Movement Disorders Emergencies

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Abstract

Many acute and potentially life-threatening medical conditions have hyperkinetic or hypokinetic movement disorders as their hallmark. Here we review the clinical phenomenology, and diagnostic principles of neuroleptic malignant syndrome, malignant catatonia, serotonin syndrome, Parkinsonism hyperpyrexia, acute parkinsonism, acute chorea-ballism, drug-induced dystonia, and status dystonicus. In the absence of definitive lab tests and imaging, only a high index of clinical suspicion, awareness of at-risk populations, and variations in clinical presentation can help with diagnosis. We also discuss the principles of management and rationale behind treatment modalities in the light of more recent evidence.

Keywords

- neuroleptic malignant syndrome
- serotonin syndrome
- acute dystonic reaction
- oculogyric crisis
- Parkinsonism hyperpyrexia
- antipsychotics
- tardive dyskinesia
- acute Parkinsonism
- drug-induced dystonia
- malignant catatonia

The neurological subspecialty of "movement disorders" focuses on conditions characterized by excessive movements (hyperkinetic), poverty of movements (hypokinetic), and gait/balance disorders. Most movement disorders are slowly progressive and neurodegenerative in nature. There are, however, many acute and emergent medical conditions in which a movement disorder becomes a predominant (or presenting) feature.

The phenomenology of the movement disorder needs to be put into perspective with other clinical features (such as delirium, dysautonomia, and hypermetabolic states) for better diagnosis and management. The pathophysiology of many of these rare disorders is still unclear, so the presentation of the associated movement disorder can be used to gain insights into which parts of the nervous system are hyperactive or hypoactive, and thus devise management strategies. In this review, we discuss in detail some of these rare but well-reported acute syndromes in emergency neurology with a focus on clinical pattern recognition. ►**Supplementary Fig. 1A–E** (online only) highlights the important movement disorder emergencies presenting with a predominant movement disorder phenomenology.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) was initially described in the 1950s and 1960s as a side effect of phenothiazine antipsychotics, particularly chlorpromazine.[1] Although classically described as a syndrome of delirium, rigidity, high fever, and dysautonomia in the context of exposure to a dopamine antagonist medication, it has been reported in other contexts. More than 10 diagnostic criteria have been proposed since the 1980s with most of the cardinal features retained through the iterations. Identifying at-risk populations and maintaining a high level of clinical suspicion are key in preventing morbidity and mortality. The incidence and mortality rates of NMS have declined over the years, possibly due to improved awareness and newer drugs with more restricted neurotransmitter activity which have influenced prescribing practices.

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Table 1 Drugs associated with neuroleptic malignant syndrome

Drug class	Examples of drugs
Psychiatric	Risperidone, ziprasidone Haloperidol Clozapine, loxapine, quetiapine Chlorpromazine, fluphenazine, thioridazine Thiothixene Olanzapine
Antiemetics	Prochlorperazine, promethazine
Properistaltic	Metoclopramide, domperidone
Antiparkinsonian	Dopamine agonists, Levodopa

Widespread use of first-generation antipsychotics (see ►**Table 1**) may have resulted in higher incidence of NMS (3%) in the past but recent data show incidences of 0.01 to 0.04% among those treated with antipsychotics.[2,3] A higher incidence of NMS has been reported in males of 20 to 50 years of age in the past, but more recent studies suggest a predominance in patients 50 years or older.[4] However, this could reflect increased use of antipsychotics in older individuals especially in delirium and dementia. Generally, it is advisable to consider NMS in all age groups and sexes. Mortality rates have dropped from 25% to approximately 10%.[3,5] Mortality rate is substantially lower for atypical antipsychotics (3.3%) compared with typical antipsychotics (7.3%).[4]

Clinical Presentation

The syndrome typically presents within 4 weeks of exposure to antipsychotics, and constitutes a clinical tetrad of altered mental status, hyperthermia, rigidity, and dysautonomia. Changes in mental state and rigidity of muscles are early features, followed by fevers and dysautonomia; the latter manifests initially as tachycardia followed by labile blood pressures.[6] Although a majority of cases develop within 7 to 10 days, the duration of exposure to the offending drug and its proximity to onset of NMS are variable. Fluctuating alertness with agitation may evolve into mutism, catatonia, and coma. The "extrapyramidal" features (parkinsonism) include "lead-pipe" rigidity, slowness of movements, tremors, and dystonia.[7] Profuse sweating, tachypnea, dysphagia, and incontinence may occur.

Multiple laboratory abnormalities may be found as part of the presentation(see ►**Table 2**). Serum creatine kinase (CK) elevation reflects rhabdomyolysis and is typically >1,000 IU/L but several factors including intramuscular injections, agitation, and physical restraints can raise CK.

Table 2 Laboratory abnormalities in neuroleptic malignant syndrome

Common laboratories	Acute phase reactants
Elevated CK (>90%) Polymorphonuclear leukocytosis (75%) Hypoferremia (95%): acute phase reactant Elevated aldolase, alkaline phosphatase, AST, ALT Hypocalcemia (50%) Hypomagnesemia (60%) Proteinuria and myoglobinuria	Antichymotrypsin: elevated Fibrinogen: elevated ESR and CRP: elevated Interleukin-6: elevated Albumin: decreased

Abbreviations: ALT, alanine aminotranferease; AST, aspartate aminotransferase; CK; creatine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Source: Adapted from Rosebush et al 2008.[84]

Pathophysiology

The exact pathogenesis of NMS is not entirely clear but "central" dopaminergic hypofunction and "peripheral" sympathoadrenergic hyperactivity are suggested.[8] Offending drugs could disrupt pathways dependent on dopamine, including central thermoregulation pathways (hyperthermia), nigrostriatal pathway (rigidity, akinesia, and tremor), and the reticular activating system (alertness). Dopaminergic pathways interact with serotonergic, cholinergic, and noradrenergic pathways both centrally and peripherally, and this may explain the peripheral sympathetic activation causing hypermetabolic state (tachycardia and tachypnea) and dysautonomia.[6,7] Dopamine receptor polymorphisms have been suggested as a potential mechanism for genetic predisposition to NMS.[8]

Risk Factors

The classical description of an NMS patient portrays a young or middle-aged male with a history of psychosis who recently received an injection of haloperidol, but many studies have suggested that age, sex, and class of antipsychotics may not be as significantly correlated to the risk of NMS as previously thought.[3,9]

Historically, high-potency first-generation neuroleptic (antidopaminergic) agents such as haloperidol and low-potency agents like chlorpromazine have been associated with a higher incidence, but atypical agents such as clozapine, olanzapine, risperidone, quetiapine, and aripiprazole have all been implicated.[3] Two-thirds of cases develop within the first week of exposure to antipsychotics but prolonged exposure to the same dose of antipsychotic for months or years also has been reported as a risk factor.[6] The concurrent use of multiple antipsychotics, lithium, and serotonin reuptake inhibitors is also a notable association.[3,10] Withdrawal of dopamine replacement therapy in Parkinson's disease patients has been reported to precipitate NMS-like states (parkinsonism-hyperpyrexia syndrome, PHS).[6] The medical provider should also be aware of NMS associated with antiemetics such as prochlorperazine, promethazine, and properistaltic agents such as metoclopramide and domperidone.[7] An episode of NMS poses a significantly higher risk of subsequent NMS.[3] Worse outcomes are usually associated with dysautonomia and systemic complications such as renal failure.[4,11] A list of risk factors is provided in ►**Table 3**.

Diagnosis and Evaluation

Several diagnostic criteria have been developed over the past decades and the interested reader is directed to the extensive

Table 3 Risk factors for neuroleptic malignant syndrome

Risk factors
Higher neuroleptic doses
Hyponatremia, hypokalemia
Thyroid disease
Early postpartum period depression
Infectious encephalitis
Psychomotor agitation
Physical exhaustion and dehydration
Catatonia
Parkinsonism

review by Tse and colleagues (2015).[12] The 2011 International Expert Consensus (IEC) criteria assigned relative importance to each criterion with a scoring system and proposed cut-off values.[13] A cut-off score of 74 on the IEC when compared with the DSM-IV-TR criteria showed a sensitivity of 69.6% and a specificity of 90.7%.[14]

Cases with milder features or variable combination of symptoms have spawned the concept of "atypical NMS" especially associated with atypical antipsychotics.[11,15] The term *neuroleptic malignant-like syndrome* has been proposed by some experts to distinguish the syndrome associated with nonneuroleptic drugs.[8]

It is important to consider and exclude the more common metabolic, toxic, infectious, and cerebrovascular causes of encephalopathy. A comprehensive metabolic work-up, blood gas analyses, coagulation studies, cerebrospinal fluid (CSF) studies, and neuroimaging are often needed. See ►**Table 4** for differential diagnoses. Serotonin syndrome (SS), malignant catatonia (MC), and other closely related conditions are discussed later.

Management

Identifying and stopping the offending agent and reversing the contributory factors is the first step. Supportive care includes cooling measures, volume replacement, and correcting electrolyte and acid–base imbalances. Monitoring for the emergence of pulmonary, renal, cardiac, and neurological complications in an intensive care setting is appropriate. Recommendations regarding specific pharmacotherapy (see ►**Table 5**) are based on case series and/or expert opinion.[3] Benzodiazepines are used in catatonia, mutism, and agitation; bromocriptine and amantadine can be used to target dopaminergic pathways; and dantrolene, a skeletal muscle relaxant, can help rhabdomyolysis and hyperthermia secondary to muscular rigidity. Early withdrawal of treatment with bromocriptine and dantrolene may cause rebound symptoms, and it is therefore recommended to continue treatment for approximately 10 days after resolution of NMS symptoms.[9] Electroconvulsive therapy (ECT) has been found to be effective in NMS but potential anesthetic and systemic complications like rhabdomyolysis, dyselectrolytemia, and arrhythmias make this option one of the last resorts.[9]

Most patients recover within 7 to 10 days following discontinuation of the offending drug, but cases with persistent parkinsonism and catatonia lasting many weeks have been reported.[3,7] Complications of NMS are largely secondary to obtundation (aspiration pneumonia), dysautonomia (anoxia, arrhythmia, and cardiac failure), rhabdomyolysis (renal failure), and coagulopathies (pulmonary embolism and disseminated intravascular coagulation).[6]

Table 4 Important differential diagnoses of neuroleptic malignant syndrome

Category	Examples
Neuropsychiatric	Delirium Malignant catatonia
Toxic and metabolic	Extrapyramidal side effects of drugs Oculogyric crisis Acute dystonic reaction Malignant hyperthermia Anticholinergic delirium Serotonin syndrome Thyrotoxicosis Amphetamine abuse Dopamine agonist withdrawal Drug-induced acute parkinsonism
Infections	Sepsis Meningitis and encephalitis Postinfectious encephalomyelitis
Environmental	Heatstroke

Table 5 Targeted pharmacotherapy of NMS

Clinical features targeted	Drugs and dosages
Mild rigidity; catatonia or confusion; hyperthermia (100.4°F); tachycardia (≤100 bpm)	• Lorazepam 1–2 mg IM or IV every 4–6 h
Moderate rigidity, mutism, catatonia; confusion, stupor, hyperthermia (100–104°F), tachycardia (100–120 bpm)	• Lorazepam 1–2 mg IM or IV every 4–6 h • Bromocriptine 2.5–5 mg PO or by NG tube, every 8 h • Amantadine 100 mg PO or by NG tube every 8 h
Severe rigidity, catatonia or coma; hyperthermia (≥104° F), tachycardia (≥120 bpm)	• Dantrolene 1–2.5 mg/Kg body weight, IV every 6 h for 48 h, tapered • Bromocriptine 2.5–5 mg PO or by NG tube, every 8 h • Amantadine 100 mg PO or by NG tube every 8 h • Electroconvulsive therapy (ECT) 6–10 sessions with bilateral electrodes

Abbreviations: IM, intramuscular; IV, intravenous; NG, nasogastric tube; PO, per os; NMS, neuroleptic malignant syndrome.
Source: Adapted from Strawn et al 2007 and Katus and Frucht 2016.[3,85]

Malignant Catatonia

The syndrome of severe motor excitement, clouding of consciousness, coma, and cardiovascular collapse ending in death described by Stauder as "the deadly catatonia"

subsequently underwent several iterations and is currently referred to as MC.[16] MC is now identified as a nonspecific syndromic subtype of catatonia associated with many toxic-metabolic and neuropsychiatric illnesses. It is characterized by altered mental status, rigidity, hyperthermia, and dysautonomia with nonspecific elevation of CK, white cell count, and low serum iron, making it often indistinguishable from NMS. Similarities in pathogenesis and risk factors associated with MC and NMS have prompted many experts to suggest that NMS may be a drug-induced form of MC. Both entities are managed similarly by discontinuing offending agents, providing intensive supportive care and with targeted symptom management using benzodiazepines and ECT.

It mostly affects young adult females (mean age: 33 years), and accounts for approximately 0.07% of psychiatric admissions.[17] Mortality rates were 75 to 100% previously and have fallen to 9 to 10% since the 1980s, likely from increased awareness and early recognition.[18] There is however a discrepancy between the numbers reported from Europe and Asia and those from North America.[17]

Clinical Presentation

Traditionally catatonia has been classified as "retarded," "excited," and "malignant".[19] The "retarded" subtype is the most commonly recognized and is characterized by mutism, staring, and "waxy flexibility" where the limbs can be passively manipulated into postures. The "excited" subtype is characterized by agitation, excessive and purposeless repetitive movements called stereotypies, and delirium. In the malignant subtype (also referred to as *Bell's mania, delirium acutum*, and psychotic exhaustion), the altered mental status, mutism, posturing, and staring of catatonia are retained. Additionally, there are rigidity, hyperthermia, dysautonomia manifesting as tachycardia, labile blood pressures, profuse sweating, and hypermetabolic state indicated by tachypnea. See ►**Table 6** for core clinical features.

After reviewing cases prior to the antipsychotic era, Mann et al have identified several phases of catatonia. A prodrome lasting approximately 2 weeks with insomnia, anorexia, and labile mood is noted. The phase of motor excitement follows and is characterized by altered mental status, tachycardia, tachypnea, labile blood pressures, hyperthermia, cyanosis, and sweating. In addition to these dysautonomic symptoms, patients also exhibit catatonic mutism, hallucinations, and stupor with rigidity and posturing, with episodic exacerbations in some individuals (periodic catatonia). Days following the phase of excitement, extreme hyperthermia and cardiovascular collapse can lead to stupor and coma—a final phase of "stuporous exhaustion." There is significant overlap among clinical features of NMS, SS, neuroleptic-induced catatonia, and MC that has prompted many experts to suggest that the former are drug-induced forms of MC.[19,20]

Table 6 Core clinical features of malignant catatonia

Clinical feature	Components
Altered mental status	Mutism, negativism, staring, delirium, stupor, coma
Motor	Muscular rigidity, catatonic excitement, stereotypies, and agitation
Hyperthermia	Fevers up to 109°F (43°C)
Dysautonomia	Tachycardia, labile (often elevated) blood pressure, diaphoresis
Hypermetabolic state	Tachypnea and sweating
Laboratory findings	Elevated CK, leukocytosis, low serum iron Electrolyte abnormalities

Abbreviation: CK; creatine kinase.

Pathophysiology

The exact pathogenesis of MC is unclear. Various hypotheses have invoked dopamine, gamma-aminobutyric acid (GABA)-A, and glutamate systems to explain clinical features.[21] The therapeutic agonistic action of benzodiazepines on GABA-A receptors in catatonia has been used to explain a low GABAergic tone in the lateral orbitofrontal cortex.[17,22,23] Glutamate hyperactivity in the posterior parietal in catatonia may be behind posturing and impaired visuospatial perception. This also may partly explain why amantadine and memantine, which are antagonists to N-methyl-D-aspartate (NMDA) type of glutamate receptors, help in catatonia.[24]

Risk Factors

Catatonia, irrespective of the subtype, is more commonly seen in the context of several neuropsychiatric conditions such as bipolar disorder, schizophrenia, schizoaffective disorder, major depression, psychosis, and delirium and neurodevelopmental conditions like autism spectrum disorder.[25] In the acutely hospitalized psychiatric population (in-hospital and emergency departments), catatonia may be seen in 7 to 15% of cases.[19] Lesions of the frontal and parietal lobes, basal ganglia, and brainstem have been associated with catatonia, but medical (toxic-metabolic) causes are more common than brain lesions and even psychiatric illnesses.[26]

Diagnosis and Evaluation

Awareness of risk factors and clinical features remains the most important tool in recognizing the syndrome. There are no gold standard diagnostic tests, but CK elevation is seen in ~94%, leukocytosis in 66%, and serum transaminases in 45% of presentations.[17] Low serum iron, as seen in NMS, is also noteworthy. Nonspecific laboratory findings include hypernatremia, elevated erythrocyte sedimentation rate, and generalized slowing of electroencephalogram (EEG; reflecting encephalopathy). Many toxic-metabolic, infectious, and neurological illnesses are associated with MC, and many of their clinical features can also mimic MC. Hence like NMS, MC remains a diagnosis of exclusion.

Management

As discussed in the case of NMS, the mainstay of treatment for MC is also benzodiazepines in combination with supportive care. Extensive infectious, metabolic, toxic, and

neurologic work-up may be needed to uncover the underlying process while simultaneously managing the patient's hyperthermia, dysautonomia, and cardiopulmonary instability in the intensive care unit under a critical care–psychiatry collaborative setting.[21] Akinesia and immobility can result in deep vein thrombosis, the incidence of which is very high (25.3%) in catatonic patients.[27]

In patients with "non-MC" where there is no dysautonomia and body temperatures <39°C, benzodiazepines such as lorazepam (2 mg initially as a "challenge" followed by 2 mg three to five times daily) may be appropriate.[18] In MC, benzodiazepine therapy with ECT may be necessary. Many experts consider ECT as the first-line therapy for MC and recommend preparing the patient for ECT after initiating lorazepam.[18,19,25] Bromocriptine or dantrolene has not been shown to be effective in catatonia as noted by one large retrospective study of 34 patients.[18] The role of antipsychotics, especially atypical antipsychotics, in MC is unclear but amantadine and memantine may have a role where benzodiazepines and ECT have failed.[21] The likelihood of dopaminergic blockade precipitating NMS should always be considered.

Serotonin Syndrome

SS is a potentially life-threatening condition characterized by increased serotoninergic activity in the nervous system. Although commonly associated with the use of selective serotonin reuptake inhibitor (SSRI) class of drugs, or drug interactions leading to serotonin hyperactive states, other conditions have also been associated with SS. The syndrome of behavioral changes, motor hyperactivity, shivering, pupillary dilation, salivation, flushing, hypertension, myoclonus, and seizures was first described in animals in the context of drug interactions, after monoamine oxidase inhibitors and tricyclic antidepressants became available in the 1950s.[28] More recently the clinical features have been conceptualized as falling in a spectrum ranging from restlessness and tremors to life-threatening toxicity, associated with serotonin levels.

Incidence of serotonin toxicity is poorly documented in the literature. United Kingdom's National Health Service estimates an incidence of 0.5 to 0.9 cases per 1,000 patient months of treatment with SSRI monotherapy.[29] SS is seen in 14 to 16% of SSRI overdose cases.[29] Combination of serotonergic drugs, as opposed to single agents, can produce higher serotonin levels and worse serotonin toxicity due to cumulative effects. For example, fatal toxicities are more often seen with combinations of monoamine oxidase inhibitor (MAOI) and SSRI class of drugs.[30] Genetic deficiencies in cytochrome P450 2D6 enzyme increase susceptibility when taking SSRIs and tricyclics.[31] SS has been reported in patients of all ages, from infants to the elderly. ►**Table 7** provides a list of drugs for which monotherapy and combination therapies have been associated with SS.

Clinical Presentation

Change in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever are the most frequently noted clinical features of SS.

Table 7 Serotonin toxicity criteria adapted from Dunkley et al 2003[34]

1. A serotonergic agent has been administered in the past 5 weeks
2. One of the following combination of symptoms is seen: A. Spontaneous clonus B. Inducible clonus + agitation OR sweating C. Opsoclonus + agitation OR sweating D. Tremor + hyperreflexia E. Hypertonia + temperature >38°C (100.4°F) + opsoclonus OR inducible clonus

These features represent a spectrum with mild serotonin toxicity at one end to a fulminant SS at the other.

Neuromuscular irritability manifesting as clonus in some form is the most important diagnostic feature of SS.[32] Features of autonomic dysfunction are similar to those of NMS and MC but often can be mild.

Spontaneous clonus (myoclonus) can manifest in the limbs, face, head, and neck, and in severe cases, the whole body. Severe spontaneous myoclonus can look "rhythmic" and mimic tremors. *Opsoclonus* (or ocular clonus) consists of involuntary large amplitude and nonrhythmic multidirectional jerky eye movements, and is a cause of considerable distress for patients due to oscillopsia (the subjective sense of objects in the visual field jumping up and down).[33] Myoclonus is invariably associated with exaggerated deep tendon reflexes.

Anticholinergic toxicity, a close differential diagnosis, also presents with pupillary dilation, delirium, dry mucosa, and redness of skin. But profuse sweating, hyperactive bowels, diarrhea, hyperreflexia, and clonus are features of SS that distinguish it from anticholinergic syndrome, NMS, and MC.[33]

Pathophysiology

Clinical features, being in a spectrum, are dependent on the intrasynaptic concentration of 5-hydroxytryptamine (5-HT; serotonin) in the central nervous system (CNS).[30,34] Inhibition of serotonin reuptake, inhibition of presynaptic release, and monoamine oxidase inhibition are postulated mechanisms behind serotonin toxicity.[30] Both 5-HT1A and 5HT-2A receptors have been implicated.[34,35] Noradrenaline concentration in the CNS is elevated in SS suggesting its coactivation.[36] Interactions between dopaminergic and serotonergic systems may be contributing to the similarities between NMS and SS.

Diagnosis and Evaluation

Sternbach's criteria and the Hunter Serotonin Toxicity Criteria (HSTC) by Dunkley et al, are the two well-known clinical criteria for diagnosis of SS.[34,37] Sternbach proposed that in the setting of a recent addition or increase in a known serotonergic agent, at least three of these core clinical features should be present to diagnose SS. The HSTC (see ►**Table 8**), which is based on a much larger sample and proved to be simpler, has been shown to be more sensitive (84%) and specific (97%) when validated against

Table 8 Examples of drugs and interactions associated with serotonin syndrome

Drug class	Examples of drugs
Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs)	Sertraline Paroxetine Fluoxetine Citalopram Escitalopram Venlafaxine Desvenlafaxine Duloxetine
Monoamine oxidase inhibitors	Amitriptyline Nortriptyline Clomipramine Imipramine
Other psychiatric	Lithium Trazodone (serotonin modulator) Bupropion (dopamine/norepinephrine reuptake inhibitor)
Antiepileptic	Valproic acid
Antiemetic and properistaltic	Ondansetron Metoclopramide
Antibiotics, antiviral	Linezolid Ritonavir
Analgesics, relaxants	Tramadol Fentanyl Meperidine Cyclobenzaprine
Cough and cold	Dextromethorphan
Dietary supplements	Ginseng St. John's wort Tryptophan
Recreational and "street" drugs	Cocaine "Ecstasy" (methylenedioxymethamphetamine, MDMA). LSD (lysergic acid diethylamide)
Drug–drug interactions	Sertraline with several psychiatric medications Sertraline with monoamine oxidase inhibitors SSRIs and amphetamine (serotonin releaser) Paroxetine and buspirone Tramadol, venlafaxine, and mirtazapine Linezolid and citalopram

Source: Compiled from Gillman 1998, Gordon and Leder 2013, and Boyer and Shannon 2005.[28,32,36]

the "gold standard" of being diagnosed by a clinical toxicologist.[37,38]

SS is a diagnosis of exclusion. Various toxic-metabolic and infectious causes of encephalopathy are to be ruled out with appropriate laboratory investigations. Clinically SS can mimic NMS, malignant hyperthermia, anticholinergic toxicity, and toxicity from sympathomimetic drugs. Differential for the clinical presentation is broad. Opsoclonus, myoclonus, and hyperreflexia can be features of brainstem irritation from structural (tumors and bleeds), autoimmune, and paraneoplastic causes. Leukocytosis, elevation of transaminases, CK, and metabolic acidosis can be seen in serotonergic toxicity and are not helpful in distinguishing it from mimics.

Management

Symptoms can start as early as 6 hours after initiating the offending agent. Prompt identification and discontinuation of the offending drug (or drug interaction) is often the only treatment necessary. Residual drug-metabolites have been reported to cause SS. Longer half-lives of certain drugs need to be considered as well.[31]

Agitation and rigidity can cause rhabdomyolysis and therefore need to be managed promptly. Sedation with benzodiazepines (lorazepam or diazepam) is recommended for agitation. Benzodiazepines presumably help in calming down the hyperadrenergic state.[36,38] Hyperthermia is managed with cooling strategies, and nondepolarizing paralytics such as vecuronium are used for inducing neuromuscular paralysis if myoclonus and muscle rigidity are contributing to significant hyperthermia. Autonomic dysfunction should be closely monitored and managed with supportive care. Wide fluctuations in blood pressure can be difficult to treat and short-acting agents (nitroprusside) are recommended over long-acting β blockers.

Cyproheptadine, a 5-HT1A and 2A antagonist, binds 85 to 95% serotonin receptors is helpful in reversing serotonergic effects.[36,39] Doses of 12 to 18 mg per day (4–8 mg every 6 hours) have been tried.[37,38] Peripheral serotonin antagonism of cyproheptadine can result in hypotension. Its antihistaminic and anticholinergic actions can produce sedation which also helps in SS.[32,36] ►**Table 9** provides a summary of various therapeutic interventions.

Table 9 Suggested interventions in managing serotonin syndrome

Situation	Comments
Initial step	Discontinue offending agents
Supportive care	Vitals, oxygenation, hydration, cardiac monitoring
Hyperthermia	Cooling blankets and cooling intravenous fluids
Serotonin antagonist	Cyproheptadine
Agitation	Benzodiazepines (avoid restraints)
Severe rigidity causing hyperthermia	Induced neuromuscular paralysis with vecuronium in a critical care setting
Hypotension	Epinephrine, norepinephrine, or phenylephrine
Hypertension, tachycardia	Nitroprusside, esmolol
Poisoning, unknown offending agent	Consult toxicologist, poison control

Most cases resolve within 24 hours of discontinuing the offending drugs. Mild cases with minimal symptoms may only last 4 to 6 hours and often may not be recognized as SS. Longer-acting metabolites that linger in the patient's system should always be considered in cases that take longer to resolve. Prognosis is generally favorable.[32]

Parkinsonism Hyperpyrexia

PHS is now considered an NMS that occurs following the withdrawal of antiparkinsonian drugs. The first case in the literature was reported in 1981 by Toru et al, in a 63-year-old woman who had altered consciousness, sweating, fevers, and elevation of serum CK following discontinuation of levodopa, amantadine, and the anticholinergic biperiden.[40] The same or similar clinical picture has been reported under different names including "lethal hyperthermia," "dopaminergic malignant syndrome," "acute dopamine depletion syndrome," and most commonly neuroleptic malignant-like syndrome, but the current consensus designation appears to be PHS.[41]

The combination of circumstances that lead to PHS, i.e., rapid or abrupt withdrawal of antiparkinsonian medications in parkinsonian patients, makes it a rare condition. Literature on this entity is largely composed of case reports.[41] Males (56% of reported cases) developed PHS more often than females. Duration of parkinsonism ranges from 2 to 16 years and baseline levodopa dosage ranges from 200 to 2,100 mg per day.[41]

Clinical Presentation

The clinical features of PHS are those of NMS, with slightly more parkinsonian features early in the course. An older peritoneal dialysis (PD) patient with rigidity, stupor, and hyperthermia in the setting of levodopa withdrawal portrays the typical clinical picture of PHS.[42] Symptoms can begin within 18 hours to 7 days after change in dopaminergic medication. In comparison to NMS, patients with PHS may have a slightly increased latency to onset of symptoms.[41,42] Rigidity, tremors, with subsequent akinesia, hyperthermia, agitation, delirium, stupor, and coma are seen usually in succession. Tachycardia is an early sign of dysautonomia. Fluctuating blood pressures, tachypnea, and sweating are also seen. Hyperthermia results from a combination of central thermoregulatory dysfunction and hyperactivity of muscles. Myoclonus and seizures are not uncommon. CK and white cell counts are typically elevated.[42,43]

Pathophysiology

The etiopathogenesis of NMS has been previously discussed. Dysfunction of central dopaminergic and serotonergic activity and peripheral noradrenergic activity appears to be behind the various manifestations of NMS and most NMS-like syndromes.[6,8] Low levels of dopamine metabolites and higher levels of noradrenaline metabolites in CSF of PD patients with previous NMS-like episode seemed to suggest that central dopaminergic hypoactivity and noradrenergic hyperactivity may contribute to NMS in elderly patients with PD.[43,44]

Risk Factors

Historically, rapid reduction or complete stopping of dopaminergic medications, especially in the outdated practice of giving "drug holidays" for PD patients with psychosis may have precipitated many previously reported PHS cases.[40,41] Withdrawal, switching, or dose adjustments of all antiparkinsonian drugs have been reported to be associated with PHS thus far. Even drugs like tolcapone, a catechol-O-methyltransferase inhibitor that is used to reduce peripheral breakdown of levodopa but does not have any direct dopaminergic action, have been associated with PHS.[45] Longer duration of PD, motor fluctuations, which also correlate with longer duration of disease, psychiatric comorbidities, and older age have been associated with higher risk for PHS.[41]

Diagnosis and Evaluation

Diagnosis is largely by exclusion and clinical diagnostic criteria used for NMS can be applied here with the caveats discussed above. The general practitioner should be mindful of the social situation, as older PD patients with cognitive impairment may miss doses and develop PHS. The entity should be part of the differential diagnosis in any PD patient with fever of unknown origin. The unfortunate scenario of carelessly or inadvertently discontinuing or delaying antiparkinsonian medications when PD patients are admitted to the hospital for other reasons is not uncommon.[46]

Rigidity, hyperpyrexia, and altered consciousness appear to be the most consistent features.[43] No laboratory findings have been shown to be consistently present. Elevation in CK and leukocytosis are not as prominent as in NMS. Elevated liver transaminases and metabolic acidosis may be present. Coagulopathies, infections, and other toxic metabolic syndromes need to be evaluated both for excluding other differentials and when managing complications.

Management

PHS is a neurological emergency that requires treatment in an intensive care setting, preferably in a multidisciplinary approach with critical care, neurology, and psychiatry on board. In addition to cooling, intravenous (IV) fluids, antihypertensives, and other supportive care described in the management of NMS above, antiparkinsonian drugs including levodopa and bromocriptine should be used.[43] Since parenteral forms of antiparkinsonian medications are difficult to procure, nasogastric administration is recommended; if nasogastric feeding is contraindicated, IV levodopa infusion is necessary.

In parkinsonian patients, gastrointestinal absorption of medications is often altered due to intestinal dysmotility—a practical point that needs to be considered especially when giving levodopa in an intensive care setting. Bromocriptine 5 to 10 mg divided into three doses per day, titrated to effect, is recommended. Levodopa should be started at the premorbid dose first and can be titrated. Dopamine agonists such as ropinirole (1–2 mg three times a day) may also be tried.[47] Use of dantrolene in rigidity is discussed under the management of NMS above. Overall, PHS appears to have a shorter duration of illness and a better prognosis than NMS.[42]

Disability in PD patients who had a previous NMS-like episode was worse than those without.[44]

Acute parkinsonism

Parkinsonism consists of a constellation of motor disturbances that includes decreasing rate of movements (bradykinesia), reduced facial expression (hypomimia), rigidity, tremor, and impaired posture and gait.[48] Primary parkinsonism refers to parkinsonism resulting from a slowly progressive neurodegenerative condition such as Parkinson's disease or atypical parkinsonian disorders (e.g., progressive supranuclear palsy). In contrast, acute parkinsonism (evolving over hours to weeks) can be seen with several etiologies, as outlined in ►**Table 10**.

Clinical Presentation

When strokes cause acute parkinsonism, symptoms are often contralateral to the lesion and correspond to the vascular territory. Parkinsonism follows the initial phase of weakness. Cases of anterior cerebral artery strokes with contralateral hemiparkinsonism hypothesized as emerging from striatocortical circuit dysfunction have been reported.[49]

Cerebral hypoxia can result in delayed akinetic rigid syndromes with parkinsonism and dystonia.[50] In some cases, hypoxia can be associated with delayed demyelination and leukoencephalopathy that happens days to weeks from the initial insult.[51] Toxicity from carbon monoxide can affect the basal ganglia directly and cause acute parkinsonism from pallidal necrosis and dopaminergic neuronal loss.[52]

Injectable street drugs tainted with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analogue, caused severe akinetic rigid parkinsonism in a handful of people in the 1980s. MPTP later became a tool in developing animal models of parkinsonism due to its ability to cause selective degeneration of substantia nigra.[53]

Table 10 Examples of acute parkinsonism

Etiological class	Causes
Medications	Drug-induced parkinsonism Neuroleptic malignant syndrome Serotonin syndrome
Toxins	Carbon monoxide MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
Structural brain lesions	Basal ganglia and midbrain stroke Pontine myelinolysis Hydrocephalus Brainstem and posterior fossa tumors
Infectious and inflammatory conditions	Systemic lupus erythematosus Sarcoidosis Brainstem encephalitis Autoimmune or paraneoplastic inflammation brainstem
Neuropsychiatric	Catatonia, malignant catatonia Functional parkinsonism

Source: Adapted from Fernandez and Friedman 2013.[54]

Patients with primary parkinsonism (e.g., PD, dementia of Lewy body) can develop acute parkinsonism as a drug reaction to dopamine blocking agents such as antipsychotics (haloperidol), antiemetics (prochlorperazine), and properistaltic agents (metoclopramide).[54]

Acute onset of a parkinsonism coupled with a clinical exam that reveals atypical features and is incongruous with organic disorders should raise the concern of a psychogenic (functional) parkinsonism. Tremors in such cases may show a jerky quality as opposed to rhythmicity, may disappear with movement of the limb, and often can be distracted and "entrained."[55]

Management

The management of acute parkinsonism is first geared toward a complete work-up pertaining to the suspected etiology, with appropriate interventions tailored to avoid recurrence. A trial of levodopa to target akinesia and rigidity is recommended in all cases due to minimal associated side effects. Postsynaptic therapies (dopamine agonists) can also be considered but may not be tolerated.[54] Once the primary pathology is managed, and symptoms improve in acute parkinsonism, dopaminergic therapy can be gradually weaned off.

Acute Chorea-Ballism

Chorea is a hyperkinetic movement disorder characterized by continuous, nonrhythmic, nonpatterned involuntary movements.[56] The term "ballism" is often used to describe an extreme manifestation of chorea, with high-amplitude, forceful, flinging movements. Chorea may present acutely in several settings. The differential diagnosis includes drug or toxin exposure, metabolic derangement, vascular disease, infectious/postinfectious etiologies, mass lesions, and autoimmune conditions. This presentation is often associated with lesions affecting the basal ganglia, but other subcortical structures may be involved, and additional phenomenologies (such as dystonia) may be found on presentation.[56] If untreated, severe choreiform movements can cause hyperthermia and rhabdomyolysis.

Clinical Presentation

Children

Sydenham chorea in the setting of rheumatic fever is the most common cause of chorea in children. This is a clinical manifestation of rheumatic fever due to group A streptococcal infection.[57] The pathogenesis is incompletely understood, but likely involves cross-reactivity between antibodies to the inciting bacteria and striatal antigens. Although the incidence of acute rheumatic fever has declined significantly overall, this is still a major public health burden in developing countries.[58] There have also been recent regional outbreaks of acute rheumatic fever in the United States, and incident estimates range from 2 to 14 cases per 100,000 in the United States.[59] Chorea is a common manifestation of acute rheumatic fever but is typically a delayed sequela that

may not present until months after the acute illness.[58] Females are more often affected.[60] Chorea may be unilateral or bilateral, and brain imaging typically lacks specific findings.[61] Evaluation should be directed toward the diagnosis of acute rheumatic fever according to established guidelines, including testing for active or recent group A streptococcal infection and cardiac assessment.[62] In addition to antibiotics, a course of steroids has been shown to be beneficial for the movement disorder in several reports, including a small randomized trial that demonstrated decreased chorea severity and time to remission.[63,64] For symptomatic treatment of chorea in these patients, neuroleptics (haloperidol and pimozide) are used most commonly, though antiepileptics may also be effective and may have a more favorable side-effect profile.[63]

Adults

Basal ganglia stroke is the most common cause of acute chorea-ballism in adults.[56] Hyperkinetic movement disorders are estimated to occur in 1% of stroke patients, with chorea being the most common presentation. Ischemic or hemorrhagic stroke may cause hemichorea-ballism, with causative lesions usually affecting the contralateral basal ganglia (most commonly the thalamus) and adjacent white matter.[65,66] Dopamine receptor blocking agents (typically neuroleptics) are used for symptomatic treatment. Although there is typically partial improvement of poststroke choreiform movements, variable rates of remission have been described, and prognosis may be more favorable in the rare cases arising from cortical strokes.[66,67]

Acute-onset chorea-ballism is a rare complication of hyperglycemia.[68] Acute chorea-ballism classically occurs in nonketotic hyperglycemia but can occur infrequently in ketotic hyperglycemia.[69] The mechanism is not well understood. Symptoms are often unilateral, but bilateral involvement is also possible.[69,70] Elderly women are most commonly affected in the setting of nonketotic hyperglycemia.[70] Patients with chorea and ketotic hyperglycemia are significantly younger and are more likely to have atypical imaging findings.[69] Chorea-ballism may be the initial presentation of diabetes mellitus in significant number of cases.[69] Magnetic resonance imaging of the brain classically demonstrates T1-hyperintense lesions affecting the basal ganglia, most often the putamen.[70] This hyperintensity typically resolves on follow-up scans after several months. Treatment involves normalization of serum glucose, with neuroleptics if needed for persistent, bothersome symptoms. The prognosis is favorable, with most patients experiencing complete resolution of symptoms within 6 months, though recurrence is possible.[69,70]

Pregnancy

Chorea presenting in pregnant women is termed chorea gravidarum. Symptoms classically begin in the first trimester of pregnancy. Chorea gravidarum is associated with a history of rheumatic fever, antiphospholipid antibody syndrome, systemic lupus erythematosus, encephalitis, and syphilis.[71] However, drug exposure and any of the toxic-metabolic causes of chorea can also cause chorea gravidarum and should be considered. One-third of cases resolve spontaneously prior to delivery, while the remainder resolve shortly after delivery.[71] In cases that the chorea is jeopardizing the health of the mother or fetus, treatment with low-dose haloperidol (0.5–2 mg, two to three times daily) in the second and third trimesters is likely safe.[72]

Diagnosis, Evaluation, and Management

A complete differential for acute chorea-ballism can be found in ►**Table 11**. Diagnostic evaluation of acute chorea-ballism should include a careful history and neurologic examination. History should emphasize recently introduced medications, including over-the-counter treatments, as a wide array of drugs have been reported in association with acute chorea (including antiarrhythmics, antidepressants, anticonvulsants, antihistamines, stimulants, and oral contraceptives).[73] Neuroleptic-induced tardive dyskinesia and levodopa-induced dyskinesias are the most common drug-related causes of chorea.[73] Appropriate initial laboratory evaluations include serum glucose, complete blood count, electrolytes, assessments of renal, liver, and thyroid functions, calcium, magnesium, and pregnancy testing. Antistreptolysin O titers should be obtained in children presenting with chorea. Additional diagnostics (laboratory testing, neuroimaging, and lumbar puncture) may be appropriate depending on the clinical context.

Treatment involves discontinuation of any possible offending agents. Symptomatic therapy utilizes dopamine-

Table 11 Differential diagnosis of acquired acute chorea-ballism

Differential diagnosis of acquired acute chorea-ballism	
Category	**Examples**
Drug-induced	Antiarrhythmics, antidepressants, anticonvulsants, antihistamines, stimulants, oral contraceptives, and others
Toxins	Carbon monoxide, manganese, thallium, toluene, methanol, cyanide, mercury, cocaine, heroin, amphetamines
Metabolic	Hyper/hypoglycemia, hyper/hyponatremia, hypomagnesemia, hypocalcemia, thyrotoxicosis, chronic acquired hepatocerebral degeneration, renal failure
Autoimmune	Systemic lupus erythematosus, antiphospholipid antibody syndrome
Postinfectious	Sydenham's chorea, herpes simplex encephalitis
Vascular	Ischemic or hemorrhagic stroke
Paraneoplastic	anti-CRMP5/CV2, anti-Hu
Infectious	HIV, Creutzfeldt–Jakob disease
Other	Chorea gravidarum, polycythemia vera, mass lesions

Abbreviation: HIV, human immunodeficiency virus.
Source: Adapted from Wild and Tabrizi 2007 and Miyasaki 2011.[86,87]

receptor blocking agents. Neuroleptics are commonly used first-line due to cost and availability, though it is crucial to monitor closely for subsequent development of tardive dyskinesia. Tetrabenazine and deutetrabenazine are also options for advanced cases. The prognosis varies according to etiology.

Drug-Induced Dystonia

Acute dystonic reactions may occur following exposure to dopamine-receptor blocking agents—typically, neuroleptics and antiemetics. However, this reaction has been described in association with other medication classes, including SSRIs, calcium channel blockers, and many other drugs with diverse mechanisms of action.[74] This is a less common drug-induced movement disorder than parkinsonism or tardive dyskinesia, affecting 2 to 3% of exposed patients.[75] Typical neuroleptics are more likely to cause this reaction than atypical neuroleptics (2–6 vs. 1–2%).[76] Symptoms occur abruptly, usually within 5 days of drug exposure, and are more common in younger, male patients.[75,76] The pathophysiologic mechanism is unclear, but may involve changes in dopamine turnover, dopamine receptor sensitivity, and cholinergic activity following dopamine receptor blockade.[77]

Clinical Presentation

Acute drug-induced dystonia often affects the face and neck.[78] Oculogyric crisis is an unusual-appearing manifestation that starts with a fixed stare, followed by upward, fixed deviation of the eyes, tilting back of the head, and mouth opening with tongue protrusion.[75] Oromandibular dystonia, opisthotonos, blepharospasm, stridor, and dystonia of the trunk and limbs may also occur.[78,79] Acute dystonic laryngospasm may prove fatal.[80]

Management

Acute drug-induced dystonia is effectively treated with parenteral administration of anticholinergic medications (such as benztropine or diphenhydramine). Due to the possibility of recurrent symptoms related to the half-life of offending agents, a short course of oral anticholinergic medication is often appropriate.[79]

Status Dystonicus

Status dystonicus, also known as dystonic storm or dystonic crisis, refers to an acute worsening of generalized dystonia with severe, continuous, generalized movements. This is a rare but likely underreported condition with high morbidity and mortality related to respiratory compromise and metabolic disturbances.[81] Status dystonicus is more common in the pediatric population, and males are more frequently affected.[82] Patients with primary, secondary, or degenerative dystonias may develop status dystonicus, and tonic presentations (sustained muscle contractions) are more common than phasic.[82] Dystonia secondary to cerebral palsy is the most common underlying diagnosis overall.[82]

Clinical Presentation

In typical status dystonicus, the patient has an established or evolving dystonia disorder with development of worsening severe generalized dystonia, fever, dehydration, or rhabdomyolysis.[88] Status dystonicus usually evolves gradually over weeks to months. A precipitating factor (most often infection or change in medication) may or may not be evident.[81] Other possible precipitants include trauma, anesthesia, surgical procedures, metabolic derangement, stress, discomfort, constipation, and puberty.[83] The differential diagnosis includes NMS, SS, malignant hyperthermia, acute dystonic drug reaction, paroxysmal autonomic instability with dystonia, and intrathecal baclofen withdrawal.[83]

Management

A dystonia severity action plan may be useful for clinicians to assess risk and appropriately assign level of care for management for patients with worsening of their baseline dystonia.[83] In status dystonicus, pharmacologic treatment with anticholinergics or dopamine-receptor blocking agents is rarely sufficient, and sedation with endotracheal intubation is often necessary. In refractory cases, surgical intervention (intrathecal baclofen pump placement, thalamotomy, pallidothalamotomy, or deep brain stimulation) may be considered.[82] The frequent need for aggressive treatment makes early recognition of status dystonicus key for reducing mortality.

Conflict of Interest
None

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