Movement Disorders in the Emergency

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Introduction

Movement disorders classically have an insidious onset and slow progression and are usually not associated with emergency situations. Infrequently, there do arise rapidly evolving movement disorders or acute complications of existing movement disorders that need immediate attention and rapid management which can be life-saving [1, 2]. This chapter deals with the clinical presentation, diagnosis and management of some common movement disorders presenting to the emergency department (ED).

Classification

Although there is no formal classification of movement disorder emergencies, we shall use the following broad subtypes for a practical approach:

1. Acute presentations/exacerbations of specific movement disorders (Table 22.1)
   (a) Acute parkinsonism
   (b) Dystonic storm/status dystonicus
   (c) Oculogyric crisis
   (d) Malignant catatonia
   (e) Hemiballism-hemichorea
   (f) Tic emergencies
   (g) Abductor paresis in multiple system atrophy.

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Table 22.1 Acute presentations/exacerbations of specific movement disorders

Condition	Treatment
1. Acute parkinsonism	Levodopa/dopamine agonists/anticholinergics
(a) Infectious	Manage infectious conditions with antimicrobials
(b) Toxic	Discontinue exposure to culprit drug/toxin
2. Dystonic storm	(a) Benzhexol, tetrabenazine, pimozide, baclofen, chlorpromazine, sodium valproate, carbamazepine
	(b) Sedate with propofol/midazolam
	(c) Institute paralysis and ventilation if not responding
	(d) If still refractory, consider surgical options
3. Oculogyric crisis	Intravenous diphenhydramine/other anticholinergics/ clonazepam
4. Malignant catatonia	(a) Fluid replacement, temperature reduction and support of cardiac, respiratory and renal functions
	(b) Withhold antipsychotics
	(c) Benzodiazepines
	(d) Electroconvulsive therapy
	(e) ACTH/corticosteroids
	(f) Dantrolene
5. Hemiballism-hemichorea	(a) Treatment of the underlying cause
	(b) Tetrabenazine/haloperidol
	(c) Clonazepam, valproic acid, trihexyphenidyl, amitriptyline
6. Tic emergencies	(a) Discontinue culprit drug, if any
	(b) Pimozide/haloperidol
	(c) Botulinum toxin-A (BTX-A) for refractory vocal tics
7. Abductor paresis in MSA	(a) CPAP
	(b) BTX-A, surgical options
	(c) Emergency tracheostomy or a tracheal intubation

2. Drug-induced emergencies
   (a) Neuroleptic malignant syndrome
   (b) Parkinsonism-hyperpyrexia syndrome
   (c) Serotonin syndrome
   (d) Acute dystonia
   (e) Acute drug-induced akathisia.

Acute Presentation of Specific Movement Disorders (Table 22.1)

Acute Parkinsonism

Parkinsonism is usually a chronic condition, and patients present to the outpatient clinics and very rarely to the ED. However, acute parkinsonism can be encountered as a syndrome secondary to an identifiable, non-degenerative disorder. Most secondary forms of parkinsonism, including the drug-induced forms, usually evolve over weeks, but may sometimes develop over hours to days. Acute presentation is

typically seen after the administration of agents that deplete/block dopamine, after viral encephalitis, or after carbon monoxide or cyanide poisoning [3, 4].

Infectious Parkinsonism

Parkinsonism may occur following infection with viruses that target the substantia nigra. Von Economo was the first to recognize and classify three distinct forms of the acute illness, which he called 'encephalitis lethargica', now also called von Economo disease (ED): the somnolent-ophthalmoplegic form, the hyperkinetic form and the amyostatic-akinetic form [5]. No causative agent was ever identified for this encephalitis. Parkinsonism may occasionally accompany Japanese B encephalitis, HIV encephalopathy, encephalitis caused by Coxsackie B virus, rubella, influenza virus, cytomegalovirus, measles, St Louis encephalitis, Western equine encephalitis, West Nile virus, Epstein–Barr virus, mycoplasma pneumonia, syphilis, borreliosis (Lyme disease), basal ganglia abscesses or granulomas caused by toxoplasmosis, cryptococcosis, mucormycosis, cysticercosis and tuberculosis [4, 6, 7]. In addition to supportive measures during the acute encephalopathic phase, the timely administration of an appropriate antibiotic/antiviral agent, in proper dosage and for an appropriate duration of time, is of paramount importance in parkinsonism associated with known viral or bacterial encephalitis. When the symptoms persist, one may have to use levodopa, either alone or in combination with other adjunctive anti-parkinsonism agents, such as anticholinergics and dopamine agonists. Patients admitted as cases of encephalitis frequently receive antipsychotics and anti-epileptics for the control of behaviour and seizures, respectively. In such a setting, it is important to recognize and discontinue the culprit drugs causing parkinsonism before one can consider the possibility of an infectious/post-infectious aetiology, and initiate anticholinergic or dopaminergic agents.

Acute Toxic Parkinsonism

An acute parkinsonian state can be produced by many toxins, including MPTP, organophosphate pesticides, carbon monoxide, carbon disulphide, cyanide and methanol [4, 8]. The last four are similar, in that parkinsonism is accompanied by severe encephalopathy. There are no tremors and the condition is poorly responsive to levodopa. Acute parkinsonism has been reported to occur following bone marrow transplantation, and treatment with high-dose cytosine arabinoside, cyclophosphamide, total body irradiation, amphotericin B, paclitaxel, vincristine and adriamycin [4]. Flunarizine, a commonly used migraine prophylactic agent, is also associated with a syndrome of acute parkinsonism, especially in the elderly.

Management consists of preventing further exposure to the culprit toxin and the institution of specific antidotes, wherever possible. Symptomatic treatment in the form of levodopa, dopamine agonists and anticholinergics may be required for a variable period of time.

Points to Remember

- Parkinsonism can sometimes present acutely as a complication of encephalitis or exposure to toxins.
- Management should focus on the treatment of causative factors, viz. antimicrobials in the case of infectious parkinsonism and removal of the incriminating toxin in the case of toxic parkinsonism.
- Levodopa, dopamine agonists and anticholinergic agents can be offered as symptomatic treatment in such cases.

Dystonic Storm/Status Dystonicus

Introduction and Clinical Features

Dystonias are characterized by patterned involuntary sustained or intermittent muscle contractions causing repetitive twisting movements, abnormal postures or both. When severe muscle contractions become increasingly frequent or continuous, a patient is said to be in status dystonicus or dystonic storm [1, 2]. In practice, status dystonicus often occurs at the end of a continuum of worsening dystonia. At times, status dystonicus may present as a new onset dystonic disorder without previous history of similar movements. Status dystonicus is known to affect all age groups but up to 60% of patients are between ages 5 years and 16 years, with a male preponderance [9].

The spasms are extremely painful, at times interfering with respiration and causing metabolic disturbances, such as hyperpyrexia, dehydration, respiratory insufficiency and acute renal failure secondary to rhabdomyolysis. The contractions can be either sustained with abnormal postures, hence called tonic or rapid and repetitive dystonic, hence phasic. The tonic dystonic storms have worse outcomes. Respiratory failure can result from one or a combination of dystonic bulbar spasms (pharyngeal, laryngeal), truncal-respiratory muscle spasms, diaphragm dystonia, generalized exhaustion, aspiration pneumonia, and indeed the need for highly sedative and relaxant drugs used to control status dystonicus.

Causes and Pathophysiology

Acquired dystonias are likely to present with status dystonicus (38% of cases), CP being the most common individual secondary cause followed by the 'heredodegenerative dystonias' (particularly neurodegeneration with brain iron accumulation, Wilson disease, and mitochondrial disorders) and the 'pure primary dystonias' [10]. The precipitating factors include trauma, surgery, infection, fever, anaesthesia, 'metabolic disorder' decompensation, stress, pain, gastro-oesophageal reflux disease, constipation, puberty-related deterioration in CP and abrupt introduction, withdrawal or change in medical treatment. The trigger might not be identified in around 30% cases.

Certain drugs are known to trigger status dystonicus especially the dopamine-receptor blockers pimozide and haloperidol. Both these agents are frequently used to treat dystonia and chorea. Metoclopramide can have the same effect [11]. In

Wilson disease the introduction of chelation therapy with penicillamine, zinc sulphate, or trientine has also been implicated in status dystonicus [12, 13]. Introduction of clozapine, as well as withdrawal of lithium and tetrabenazine, is also known to be associated with status dystonicus [9]. Severe dystonia can sometimes be precipitated by deep brain stimulation failure caused by hardware problems, intrathecal baclofen pump failure as well as routine baclofen, and benzodiazepine withdrawal in general should be considered where relevant [13–15].

Investigations

The investigations are targeted at elucidating the precipitating factor as well as the primary cause of dystonia, if it is not already known. They include routine haematology and biochemistry; wet blood film for acanthocytes; assessment of uric acid, copper and ceruloplasmin, serum lactate and pyruvate, plasma and urinary amino acids; syphilis serology and CSF examination, including lactate [9, 16].

Management

It is necessary to institute paralysis, ventilation and sedation in most cases of status dystonicus to avert bulbar and respiratory complications, and to relieve the severe exhaustion and excruciating pain that results from the incessant dystonic spasms. After a period of 4–6 days, the infusion of the paralysing and sedating agents can be tailed off to assess the underlying dystonic spasms. Intravenous fluid resuscitation, antibiotics, nutritional requirements (nasogastric or parenteral) and antipyretics need to be provided in most patients. Rhabdomyolysis, if already set in, requires specific therapy in the form of intravenous fluids, urine alkalinization, dantrolene, neuromuscular paralysis and/or dialysis in acute renal failure [17].

Status dystonicus becomes life-threatening as sustained active muscle contraction leads to exhaustion and rhabdomyolysis. One of the goals of management is to achieve muscle relaxation without compromising respiration. For mild cases, clonidine in adults (1–5 μg/kg up to 3 hourly) and chloral hydrate in children (30–100 mg/kg, administered 3–6 hourly) are used for this purpose. For moderate and severe case, deeper sedation and stronger muscle relaxation are frequently required to achieve prompt resolution of the dystonic spasms. A benzodiazepine, i.e. continuous intravenous midazolam (0.02–0.1 mg/kg/h) is the preferred agent with the advantages of rapid onset of action, short half-life and easy titratability. For refractory spasms, anaesthetic agents like propofol (0.5–3.0 mg/kg/h) are used along with non-depolarizing muscle paralysing agents. Depolarizing agents, e.g. suxamethonium being associated with rhabdomyolysis are to be avoided [16–18].

While the patient is intubated, periodic evaluation of the patient's true clinical state and response to anti-dystonia measures should be done by tapering off the infusions. As paralytic ileus is a potential serious complication of both status dystonicus and the multiple drugs used in its management, it is important to minimize the combination of drugs used, the doses, though high, but titrated against oxygen saturations, heart rate and blood pressure [16, 17].

Specific anti-dystonia drugs: The preferred agents are an anticholinergic (trihexyphenidyl), a dopamine blocker (haloperidol or pimozide) and a catecholamine

depleter (tetrabenazine). Gabapentin has been found to be of remarkable benefit in refractory status dystonicus associated with Wilson disease and can be tried in that associated with other aetiologies [13].

Other agents used in anecdotal way with limited success include benzodiazepines like clonazepam, flurazepam, diazepam, oral baclofen, levodopa, or levodopa-carbidopa, sodium valproate, carbamazepine, primidone, phenytoin, acetazolamide, benztropine, biperiden, lithium, bromocriptine, chlorpromazine, olanzapine, clozapine and risperidone [9, 17].

The response to oral anti-dystonia drugs is generally reported to be poor, with significant risk to patients who develop dependence on sedative or anaesthetic agents and remain in refractory status dystonicus. Therefore, more invasive surgical therapies including intrathecal baclofen (ITB), deep brain stimulation (DBS) or pallidotomy are now considered early, once acute systemic infections have been either excluded or treated. Intrathecal baclofen (ITB) therapy has been successfully used in refractory cases of SD [15, 17]. Tolerance may potentially limit the use of ITB over long periods. ITB, although less invasive than brain surgery, is also known to be associated with risks such as over-dosage, withdrawal syndrome and catheter migration/ breakage. Deep brain stimulation of the bilateral globes pallidus internal has been found to be an effective treatment for SD in the majority of treated patients [14, 19]. Benefit has been reported to occur usually within days or weeks. It has largely replaced the lesions procedures of pallidotomy, thalamotomy and pallidothalamotomy for the treatment of dystonia. However, if DBS is not available, unilateral pallidotomy could be considered [19, 20].

Points to Remember

- Dystonic storm or status dystonicus consists of severe and potentially fatal exacerbations of dystonic conditions.
- These are usually triggered by trauma, surgery, infection, fever, abrupt introduction/withdrawal or change in medical treatment.
- In most cases, it is necessary to institute paralysis with assisted ventilation and sedation to avoid bulbar and respiratory complications while instituting anti-dystonia therapy.
- DBS, unilateral pallidotomy or ITB should be considered early in refractory SD.

Oculogyric Crisis

Introduction

An oculogyric crisis is characterized by tonic conjugate ocular deviation that may last from a few minutes to many hours. Oculogyric crisis can occur both in acute and tardive dystonia [1].

Causes and Pathophysiology

Oculogyric crisis (OGC) is most commonly seen following exposure to neuroleptics. Tetrabenazine, gabapentin, domperidone, carbamazepine and lithium carbonate

have all been reported to trigger OGC [1, 2, 21]. There are reports of OGC associated with structural brain lesions, such as bilateral paramedian thalamic infarction, herpes encephalitis, cystic glioma of the posterior third ventricle and as the initial manifestation of Wilson disease [21].

Management

Regardless of its cause, OGC can be terminated with an injection of intravenous diphenhydramine (25–50 mg). Oral clonazepam may be effective for patients with chronic neuroleptic-induced OGC that is resistant to anticholinergics [21].

Malignant Catatonia

Introduction and Clinical Features

Catatonia may be conceptualized as a continuum, with milder forms at one end (termed simple or benign) and more severe forms, with hyperthermia and autonomic dysfunction (termed malignant catatonia or MC), at the other [22]. Stuporous catatonia is characterized by varying combinations of mutism, immobility and waxy flexibility; the associated features include posturing, negativism, automatic obedience, 'echo' phenomena—echolalia and echopraxia, hyperthermia, altered consciousness, autonomic instability manifested by diaphoresis, tachycardia, labile or elevated blood pressure and varying degrees of cyanosis [22, 23]. Catatonics remain alert in stark contrast to the somnolence or decreased level of consciousness seen in all other forms of stupor.

Causes and Pathophysiology

Organic causes of catatonia include cerebrovascular disorders involving the anterior cingulate gyri or temporal lobes, normal-pressure hydrocephalus, cerebral anoxia, subacute sclerosing panencephalitis in stage I, glioma involving the splenium of the corpus callosum, closed head trauma, surgical removal of lesions near the hypothalamus, viral encephalitis, bacterial meningo-encephalitis, septicaemia, hyperthyroidism, Addison disease, Cushing disease, Wernicke encephalopathy and sedative-hypnotic withdrawal [22, 23].

Investigations

Investigations are targeted to exclude medical or drug-induced causes of MC with the help of clinical features and neuroimaging. The most consistent laboratory findings in MC include elevation of the creatine kinase level and leucocytosis. Elevation in serum transaminases, generalized slowing on electroencephalogram, hyperglycaemia, elevated serum creatinine, hyponatraemia, hypernatraemia and dehydration are not uncommon [22, 24].

Management

Management involves early institution of intensive medical care focusing on fluid replacement, temperature reduction, and support of cardiac, respiratory and renal

functions [22, 23]. Antipsychotics should be withheld. Catatonia is best managed with benzodiazepines. If simple catatonia proves unresponsive to benzodiazepines after 1–2 days of treatment, electroconvulsive therapy (ECT) should be considered. Electroconvulsive therapy appears effective, however, only if initiated before severe progression of the symptoms. ACTH or corticosteroids may be tried if ECT proves ineffective. Dantrolene, a drug that inhibits contraction and heat production in muscle, may also be administered. It should be started at a minimum dose of 1 mg/kg, the maximum cumulative dose being 10 mg/kg. The oral dosage is 4–8 mg/kg/day, in three or four divided doses. In MC occurring as a consequence of a medical illness, treatment must be directed at the underlying disorder [2, 22, 23].

Points to Remember

- Catatonia is characterized by mutism, immobility, waxy flexibility, posturing, negativism and 'echo' phenomena.
- Causes are diverse and must be excluded by a detailed history, neuroimaging, CSF studies and other investigations.
- Management consists of fluid replacement, temperature reduction, and support of cardiac, respiratory and renal functions, along with the administration of benzodiazepines.
- Refractory cases may require ECT.

Hemiballism-Hemichorea

Introduction

Hemiballism refers to large-amplitude, flinging, at times violent movements of one side of the body [25]. As acute hemiballismus resolves over days to weeks, the movements often become choreiform. Stroke is the single most common cause of hemiballism with localization being classically in the contralateral subthalamic nucleus or rarely deep white matter. Hemiballism associated with non-ketotic hyperglycaemia is the second most common cause. With this disorder, chorea or ballism may be unilateral or bilateral. It occurs more in women, and it may sometimes be the initial presentation of diabetes mellitus. Other conditions reported to have caused acute onset hemiballism-hemichorea include neoplastic metastases and primary CNS tumours; infections, especially with cryptococcal granuloma, toxoplasmosis and tuberculoma; SLE—often with anticardiolipin antibodies; scleroderma; Behçet disease; Sydenham chorea; medications, including oral contraceptives, levodopa and ibuprofen; vascular: including cavernous angioma and post-surgical complications [1, 3, 25].

Clinical Features

Hemiballistic movements increase with action and stress are only rarely suppressible for more than a few seconds and disappear in sleep [25]. In patients with hyperglycaemic chorea, as the blood glucose is corrected, the disorder usually resolves completely, although mild symptoms persist for more than 3 months in 20% of

patients [25, 26]. Hemichorea refers to movements that are lower in amplitude than hemiballismus, affecting both the distal and proximal limbs; are classically irregular jerky quasi-purposive.

Management

Treatment of the underlying cause may resolve the hemiballism, although severely affected patients may still require concomitant pharmacological therapy. If stroke is the cause, standard stroke management, such as antiplatelet therapy, and secondary preventive measures, such as control of blood pressure and normalization of blood sugar, must be implemented. Padding of the affected limb and the management of systemic complications, such as exhaustion, dehydration and rhabdomyolysis, are mainstays of treatment. In the very rare case of extremely severe hemiballism causing dangerous complications, patients may require sedation or even intubation with neuromuscular blockade as a temporary bridge until effective pharmacological therapy is instituted. Tetrabenazine is the preferred symptomatic treatment for patients with persistent hemiballism. The dosage can start at 12.5 mg two or three times daily and be titrated upward to a maximum of 250 mg per day. If tetrabenazine is unavailable, ineffective or associated with severe side-effects, or if the patient has a history of severe depression, typical neuroleptics should be tried. Haloperidol is the favoured drug and is started at a dosage of 0.5–1 mg twice daily, to be titrated upwards as needed. In emergency situations, it can be given as an intramuscular dose of 1 mg. If this is ineffective, 2 mg can be repeated 4 h later. There have been reports of effective treatment with clonazepam, valproic acid, trihexyphenidyl and amitriptyline. If effective, treatment should be maintained for a period of approximately 3 months, after which the medication should be gradually withdrawn [25, 26].

Points to Remember

- Hemiballism consists of flinging movements of unilateral proximal limb.
- Stroke and non-ketotic hyperglycaemia are common causes.
- Hyperglycaemic hemiballism-hemichorea resolves with correction of blood glucose.

Tic Emergencies

Tics are sudden, brief, intermittent repetitive and stereotypic movements (motor tics) or sounds (vocal or phonetics) usually affecting children [1, 27]. They are temporarily suppressible, often preceded by a premonitory sensation or an urge to perform them, and usually produce a sense of relief. As the long-term history of tics is generally benign, the primary aim of treatment is to maintain a child in the school environment so as to achieve near-normal socialization. Rarely, tics are severe enough to cause a neurological emergency. At times, intensely frightening exacerbations may occur in the context of the waxing and waning course of a tic disorder. The drugs reported to exacerbate tics include methylphenidate, pemoline, levodopa,

phenytoin, carbamazepine, lamotrigine, phenobarbital, imipramine, clomipramine, fluoxetine, sertraline, amphetamine and cocaine; discontinuation of the precipitating agent reverses the problem [1, 27]. If there is no such causative agent, drugs for tic suppression may be warranted. As pimozide is more effective and better tolerated than haloperidol, it is the treatment of choice for acute, disabling tics. The lowest possible dose, 1 mg in the case of pimozide and 0.25 mg in the case of haloperidol, should be used. Disruptive vocal tics can be managed with intralaryngeal botulinum toxin injections [28, 29]. Tic disorders can cause various types of acute pain syndromes, including pain resulting from the actual performance of the tic (such as neck pain caused by sudden neck movements); pain resulting from a traumatic injury due to being struck by a body part involved in tics; pain caused by the effort of tic suppression (excessive isometric muscle contraction); self-inflicted pain in order to reduce tic expression and pain caused by behavioural abnormalities accompanying the tic disorder, such as self-mutilating compulsions.

The chronic tic patient may present for an urgent consultation because of the onset of new abnormal movements secondary to anti-tic medications. As opposed to tics that are generally perceived as 'voluntary' and suppressible, patients usually perceive tardive dystonic or choreic movements as 'involuntary' and not suppressible. Unlike tics, dystonic or choreic movements remain unchanged or even increase during distraction or the performance of skilled tasks. Usually, a significant decrease in the neuroleptic medication is required to achieve relief of movements like akathisia. If the neuroleptic dose cannot be reduced, the addition of anticholinergics, amantadine or β-blockers may be helpful. At times, patients may present to the emergency room with loud, uncontrollable barking, yelping, shouting of obscenities or other vocal utterances. Parenteral neuroleptics may be required to control such severe phonic tics. Botulinum toxin A (BTX-A) injections into the thyroarytenoids have been shown to be a particularly useful option for patients with severe, loud and disabling involuntary vocalizations [29, 30].

Points to Remember

- Tics are sudden, brief, intermittent, repetitive and temporarily suppressible stereotypic movements.
- When exacerbated by drugs, acute tics are managed by discontinuation of the precipitating agent.
- Tics can also be managed with pimozide and haloperidol.
- One needs to differentiate tics from drug-induced dyskinesias and akathisia.

Abductor Paresis in Multiple System Atrophy

Introduction and Clinical Features

The onset of stridor, initially at night but later throughout the day, is a grave symptom in the setting of atypical parkinsonism, especially multiple system atrophy (MSA). The mean survival is less than 1 year. Classic abductor paresis (AP) can appear at any time in the course of MSA, even as an initial or an isolated symptom.

Causes and Pathophysiology

Neurogenic atrophy of the posterior cricoarytenoid muscle, which is the abductor of the vocal cords, is caused by neuronal loss in the nucleus ambiguus. In patients with MSA and AP, inspiratory negative pressure caused by diaphragmatic contraction occurs concurrent with or even before a full opening of the vocal glottis, because of the delay in abduction. Paradoxical movement of the vocal cords occurs with inspiratory adduction and expiratory abduction [31, 32].

Investigations and Management

Diagnosis of MSA is made on the basis of clinical criteria. A definite diagnosis of AP is made by fibre optic laryngoscopy, performed both during wakefulness and sleep. If the larynx is the culprit and the spasm is severe, an emergency tracheostomy is indicated. Nasal continuous positive air pressure at night can successfully treat nocturnal stridor and apnoea in patients who choose not to undergo tracheostomy. Other therapeutic options include arytenoidectomy, cord lateralization, cordectomy and BTX-A injection into the adductors [1].

Course and Prognosis

Abductor paresis usually takes two different courses: slowly progressive and rapidly progressive. In the former, there is a gradual deterioration over 1–3 years as a result of paralytic denervation of the abductor. In the rapidly progressive type, an emergency tracheostomy or a tracheal intubation is often needed, even if the patient is already known to have AP [1].

Points to Remember

- Stridor due to abductor paresis is a common complication of MSA.
- It is caused by neurogenic atrophy of the posterior cricoarytenoid muscle.
- Emergency tracheostomy may be required for acute management.

Drug-Induced Emergencies (Table 22.2)

Neuroleptic Malignant Syndrome

Introduction and Clinical Features

Neuroleptic malignant syndrome (NMS) is a drug-induced disorder resulting from exposure to neuroleptics that act by blocking dopamine receptors. Both typical and atypical neuroleptics are known to be associated with NMS. Other medications such as prochlorperazine, metoclopramide, amoxapine, tetrabenazine, droperidol, lithium and promethazine are also implicated. Although the incidence of NMS is 0.02–3.2% among patients prescribed antipsychotic medications, it is important to recognize this potentially fatal reaction (mortality rate 5–20%). It is characterized by rigidity, fever, autonomic instability and altered level of consciousness [31–34]. The other signs include catatonia, tachycardia, tachypnoea, labile blood pressure, dysarthria, dysphagia, diaphoresis, sialorrhoea, incontinence, myoclonus, tremors

Table 22.2 Drug-induced emergencies

Condition	Treatment
1. Neuroleptic malignant syndrome	(a) Discontinue the antipsychotic (b) Parenteral hydration (c) External cooling (d) Bromocriptine, dantrolene or amantadine (e) ECT for refractory cases
2. Parkinsonism-hyperpyrexia syndrome	(a) Re-institute the discontinued drug (b) Intravenous levodopa/apomorphine
3. Serotonin syndrome	(a) Discontinuation of the precipitating drugs (b) Benzodiazepines (c) Cyproheptadine
4. Acute dystonia	Anticholinergic drugs
5. Acute drug-induced akathisia	Beta-blockers, anticholinergics, benzodiazepines, clonidine, vitamin B_6

and elevation of serum creatine kinase. Symptoms often begin after initiation or an increase in the antipsychotic dose. NMS increases in severity over 48–72 h and lasts 2–14 days. The differential diagnoses include CNS infections, porphyria and tetanus.

Medical complications of NMS include renal failure from rhabdomyolysis, respiratory failure from decreased chest wall compliance, potentially fatal arrhythmias, aspiration pneumonia and other complications of immobility such as deep venous thrombosis, pulmonary embolism and pressure sores.

Causes and Pathophysiology

Neuroleptic-induced dopamine blockade in different parts of the brain accounts for the various features of NMS. Dopamine reduction in the hypothalamus causes fever and autonomic instability; in the nigrostriatal system it leads to rigidity; and reduction in corticolimbic dopamine activity accounts for the altered consciousness [34–36]. However, the dopaminergic blocking theory alone does not explain why NMS develops at a given time in a given patient. There are probably other genetic, constitutional, environmental and pharmacological factors that interact to produce the syndrome [36].

Treatment

The most critical step in the treatment is to recognize the clinical features of the syndrome and discontinue the antipsychotic drug without delay. Supportive interventions include cooling blankets for fever, cardiac monitoring, monitoring for urine output and renal function, and parenteral rehydration [37]. Haemodialysis may be required in the case of acute renal failure associated with myoglobinuria. Trials of bromocriptine, dantrolene or amantadine may be helpful for patients with moderate to severe symptoms [38]. Bromocriptine in a dosage of 5–10 mg thrice a day provides relief from the symptoms, especially muscle rigidity. Other *dopaminergic agents* including carbidopa/levodopa, ropinirole and pramipexole are likely effective.

Muscle relaxant dantrolene, classically used in malignant hyperthermia, is helpful in decreasing rigidity, hyperthermia and tachycardia. The usually recommended dosage is 1–3 mg/kg/day orally or intravenously, in four divided doses. *Anticholinergics* are generally best avoided as they may impair heat dissipation in febrile patients. *Benzodiazepines* may be useful for agitation and rigidity. *Electroconvulsive therapy* can be useful when the NMS symptoms are refractory or when there is a need for psychiatric treatment owing to a prolonged absence of antipsychotic pharmacotherapy [38].

Most patients with NMS respond to the discontinuation of antipsychotics and fluid replenishment. Treatment should continue for 7–10 days depending on the half-life of the culprit antipsychotic. It is recommended to wait for at least 2 weeks before re-starting antipsychotics after NMS has cleared as 1/3rd of the patients may relapse if the antipsychotics are re-started too early.

Points to Remember

- NMS is a life-threatening complication of the use of neuroleptics, both typical and atypical.
- It is characterized by fever, rigidity, confusion, autonomic instability and raised creatine kinase.
- Most patients respond to discontinuation of the neuroleptic agent, along with supportive measures.

Parkinsonism-Hyperpyrexia Syndrome

Introduction and Clinical Features

Parkinsonism-hyperpyrexia syndrome (PHS) is clinically indistinguishable from NMS except that it occurs in patients with pre-existing parkinsonism, in whom levodopa or other dopaminergic drugs are suddenly withdrawn or altered [39]. Time of onset of the symptoms after change in dopaminergic therapy ranges from 18 h to 7 days. Initial feature in most patients is severe rigidity, along with tremor and dysautonomia. Within 72–96 h, most patients are febrile and have an altered mental status, ranging from agitation and confusion to stupor and coma [39, 40]. After the inciting event, the period between latency and the onset of symptoms is usually twice as long (93 h vs. 49 h) for PHS as for NMS. NMS is a more aggressive disorder than PHS, and carries a poorer prognosis [40].

Causes and Pathophysiology

Hypodopaminergic state usually triggers the syndrome, as in NMS. Parkinsonism-hyperpyrexia syndrome has been seen in patients of Parkinson disease following sudden cessation or even partial withdrawal of dopaminergic therapy or when regimens of medication are changed. With the advent of bilateral subthalamic nucleus stimulation for advanced Parkinson disease, similar presentations have occurred when stimulators were accidentally turned off [39]. It can also be precipitated by aggressive medication adjustments after DBS surgery in PD. It is important to recognize that DBS surgery does not protect the patient from PHS.

Management

As in NMS, any patient presenting with 'febrile encephalopathy' and extrapyramidal features must also undergo brain imaging to exclude encephalitis or structural lesions. Creatine kinase and white blood cells are usually not as elevated as in NMS associated with neuroleptic use. When discontinuation of medication is the cause, the drug most commonly responsible is levodopa, and it should be re-instituted, via a nasogastric tube if necessary, at the same dosage as earlier. When nasogastric feeding is contraindicated because of a gastrointestinal problem such as ileus, intravenous levodopa infusion can be started. 50–100 mg of levodopa should be infused using an infusion pump over 3 h, and this should be repeated 3–4 times a day until oral intake of levodopa becomes possible. If an intravenous formulation of levodopa is unavailable, apomorphine injections may be tried at a dosage of 1.0–2.0 mg/h [41]. The rest of the management is similar to that of NMS, including rehydration with intravenous fluids and treatment of hyperthermia with antipyretics and cooling blankets, as well as supportive measures such as mechanical ventilation, cardiovascular monitoring and prevention of thrombophlebitis. Because these patients are at risk for infections such as aspiration pneumonia, it is reasonable to initiate antibiotic therapy while awaiting the work-up. Additional medical therapy with bromocriptine or other dopamine agonists and dantrolene should be utilized at the same dosages as for NMS. Steroid pulse therapy might shorten the course of the illness. Electroconvulsive therapy has also been successfully tried in refractory cases [41].

Prevention

If reduction in dopaminergic therapy is needed, gradual reduction is mandated and patients should be made aware of the possible occurrence of PHS. This applies to patients with idiopathic Parkinson disease as well as those with Parkinson plus syndrome or secondary parkinsonism receiving levodopa therapy.

Points to Remember

- PHS resembles NMS and occurs on sudden discontinuation or change of dosage of anti-parkinsonian drugs.
- Fever, altered mental status and rigidity are the characteristic features.
- It responds to re-institution of the previous dosage of levodopa/dopamine agonist drug.
- Recovery is more rapid and complete than in NMS.

Serotonin Syndrome

Introduction and Clinical Features

The serotonin syndrome is a largely under-recognized, potentially life-threatening adverse drug reaction that results from overstimulation of serotonin (5-HT) receptors by various serotonergic agents. The clinical features include fever with

tremors, shivering, diaphoresis, myoclonus, hyperreflexia, changes in behaviour, hypertension, mydriasis, hyperactive bowel sounds and horizontal ocular clonus [42, 43].

Causes and Pathophysiology

Serotonin syndrome is thought to result from stimulation of the 5-HT1_a and 5-HT$_2$ receptors [44]. The drugs associated with the serotonin syndrome include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), opiate analgesics, valproate, linezolid, sibutramine, ondansetron, metoclopramide, sumatriptan, methylene dioxymethamphetamine (MDMA, or 'ecstasy') and lysergic acid diethylamide (LSD) [42].

Management

Management of the serotonin syndrome entails discontinuation of the precipitating drugs, in addition to supportive care. Agitation usually needs to be controlled with benzodiazepines. Cyproheptadine, a 5-HT$_{2a}$ antagonist, is a specific therapy, although its efficacy has not been rigorously established [44, 45]. After an initial dose of 12 mg, 2 mg of cyproheptadine is administered every 2 h if the symptoms continue. Maintenance dosing involves the administration of 8 mg of cyproheptadine every 6 h. In most cases, the serotonin syndrome is a self-limiting condition that improves on cessation of the offending drugs. In severe cases, patients require intensive care as the syndrome may be complicated by severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and/or adult respiratory distress syndrome [44].

Points to Remember

- Acute onset fever, tremors, myoclonus, hyperreflexia, changes in behaviour, hypertension and hyperthermia in a patient taking 2 or more serotonergic medication(s) should raise the suspicion of serotonin syndrome.
- The treatment consists of discontinuation of the offending drug(s) and the administration of cyproheptadine.

Acute Neuroleptic-Induced Dystonia

Introduction and Clinical Features

Dystonia is a movement disorder characterized by sustained muscle contractions producing torsional and repetitive movements or abnormal postures [46]. Acute dystonia can be in the form of orofacial dystonia, back arching, neck extension and even life-threatening laryngospasm. Acute dystonic reactions are most common after injectable high-potency antipsychotics, but also occur shortly after the introduction of oral antipsychotics and occasionally, after an increase of dosage [47]. Dystonia begins within 24 h of exposure, and 90% of reactions occur within 5 days. Acute dystonia is more likely to occur with typical antipsychotics (6%)

than the newer atypical drugs (1–2%) [48]. A form of acute dystonic reaction characterized by tonic lateroflexion of the trunk, appearing 3–10 days after starting dopamine-blocking agents, is known as the Pisa syndrome [47].

Pathophysiology

Dopaminergic blockade results in relative cholinergic overactivity, leading to dystonia. There may also be paradoxical dopaminergic hyperfunction induced through blockade of presynaptic dopamine receptors [48, 49].

Management

Acute dystonic reactions may be prevented by the use of anticholinergic drugs. Patients at high risk for acute dystonia (young patients, cocaine abusers, AIDS patients, those with a previous/family history of dystonia) requiring antipsychotics may be prescribed prophylactic anticholinergics [50]. Acute dystonia responds well to injectable anticholinergic drugs, notably diphenhydramine (25 or 50 mg). The response to this is so consistent that if a patient with suspected drug-induced acute dystonia fails to respond, an alternative diagnosis should be considered [49].

Points to Remember

- Neuroleptic use may be complicated by acute dystonic reactions in susceptible individuals.
- These may be managed with anticholinergics and prevented by prophylactic anticholinergics.

Acute Drug-Induced Akathisia

Introduction and Clinical Features

Akathisia literally means ‘inability to remain seated’. Drug-induced acute akathisia is defined as a subjective feeling of restlessness and an intensely unpleasant need to move, occurring secondary to antipsychotic treatment. Akathisia is estimated to occur in 20–75% of patients treated with conventional antipsychotics [50, 51]. Atypical antipsychotics are less likely to cause akathisia. It tends to occur within the first 4 weeks of initiating or increasing the dosage of antipsychotic medication. Patients with akathisia tend to have subjective complaints of ‘inner restlessness’, most often in the legs. This is manifested as fidgeting, frequent changes in posture, crossing and uncrossing of the legs, rocking while sitting, marching in place and shuffling when walking. Akathisia is often associated with dysphoria, anxiety and irritability. Akathisia in a psychotic patient can easily be mistaken for worsening of psychotic features, which may cause the clinician to increase the dosage of the antipsychotic, exacerbating the akathisia [49].

Management

The initial approach is to try and reduce the risk of developing akathisia by minimizing the dosage of antipsychotic medication. The use of atypical antipsychotics should be considered because they are associated with a lower risk of akathisia. Specific anti-akathisic drugs can be initiated. These include beta-blockers, anticholinergics, benzodiazepines, clonidine and vitamin B_6 [52].

Points to Remember

- Acute akathisia is a not so uncommon complication of neuroleptic use.
- Reducing the dosage of conventional antipsychotics and preferential use of atypical antipsychotics can prevent most such reactions.

Conclusion

Although most movement disorders have a chronic presentation, physicians need to be familiar with the recognition and management of acute movement disorders in the emergency. These may sometimes be life-threatening. A detailed history, including a history of the drugs used by the patient, is vital for the recognition of individual conditions. Although treatment is usually supportive, early recognition and management of the precipitating factors, along with well-tailored symptomatic management, are vital in determining the prognosis.

Table 22.3 gives details of drugs used in the treatment of various movement disorders.

Table 22.3 Drugs used in the treatment of various movement disorders

Drug	Dosage	Adverse events	Interactions
Carbidopa/levodopa	TID: 25 mg carbidopa + 100 mg levodopa ('25/100' tablet), half a tablet twice or three times a day MD: 200–1200 mg levodopa • No dosage adjustment is required for patients with renal or hepatic insufficiency • Avoid in pregnancy	• Cardiac arrhythmias • Orthostatic hypotension • Nausea, vomiting • Peripheral oedema • Psychosis, confusion	• Neuroleptic drugs reduce the effect of levodopa • Levodopa enhances the effect of any drugs that lower blood pressure • Risk of cardiac arrhythmias with volatile liquid anaesthetics, such as halothane

(continued)

Table 22.3 (continued)

Drug	Dosage	Adverse events	Interactions
Bromocriptine	TID: 1.25 mg twice a day MD: 3.75–40 mg Avoid in pregnancy	• Confusion, euphoria, agitation, anxiety • Nausea, vomiting • Cardiac arrhythmias, hypotension • Polyuria, incontinence • All the ergotamine derivatives can cause pulmonary, retroperitoneal and pericardial fibrosis	Dopamine agonists must be avoided in patients with psychiatric disease or dementia. The elderly are at particular risk for confusion Metoclopramide antagonizes the effects of these drugs Dopa agonists enhance the effect of any drugs that lower blood pressure Risk of cardiac arrhythmias with volatile liquid anaesthetics, such as halothane
Ropinirole	TID: 0.25 mg three times a day MD: 1.5–24 mg Avoid ropinirole in patients with severe renal insufficiency Reduce the dose of ropinirole in severe hepatic insufficiency	• Confusion, euphoria, agitation, anxiety • Nausea, vomiting • Cardiac arrhythmias, hypotension • Polyuria, incontinence • Obsessive behaviour, pathological gambling	
Amantadine	TID: 100 mg per day MD: 200–400 mg per day Reduce the dose of amantadine in patients with moderate renal insufficiency		• Dopamine antagonists may diminish the effectiveness
Apomorphine	Should be used as subcutaneous injections only, not for i.v. use as i.v. crystallization leads to thrombus formation and pulmonary embolism TID: 0.2 ml (2 mg) Maximum dose: 0.6 ml (6 mg) Starting dose should be reduced to 1 mg when administrating to patients with mild or moderate renal impairment	• Nausea, vomiting • Orthostatic hypotension, syncope • Prolongs the QT/QTc interval, causes torsades de pointes • Hallucinations, somnolence • May cause dyskinesia or exacerbate pre-existing dyskinesia • Priapism • Injection site reactions including bruising, granuloma and pruritus	• Concomitant use of apomorphine with drugs of the 5HT3 antagonist class such as ondansetron is contraindicated as it causes profound hypotension and loss of consciousness • Caution should be exercised when prescribing apomorphine concomitantly with drugs that prolong the QT/QTc interval

Table 22.3 (continued)

Drug	Dosage	Adverse events	Interactions
Anticholinergics			
Trihexyphenidyl HCl	TID: 1 mg twice a day MD: 2–15 mg Although not contraindicated for patients with cardiac, liver or kidney disorders, or with hypertension, such patients should be maintained under close observation It should be used with caution in patients with glaucoma, obstructive disease of the gastrointestinal or genitourinary tracts, and in elderly males with possible prostatic hypertrophy	• Dryness of the mouth, blurring of vision, dizziness, nausea, vomiting • Mental confusion, agitation, disturbed behaviour • Constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilatation of the pupil, increased intraocular tension, weakness, vomiting and headache	
Diphenhydramine	10–50 mg i.v. at a rate not exceeding 25 mg/min or deep i.m. Maximum daily dose: 400 mg Antihistamine therapy is contraindicated in nursing mothers		
Dopamine depleter Tetrabenazine	TID: 25 mg per day MD: 50–200 mg per day • Dosage should be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers • Contraindicated in hepatic impairment • Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus	• Sedation/somnolence/fatigue • Orthostatic hypotension • Hyperprolactinaemia • Akathisia • Increase in the corrected QT interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia • Depression, suicidal tendencies	• Contraindicated in patients taking monoamine oxidase inhibitors • Should be avoided in combination with other drugs that are known to prolong QTc • Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetrabenazine should be halved

(continued)

Table 22.3 (continued)

Drug	Dosage	Adverse events	Interactions
Sedative-hypnotics Propofol	Initial IV bolus of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg i.v. (25% of initial dosage) as needed to achieve the desired level of sedation Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available	• Respiratory depression • Hypoxaemia • Hypotension	• May produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics
Benzodiazepines			
Midazolam	0.01–0.05 mg/kg for induction of sedation For maintenance of sedation, the usual initial infusion rate is 0.02–0.1 mg/kg/h	• Respiratory depression • Hypoxaemia • Hypotension	May produce additive cardio-respiratory effects when administered with other cardio-respiratory depressants such as sedative-hypnotics and narcotic analgesics Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system such as cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole; these may result in prolonged sedation due to a decrease in plasma clearance of midazolam

Table 22.3 (continued)

Drug	Dosage	Adverse events	Interactions
Clonazepam	TID: 0.25–0.5 mg per day Maximum dose: 20 mg per day		
Skeletal muscle relaxant Dantrolene	Oral: 4–8 mg/kg per day Intravenous: TID: 1 mg/kg MD: 10 mg/kg per day • Should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus	• Decrease in grip strength and weakness of leg muscles • Lightheadedness • Liver dysfunction • Thrombophlebitis • Pulmonary oedema	• If patients judged malignant hyperthermia susceptible are administered dantrolene, avoidance of known triggering agents must be done • Combination with calcium-channel blockers can precipitate cardiac arrhythmias
Antipsychotics			
Haloperidol	Oral TID: 0.25 mg per day MD: 5–20 mg per day Parenteral: 2–5 mg	• Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness • Tachycardia, hypotension and hypertension • Extrapyramidal symptoms including dystonia, tardive dyskinesia • Neuroleptic malignant syndrome (NMS) • Tachycardia, hypotension and hypertension • QT-prolongation and torsades de pointes	Haloperidol should be administered cautiously to patients: • with severe cardiovascular disorders • receiving anticonvulsant medications because haloperidol may lower the convulsive threshold

(continued)

Table 22.3 (continued)

Drug	Dosage	Adverse events	Interactions
Pimozide	TID: 1 mg per day MD: 5–10 mg per day		
Serotonin blocker Cyproheptadine	TID: 0.25 mg/kg per day MD: 4–32 mg per day Contraindicated in nursing mothers	• Sedation and sleepiness • Disturbed coordination • Acute labyrinthitis, blurred vision, diplopia, • Hypotension, palpitation, tachycardia • Dryness of nose and throat, • Urinary frequency, difficulty in urination, urinary retention	• MAO inhibitors prolong and intensify the anticholinergic effects of antihistamines • Should be used with caution in patients with history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease and hypertension

TID treatment initiating dose, *MD* maintenance dose, *MAO* monoamine oxidase

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