy of these drugs for this disorder. One investigation reviewed 734 reported cases of MC associated with neuroleptics, and suggested that amantadine, bromocriptine, and dantrolene, when used singly or in combination, produced either improvement, decreased subsequent relapse rates, or both.[25] Another study, however, suggested that when dantrolene and bromocriptine are used to treat MC, they may actually prolong the illness.[26] Benzodiazepines have also been used to treat MC. In one report of 44 cases, a clear benefit was noted in approximately one-third of patients treated with benzodiazepines. In addition, partial or transient benefit was noted in another one-third of the patients.[20,21] In this study, several patients had rapid defervescence and/or stabilization of autonomic instability, while others experienced decreased muscle rigidity or clearing of delirium and willingness to take fluids and solids. In light of the severity of potential medical complications seen in MC, even a partial response to early treatment with benzodiazepines may be life-saving until definitive treatment can be started. Several other medications with anecdotal case report support have been used to treat MC, including calcium channel antagonists, corticosteroids, anticholinergic agents, neuromuscular blocking agents, carbamazepine, and levodopa. All have been reported to be effective in single case reports or small case studies; no large investigations, however, have established the effectiveness of these medicines.[20,21]

While prospective, randomized studies on the use of electroconvulsive therapy (ECT) in treating MC are not available, ECT seems to be the most effective method of treating MC when it occurs in the setting of a functional psychiatric disorder. Favorable effects of ECT may be seen after the first treatment. ECT is only effective, however, if it is initiated *before* severe progression of the MC has occurred. In 19 cases where ECT was begun within five days of the onset of MC, 16 patients survived, while ECT had no effect on 14 patients who were treated after the onset of the illness.[20,21]

Thyrotoxicosis

Thyroid storm is a rare, life threatening exacerbation of the hyperthyroid state, with an incidence of less than 1% and a mortality of 20-30%. Historically, thyroid storm was seen as a complication of thyroid surgery. (These surgical crises have markedly decreased due to preoperative treatment.) Medical thyrotoxic crisis, most often caused by antecedent Graves disease, is now the most frequent cause of thyroid storm. In most cases of thyroid storm, a precipitating event can be identified. These precipitants include infection, surgery, radio iodine therapy, iodinated contrast dyes, withdrawal of antithyroid drug therapy, amiodarone, thyroid hormone ingestion, diabetic ketoacidosis, congestive heart failure, toxemia of pregnancy, severe emotional stress, pulmonary embolism, and cerebral vascular accident. A systematic search for a precipitant is necessary because a precipitant's identification and treatment improve chances of a successful outcome.

The exact pathogenesis of thyroid storm has not been elucidated, although many theories have been proposed. Although it would seem logical that levels of circulating thyroid hormone would be higher than those seen in uncomplicated thyrotoxicosis, values are not significantly different. The rapidity with which thyroid hormone levels rise may be more important than absolute levels. One mechanism for causing a sudden change in hormone levels would be an alteration of the binding proteins. This finding has been noted in patients with systemic nonthyroidal illnesses and may help to explain the wide variety of precipitants to thyroid storm. Another theory, as opposed to a sudden increase in hormone levels, is based upon the development of tissue intolerance to tri-iodothyronine (T3) and thyroxine (T4). This intolerance has been termed "decompensated thyrotoxicosis." The mechanism is unknown, but it would explain decompensation seen in thy-

roid storm in the setting of hormone levels that are similar to those found in uncomplicated thyrotoxicosis. Yet another explanation for the pronounced abnormality seen in the thyroid storm patient involves the adrenergic nervous system. The dramatic response of the thyrotoxic patient to adrenergic blockade has caused speculation regarding the role of adrenergic hyperactivity in thyroid storm. Activation of the adrenergic nervous system accounts for many of the signs and symptoms seen during this illness. Plasma levels of epinephrine and norepinephrine are not increased during thyroid storm, but thyroid hormone does increase the density of beta-adrenergic receptors and decreases the density of alpha-adrenergic receptors. This relative change in adrenergic receptor density has been postulated to increase the sensitivity of some tissues to catecholamines in thyrotoxic patients.

Clinical Presentation. Thyroid storm is a clinical diagnosis, (i.e., no single laboratory investigation will confirm or exclude the diagnosis). Rather, the diagnosis must be based on clinical impression, as there are no pathognomic findings or confirmatory tests. Patients usually have many of the typical features of hyperthyroidism, but they are exaggerated. Exophthalmos, widened pulse pressure, goiter, and a history of thyroid disease are frequently present. In addition, there is evidence of decompensation of one or more organ systems secondary to the severe state of hypermetabolism. The earliest signs are fever, tachycardia, diaphoresis, increased CNS activity, and emotional liability. Core temperatures exceeding 106°F have been reported. Sweating may be profuse, leading to dehydration. CNS disturbances occur in 90% of patients; these symptoms vary from restlessness, agitation, emotional liability, manic behavior, and psychosis to obtundation and coma. *(See Table 7.)*

Thyrotoxic myopathy, with associated weakness of the proximal muscles, can occur. Cardiovascular abnormalities are present in approximately 50% of patients. The pulse pressure is frequently widened, with an increase in systolic blood pressure. Atrial arrhythmias, premature ventricular contractions, and malignant ventricular tachyarrhythmias are common and can be complicated by high output failure. Progression to congestive heart failure, refractory pulmonary edema, circulatory collapse, coma, and death may occur within 72 hours. Gastrointestinal symptoms, including nausea, vomiting and diarrhea, contribute to dehydration. Anorexia and crampy abdominal pain can be mistaken for an acute abdomen. Jaundice, a poor prognostic sign, and hepatomegaly due to passive congestion of the liver or hepatic necrosis have been reported.

Management. Early treatment of thyroid storm based upon the physician's clinical impression is of utmost importance. *(See Table 8.)* Before therapy is started, blood for thyroid hormone assays should be drawn along with other routine laboratories. The three major components of treatment include providing supportive care, correcting the hyperthyroid state and end organ effects of the syndrome, and managing the precipitating event. Dehydration and electrolyte imbalances must be aggressively treated with intravenous fluids. Fever should be controlled with antipyretics and additional cooling measures. Aspirin should be avoided since salicylates decrease protein binding and thus increase free levels of T3 and T4. Caution should be exercised with administration of sedatives because the mental status is a very useful marker of clinical response to therapy. Cardiac arrhythmias should be treated in the usual fashion. Glucocorticoids should be administered for relative adrenal insufficiency. Thyrotoxic patients have accelerated degradation of cortisol and frequently have inappropriately low (i.e., normal) serum cortisol levels in the setting of significant levels of physiologic stress.

Propylthiouracil (PTU) and methimazole (MMI) block synthesis of thyroid hormone by inhibiting organification of tyrosine residues. Onset of action begins within one hour of administration but the maximal effect is not achieved for weeks. Both preparations must be given orally or through a nasogastric tube as there are no parenteral preparations. PTU is preferred over MMI because it inhibits the peripheral conversion of T4 to T3. The initial loading dose of PTU is 900-1200 mg followed by 30-60 mg daily for 3-6 weeks. These drugs inhibit the synthesis of new thyroid hormone but do not affect the release of stored hormone.

Release of preformed thyroid hormone within the gland also must be blocked. Iodide or lithium carbonate (if iodine cannot be used) are administered after inhibition of further thyroid synthesis has been achieved by PTU or MMI. This treatment is usually initiated one hour after the loading dose of PTU or MMI. In large doses, iodide can acutely inhibit hormone synthesis by blocking organification. Without prior treatment using the antithyroid drugs, however, iodide could increase the intrathyroidal hormone stores by providing further substrate for hormone synthesis. Iodide may be orally administered as a saturated solution of potassium iodide, 5 drops every 6 hours, or as Lugol's solution, 30 drops each day in 4 divided doses.

Blockade of peripheral thyroid hormone effects is the mainstay of therapy for thyroid storm. Currently, beta-adrenergic blocking agents are the drugs of choice. Propranolol dramatically reduces sympathetic hyperactivity and also partially blocks the peripheral conversion of T4 to T3. It can be given intravenously at 1 mg/min with incremental increases of 1 mg every 15 minutes to a total of 10 mg. Cardiac and psychomo-

tor improvement should be seen within this time frame. The oral dose of propranolol is 20-120 mg every 4-6 hours and has an onset of action of about one hour. The usual contraindications to propranolol include bronchospastic disease and heart block. Esmolol may be a reasonable alternative in the patient with a relative contraindication to beta-adrenergic blockade. Guanethidine and reserpine were extensively used in the past to provide effective autonomic blockades and are alternatives to beta-adrenergic blockade; these medications deplete catecholamine stores and block their release.

It is important to search for and treat the precipitating event, especially infection. Blood, urine, sputum cultures, and chest radiographs should be obtained. Symptomatic improvement of thyroid storm should occur within a few hours and is primarily the result of adrenergic blockade. Degradation of the circulating thyroid hormones must occur for complete resolution of the active illness. The serum half-life is six days for T4 and 22 hours for T3. The average duration of thyroid storm is three days, but the event may last as long as one week.

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Physician CME Questions

41. Laboratory findings suggestive of the diagnosis of neuroleptic malignant syndrome (NMS) include:
    A. increased serum creatinine phosphokinase.
    B. leukocytosis.

C. electrolyte abnormalities.
D. All of the above.

42. NMS affects men twice as often as women, with a mean age of:
A. 25 years at syndrome onset.
B. 40 years at syndrome onset.
C. 60 years at syndrome onset.
D. None of the above.

43. Factors that appear to give additional risk for NMS development include all of the following *except*:
A. physical exhaustion.
B. lithium therapy.
C. weight gain.
D. dehydration.

44. Laboratory abnormalities seen in malignant hyperthermia (MH) include all of the following *except*:
A. depressed CPK values.
B. hyperkalemia.
C. metabolic acidosis.
D. hypoxemia.

45. Malignant catatonia (MC) occurs in the setting of psychiatric disease:
A. in almost no cases.
B. in about 88% if cases.
C. in 10% of cases.
D. in almost 25% of cases.

46. A universal finding in *all* patients with MC is:
A. hyperthermia.
B. psychosis.
C. depressed CPK.
D. use of anti-psychotic agents.

47. Precipitating events to cases of thyroid storm may include:
A. amiodarone.
B. pulmonary embolism and congestive heart failure.
C. radio iodine therapy.
D. All of the above.

48. Fever caused by thyroid storm should be controlled with:
A. antipyretics.
B. aspirin.
C. cooling measures.
D. Both A and C are correct.

In Future Issues

Altered Mentation and Muscular Rigidity: Part II