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Emergencies in movement disorders

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Abstract

Movement disorders can be defined as the abnormality of the speed and form of body movements. Although movement disorders often occur chronically, they can sometimes develop acutely or sub-acutely, and some can be fatal if not diagnosed and treated early. Here, emergencies in movement disorders are discussed under two main headings, as emergencies related to hyperkinetic movement disorders and emergencies related to hypokinetic movement disorders. This review draws attention to the importance of that accurate diagnosis and early treatment can be life-saving in emergencies in movement disorders. It also provides recommendations for diagnosis and therapy.

Keywords: movement disorders, emergencies, hyperkinetic movement disorders, hypokinetic movement disorders

1. Introduction

Movement disorders can be defined as the abnormality of the speed and form of body movements. Most of this group of disorders are due to deviations from the typical basal ganglia-cortex cycle (1). However, some movement disorders, such as myoclonus, may arise from pathologies in the spinal cord and other structures (1). Movement disorders are divided into two groups (1): 1) Hyperkinetic movement disorders are excessively unwanted movements and include tremor, chorea, ballism, dystonia, stereotypy, tics, and myoclonus. 2) Hypokinetic movement disorders include akinesia (loss of movement), hypokinesia (decreased amplitude of movement), bradykinesia (slowing of movement), and rigidity. Sometimes akinesia can be used broadly to include hypokinesia and bradykinesia. Therefore, hypokinetic movement disorders can also be expressed as akinetic-rigid disorders (1). Parkinsonism is an example of a hypokinetic movement disorder. Although movement disorders often occur chronically, they can sometimes develop acutely or sub-acutely, and some can be fatal if not diagnosed and treated early. Studies on the frequency of emergent movement disorders are few. In a prospective study (2), 6690 of 131,537 patients admitted to the emergency department underwent neurologic evaluation, of which 1.4% were diagnosed with acute movement disorders. It was revealed that 73.9% of these patients had hyperkinetic, 26.1% hypokinetic and 19.8% mixed movement disorders (2). There are few publications about emergencies in movement disorders in English literature. Here, emergencies in movement disorders have been discussed under two main headings, emergencies related to hyperkinetic movement disorders and emergencies related to hypokinetic movement disorders. Here, we have discussed the clinical features (ie, definition, brief pathogenesis, causes, and diagnosis) and emergency treatment of each emergency movement disorder.

2. Emergencies related to hyperkinetic movement disorders

This group includes acute chorea and ballismus, immediate myoclonus, emergencies in tic disorder, and acute dystonia and dystonic storm.

2.1. Acute chorea and ballismus

Clinical features

Chorea is irregular, unpredictable, short, and non-stereotypical aimless movements that flow rapidly from one body part to another (3). Ballismus is a proximally dominant, irregular, abrupt, rough and bouncing rocking or throwing movement and is closely related to chorea (4). Indeed, ballismus and chorea are two hyperkinetic movements that differ in speed and amplitude, one of which may represent the continuity of the other (5). Hemiballism is ballistic movements on one side of the body. Movements can be self-destructive, tiring, or troublesome. Movements often improve after days to weeks, and ballistic movements often become choreiform (3). The most common cause is stroke [affecting the contralateral subthalamic nucleus (STN)], followed by non-ketotic hyperglycemia (3). Acute severe chorea and ballismus, if left untreated, can cause hyperthermia, dehydration, and rhabdomyolysis (5). Table 1 shows the causes of acute chorea and ballismus (5).

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Table 1. Causes of acute chorea and ballismus

Vascular	Autoimmune	Metabolic	Infectious	Structural	Drug/toxin
Stroke (Ischemic / hemorrhagic)	Sydenham / chorea gravidarum	Uremic encephalopathy	Cryptococcal granuloma	Basal ganglia lesion/mass	Alcohol
Malformation	Paraneoplastic*	Hypoglycemia	Toxoplasma	Cerebellar lesion	Antiepileptics
Cerebral anoxia	Multiple sclerosis	Hypoparathyroidism	Tuberculoma	Subthalomotomy	Methadone
Postpump chorea	SLE	NKHG	HIVE	Thalamotomy	Amphetamine
	Scleroderma	Hyperthyroidism			Morphine
	Behcet's disease	Polycythemia vera			Oral contraceptive
	APS				Levodopa
	Sarcoidosis				Cocaine
	PAN				

*May be anti CV2/CRMP-5 antibody-positive; SLE, Systemic lupus erythematosus; NKHG, Non-ketotic hyperglycemia; HIVE, Human immunodeficit virus encephalitis; APS, Anti-phospholipid antibody syndrome; PAN, *Polyarteritis nodosa*

Diagnosis is supported by laboratory investigations appropriate to clinical findings after clinically evaluating patients (5). Magnetic resonance imaging (MRI) is often the first step, and a change in intensity in the basal ganglia may be seen. Auto-antibodies [e.g., α-streptolysin-O (ASO) and α-DNAase-B antibodies for a patient with Sydenham chorea] and other biochemical studies may be required for diagnosis and differential diagnosis (6). Sometimes functional imaging [e.g., *fluorodeoxyglucose*-positron emission tomography (FDG-PET)] may be needed. It has been reported that striatal hypermetabolism in FDG-PET is present in the acute phase of the disease in patients with Sydenham's chorea (6, 7), whereas striatal hypometabolism has been reported in FDG-PET in degenerative chorea (e.g., Huntington's disease) (7).

Treatment

Here, we will first define the general principles of the approach and then add specific treatments in some special clinical situations. In the general approach, the dose of the causative drug, if any, should be reduced first, or the drug should be temporarily stopped. Rehydration should be provided to meet the fluid deficit and prevent complications such as acute renal failure due to rhabdomyolysis. Dopamine receptor blockers (e.g., antipsychotics) or dopamine depleters (e.g., inhibitors of the presynaptic vesicular monoamine transporter type 2 - VMAT2 such as tetrabenazine) can be used to reduce symptomatic chorea and ballism (4, 6). If there is hyperthermia, antipyretic approaches (e.g., cooling the body) and drugs (e.g., paracetamol) should be given. If necessary, sedation (e.g., diazepam) should be provided. Since movements may disappear over time in hemiballism, treatment should be discontinued after three months, and the patient should be re-evaluated (3). On the other hand, it is crucial to investigate the underlying pathological condition or disease (Table 1.) and perform specific treatment accordingly (3).

Chorea due to non-ketotic hyperglycemia

Clinical features

Chorea due to non-ketotic hyperglycemia is more common in the elderly, women and people of Middle Asian origin (5, 8). It has been reported that GABA insufficiency may play a role in the mechanism of emergence of chorea in this group of patients since it causes deterioration of the basal ganglia functions (8). Because it has been reported in these patients that GABA is rapidly depleted due to both the use of GABA as energy and the lack of acetoacetate, which can be used to synthesize GABA (8). The clinic often presents as hemichorea (often ipsilateral extremity, sometimes predominant in the facial muscles, jaw and tongue) or hemiballism, with an acute/subacute onset (3, 5). Biochemical examination reveals high blood sugar and negative ketones in the urine, while T1-weighted MRI shows a change in intensity in the basal ganglia (Fig. 1) (3, 5).

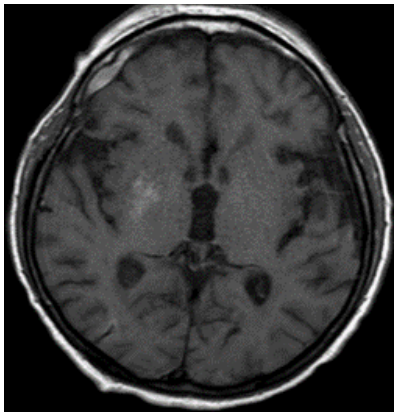

Fig. 1. T1-weighted MRI of a 67-year-old male patient with left hemichorea due to non-ketotic hyperglycemia shows hyperintensity in the right globus pallidus.

Treatment

Blood glucose regulation, supportive care, and symptomatic treatment (e.g., dopamine receptor blockers and, if necessary, sedation) should be given (mentioned in the general approach to chorea) (4,6,8).

Sydenham's chorea

Clinical features

Sydenham's chorea may begin abruptly 1 to 6 months after streptococcal pharyngitis (3, 9). It has been reported that autoimmune pathologies in persons with genetic predispositions are involved in the pathogenesis of Sydenham's chorea (6). It has been reported that anti-basal ganglia antibodies (e.g., antibodies developed against epitopes of M-

proteins) against A β-hemolytic streptococcus cause pathological changes that will lead to loss of function by acting against neuronal tubulin and D1 and D2 receptors in basal ganglia (6). Although chorea is often generalized clinically, it can also occur as hemichorea at a rate of 20% (6). Behavioral changes such as obsessive-compulsive disorder, hyperactivity, anxiety and emotional lability may accompany chorea (6). Weakness and hypotonia may be prominent, and even paralytic chorea may develop in 1.5% of cases (6, 10). Oculogyric crisis, hypometric saccades, and rarely vocal tics and dysarthria have also been reported (6, 10). The diagnosis is made clinically, but high ASO and anti-DNAse B antibody titers support the diagnosis (5, 6, 10). It has been reported that FDG-PET and Single Photon Emission Computerized Tomography (SPECT) performed in the acute phase of the disease revealed the striatal abnormality (striatal hypermetabolism and hyperperfusion, respectively) (6).

Treatment

In addition to supportive treatment, GABAergic drugs (e.g., benzodiazepines, valproic acid at a dose of >1500mg/day or carbamazepine), dopamine receptor blockers or dopamine depleting agents can be used in the symptomatic treatment of chorea (6, 10). In Sydenham's chorea, immunomodulatory therapy is recommended to shorten the disease duration and prevent relapses and complications (e.g., 25 mg/kg/day intravenous methylprednisolone for five days followed by oral deflazacort 0.9 mg/kg/day for three months, especially in severe or persistent cases of chorea, 1-2 gr/kg/day for two days or 400 mg/kg/day for five days intravenous immunoglobulin or plasma exchange) (10-12). It has been reported that penicillin can prevent cardiac complications of rheumatic fever (sometimes it may take several years) (10-12).

Chorea gravidarum

Clinical features

Chorea gravidarum (CG) often begins in the first trimester of pregnancy and may rarely cause an emergency (3). It is estimated that chorea may be related to increased sensitivity to dopamine in the striatum due to hormonal changes in patients (12). On the other hand, it has been reported that antiphospholipid antibody syndrome (APAS) is a common cause of CG in some people (3). It has been reported that it may also be associated with previous Sydenham's chorea (5, 12). Chorea can be unilateral or bilateral, often, the face and extremities are affected, and dysarthria is common (3). Psychiatric complaints may accompany chorea (13).

Treatment

In CG, chorea usually resolves in the last trimester or disappears shortly after birth (14). In severe cases, general acute chorea therapy (e.g., haloperidol symptomatically) is administered (5). Abortion or premature delivery may be indicated rarely (15).

Antiphospholipid antibody syndrome (APS)

Clinical features

Antiphospholipid antibody syndrome may cause acute generalized chorea (3). Antiphospholipid antibody syndrome may be primary or secondary to systemic lupus erythematosus (3). It has been reported that antiphospholipid antibodies, which cause inflammation and increase the permeability of the blood-brain barrier by binding to the intracranial endothelium, cause chorea due to direct binding to the basal ganglia neurons (12). Antiphospholipid antibodies (i.e., lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein-I) are used for diagnosis (16).

Treatment

Treatment consists of general acute chorea treatment, immunosuppressive/immunomodulatory treatment of APS, and follow-up and treatment of its complications (deep vein thrombosis, pulmonary embolism, stroke, thrombotic microangiopathy, thrombocytopenia, and hemolytic anemia) (12).

2.2. Immediate myoclonus

Clinical features

Myoclonus can be defined as a sudden-shock-like involuntary contraction (positive myoclonus) or inhibition (negative myoclonus) of muscle (agonist or antagonist) or muscle groups (3, 17). The pathogenesis of myoclonus is related to the source of the stimulus (e.g., it can be cortical, subcortical, brain stem, spinal cord or peripheral) (1, 18). Table 2 shows the causes of immediate myoclonus (3, 18).

Table 2. Causes of immediate myoclonus and clinical pictures

Etiology	Clinical picture(s)
Cerebral anoxia	Postanoxic myoclonus, Myoclonus SE
Metabolic disorders; Hepatic and uremic encephalopathy	Asterix
Toxic disorders; MAO inhibitors, SSRI, SNRI and tricyclic antidepressants, opiates, levodopa, gabapentin, triptans, LSD, amphetamines, cocaine, MDMA or ecstasy	Serotonin syndrome and NMS
Structural disorders; Thalamic lesion (contralateral)	Acute focal Asterix, positive myoclonus

SE, Status epilepticus; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin noradrenaline reuptake inhibitor; NMS, Neuroleptic malignant syndrome; LSD, Lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine

Postanoxic myoclonus (Lance-Adams syndrome)

Clinical features

Lance-Adams syndrome is seen after recovery from anoxia (delayed onset) (3). It is action myoclonus (often intentional), absent at rest, and stimulus sensitive (3, 19). Myoclonus is of cortical origin, and it may be accompanied by mild cognitive impairment, dysarthria, ataxia, pyramidal signs, rigidity, and epilepsy (3, 19). It may resolve spontaneously over the years (3, 19).

Treatment

Clonazepam, primidone, valproic acid, or levetiracetam can be used alone or in combination for the symptomatic treatment of myoclonus (3).

Myoclonus status epilepticus

Clinical features

Myoclonus status epilepticus is a persistent generalized or multifocal myoclonus involving the face, extremities and axial muscles in coma patients and is spontaneous or sensitive to sound (3, 20). It is reported that it is seen in 30% of comatose adults who develop after cardiac arrest (21). It may begin in the hours immediately after cerebral anoxia (3). It may be of cortical (giant SEP; abnormal EEG) or subcortical (SEP and EEG normal) origin (20). Myoclonus status epilepticus is often considered to be a poor prognostic sign of cerebral anoxia (22). Additional poor prognostic features are defined as 1) death, 2) persistent unconsciousness after one month, or 3) severe disability requiring complete care after six months (3).

Treatment

After venous access is established, respiratory-circulatory support and therapeutic hypothermia should be applied to the patient as supportive treatment. While levetiracetam or Pracetam is the first choice for the cortical origin for the symptomatic treatment of myoclonus, valproic acid, phenytoin, phenobarbitone, and benzodiazepines can be used in combination with levetiracetam or Pracetam if there is no adequate response (23). Subcortical origin is often treated with clonazepam (23). In cases that cannot be controlled with these treatments, anesthesia should be provided with propofol (supports GABA) infusion. However, propofol can cause myoclonus (case reports) (20).

2.3. Emergencies in tic disorder

Clinical features

Tic disorder is defined as semi-voluntary, sudden, rapid, non-rhythmic, intermittent, repetitive movements (motor tics) or sounds (voice tics) (3, 24, 25). Pathogenetically, it results from the disinhibition of the loop between the cortex-basal ganglia-cortex (24). Conditions that require urgent evaluation in tic disorder include tic exacerbation (i.e., increase in amplitude, efficacy, or frequency) and neurological effects associated with severe exacerbation (e.g., spacing-subdural hematoma, compressive neuropathy, and myelopathy) (3). Factors that worsen tics include fatigue, physical or mental stress, anger, infection, stimulants and tricyclic and SSRI group antidepressants (for the treatment of comorbid conditions such as attention-deficit/hyperactivity disorder or OCD that may accompany tics) (3).

Treatment

First of all, removing the precipitating factor is very important to reduce the severity of deterioration (2, 3). Neuroleptics such as pimozide, haloperidol and risperidone, anti-hypertensives such as clonidine and guanfacine and tetrabenazine (dopamine-depleting agent) can be used as symptomatic treatment of tic attack (2,3). Botulinum toxin injections may be appropriate for focal tics (25). For tics resistant to pharmacological treatment, surgical treatment (e.g., deep brain stimulation) may be an option (26). In addition, the treatment of complications is essential.

2.4. Dystonic emergencies

Dystonic storm or status dystonicus

Clinical features

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions that cause abnormal, frequently repetitive, patterned movements, postures, or both (25). A dystonic storm is defined as continuous severe dystonic contractions in patients with dystonia (2). Dystonic storms can cause acute worsening (2). Aggravating factors include infection, drug changes, and trauma (2).

Treatment

Pharmacologically, anticholinergics, dopamine receptor blockers, dopamine depleters, sedative and paralytic agents can be given (2). In cases where there is no response to drug treatment, surgical methods such as deep brain stimulation can be applied (2).

Dystonic reaction

Clinical features

Acute dystonic reactions may occur 24 hours after exposure to dopamine receptor blockers (2). It has been reported that the risk increases in men and when the dose is titrated rapidly (2). Blepharospasm, cervical, laryngeal or limb dystonia, and oculogyric crisis may occur singly or in combination (2). When the larynx or pharynx is affected, there may be a danger of respiratory failure (2).

Treatment

First of all, the etiological drug should be discontinued, and then parenteral anticholinergics or antihistamines (e.g., diphenhydramine 25-50 mg) should be administered (3). It is recommended to take oral anticholinergics for a few more days to prevent the risk of relapse (3).

3. Emergencies related to hypokinetic movement disorders

When emergencies related to hypokinetic movement disorders are mentioned, emergencies in Parkinsonism and Parkinson's disease come to mind first. Parkinsonism is defined as the condition where bradykinesia is accompanied by one or more rest tremors, rigidity, and impaired postural reflexes (27). Parkinson's disease (PD) is the most common cause of parkinsonism and presents with non-motor symptoms and motor symptoms like parkinsonism (28). The emergencies in this group of diseases can be grouped under two headings: Specific and nonspecific (2, 3, 29). Specific ones will be discussed under hyperpyrexia syndromes, acute parkinsonism, acute worsening of parkinsonism, severe motor complications such as severe Off and severe dyskinesia, falling and psychosis (29). Nonspecific include infection (21-32% of PD patients presenting to the emergency department), cardiovascular or cerebrovascular events (12-26% of PD patients presenting to the emergency department), gastrointestinal disorders (8-11% of PD patients presenting to the emergency department), and metabolic disorders (2-6% of PD patients admitted to the emergency department) (29).

3.1. Hyperpyrexia syndromes

Parkinsonism hyperpyrexia syndrome

Clinical features

Parkinsonism hyperpyrexia syndrome (PHS) is defined as a sudden clinical worsening in which UPDRS scores increase by ≥20 points and temporary unresponsiveness to therapeutic doses of dopaminergic drugs or rescue drugs for three days (30). PHS was first described in 1981 (31). PHS is clinically characterized by severe akinesia, severe rigidity, hyperthermia, dysautonomia (tachycardia, fluctuation in blood pressure, incontinence and sweating) and altered consciousness, which mimics neuroleptic malignant syndrome (NMS) and does not respond temporarily to dopaminergic therapy (2, 32). Studies have reported that dopamine active transporter (DAT) activity is markedly decreased in PD patients with akinetic crises (30). It has been reported that the decrease in DAT expression may occur in response to the sudden decrease in striatal dopamine levels and mitochondrial function due to the abrupt discontinuation of exogenous DA'ergic drugs (30). It is clear that DA transmission to the striatum, hypothalamus, and cortex decreases due to the decrease in DAT expression. It has also been reported that a decrease in binding to post-synaptic striatal D2 receptors (due to decreased striatal dopamine receptor expression and affinity) and an increase in calcium and pyrogen release from the sarcoplasmic reticulum in skeletal muscle are also involved in the pathogenesis (30, 33). From clinical history, determining the presence of one or more of the triggers such as reduction or stopping of dopamine agonists, levodopa and amantadine (18 hours to seven days later: malignant withdrawal syndrome), closure of STN-deep-brain stimulation (DBS) (malignant STN-DBS withdrawal syndrome), trauma, gastrointestinal system diseases, infections, excessive heat and dehydration may be a clue for diagnosis (2, 3, 30, 33). Although the diagnosis of PHS is considered when the neurological examination reveals severe akinesia, severe rigidity, hyperthermia, dysautonomia, and altered consciousness, the diagnosis should also be supported by determining the increase in serum white blood cell (WBC), creatine kinase (CK) and liver enzyme levels (2, 3, 32, 33). Complications of PHS include venous thrombosis, pulmonary embolism, aspiration pneumonia, DIC (disseminated intravascular coagulation) and kidney failure (30, 34).

Treatment

As in NMS, supportive measures such as intravenous (IV) hydration, antipyretic, and, if necessary, mechanical ventilation and hemodialysis are crucial. Dopaminergic therapy needs to be restarted. For this, liquid levodopa, bromocriptine (7.5-15mg 3 times a day), ropinirole (1-2mg 3 times a day), pramipexole (0.18-0.36mg 3 times a day), subcutaneous apomorphine (1- 2mg/hour) and transdermal rotigotine (2-4mg/day) are recommended (3, 34). Solving the underlying etiological problems will accelerate the healing process. As additional treatments, IV administration of dantrolene (relaxes muscles at muscle level), which prevents calcium release from the sarcoplasmic reticulum and thus muscle contraction, is recommended in severe or resistant rigidity (starting with 1 mg/kg, maximum 10 mg/kg/day in 3-4 doses) (34). High-dose IV methylprednisolone (e.g., 3-day pulse therapy) has been found to be effective (e.g., reduction in disease duration and significant clinical improvement) in small randomized trials (35, 36). Electroconvulsive therapy was found to be effective in case samples (36). Follow-up and treatment of complications are crucial. Despite treatment, 10-30% of permanent worsening and death have been reported (37).

Dyskinesia hyperpyrexia syndrome (DHS) in Parkinson's disease

Clinical features

DHS can be defined as the presence of severe and persistent dyskinesia, which causes mental status changes, hyperthermia, and elevated serum CK and BK, without rigidity, in patients with advanced Parkinson's disease (2, 38). Non-physiological (intermittent) dopaminergic stimulation predisposes to DHS, especially in long-term disease (38). In preclinical studies, an increase in ambient temperature has increased dopamine receptor sensitivity and dopaminergic transmission (38). Chauhan et al. (39) showed an increase in dopamine and glutamate in the blood and hypothalamus and the presence of hypothalamic inflammation at high ambient temperature (45 ± 0.5 °C) in rats. The abnormality of thermoregulation, one of the autonomic impairments in PD, may cause a more noticeable increase in dopaminergic receptor sensitivity at high ambient temperatures (38). On the other hand, dehydration may exacerbate the abnormality of thermoregulation (38).

Increasing the daily dose of DA'ergic therapy and multiple concomitant therapies, presence of infection, high ambient temperature (especially during long illness), trauma and dehydration are reported as risk factors (38). DHS is defined in a case where severe diffuse chorea and dystonia developed and body temperature increased to 42°C, serum CK to 16040 U/L and BK to 14200 while taking 1500 mg/day of L-dopa carbidopa intestinal gel (LCIG) in the summer heat (38).

Treatment

General approach methods such as antipyretic measures, IV copious fluids, and reducing or treating the number of risk factors (e.g., reducing or stopping the number and dose of antiparkinsonian drugs, administering antibiotics if there is an infection) can be life-saving (3, 38). Treatment (e.g., respiratory-circulatory support, dialysis) of developing complications (e.g., rhabdomyolysis, renal failure, and heart failure) is crucial (3, 38). Despite treatment, there is a risk of increased mortality (38). Table 3 shows the comparison of clinical and laboratory features of hyperpyrexia syndromes (2, 3, 30, 34, 38, 40, 41).

Table 3. Comparison of clinical and laboratory features of hyperpyrexia syndromes

Feature	PHS	DHS	NMS*	SS	MH
Age	Old	Old	Young	All ages	Child
Underlying disease	Parkinsonism	Parkinsonism	Psychosis	Psychiatric	Gene mutation**
Onset	Acute	Acute	Acute	Subacute	Acute
Triggering factor (s)	DBS and DA'ic drug withdrawal, surgery, trauma, infection	DA'ic drug, trauma, infection, high ambient temperature, dehydration	Antipsychotic use (Idiosyncratic)	SSRI, SNRI, MAOi, TCA Amphetamine, Cocaine	Volatile anesthetic, Succinylcholine
Fever	-/+	++/+++	+++	++	+++
Rigidity	+++	-	+++	++	+++
Other motor sign(s)	Other parkinsonian sign(s)	Dyskinesia	Tremor	Myoclonus, stereotypy, hyperreflexia	-
Autonomic instability	-/+	-/+	++/+++	+++	+++
Confusion	++/+++	-/+/++	+++	+++	+
Serum CK elevation	++	+++	+++	++	+++
Metabolic acidosis	+	-/+	+	+	++
Medication	LD, BC, PP, AM, DR	Dose reduction or interruption	BC, ATN, DR	CHDN, MTGT	DR

PHS, Parkinsonism hyperpyrexia syndrome; NMS, Neuroleptic malignant syndrome; SS, Serotonergic syndrome; MH, Malignant hyperthermia; DBS, Deep brain stimulation; DA, Dopamine; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin-norepinephrine reuptake inhibitor; MAOi, Monoamine oxidase inhibitor; TCA, Tricyclic antidepressant; - None; + Mild; ++ Moderate; +++ Severe; CK, Creatine kinase; LD, Levodopa; BC, Bromocriptine; PP, Pramipexole; AM, Apomorphine; ATN, Amantadine; DR, Dandrolen; CHDN, Cyproheptadine; MTGT, Methysergite; *Three major (fever, rigidity, elevated CK) or two major and four minor (tachycardia, variable blood pressure, tachypnea, diaphoresis, mental status change, leukocytosis) criteria are required for the diagnosis of NMS **Type 1 ryanodine receptor (RYR1) gene encoding the ryanodine receptor found in skeletal muscle

3.2. Acute parkinsonism

Clinical features

The terms acute worsening of parkinsonism or abruptly worsening OFF periods are also used synonymously with acute parkinsonism. Potential causes of abrupt change include parkinsonian drugs, particularly dopamine receptor blockers (e.g., antipsychotics and antiemetics), concomitant infection (e.g., urinary tract infection and pneumonia) or metabolic disruption (e.g., central pontine myelinosis), subdural hematoma (a history of falling can be obtained in patients with suddenly worsening PH), hypoxic-ischemic encephalopathy, toxicity (e.g., carbon monoxide, methanol, and manganese), acute hydrocephalus, spinal cord lesion, and brain tumor (2, 3, 42).

Treatment

Correction or elimination of the underlying cause is very important (2). When necessary, symptoms should be treated with antiparkinsonian drugs (2).

3.3. Severe motor complications

It has been reported that 8% of Parkinson's patients admitted to emergency departments have motor complications (29).

Severe OFF periods

Clinical features

OFF periods can be defined as the reappearance of signs and symptoms of the disease seen in the later stages of PD. In severe OFF periods, significant akinesia may be accompanied by nonmotor symptoms such as abdominal discomfort, pain, and dysautonomia (e.g., diaphoresis, variations in blood pressure, and tachycardia) and panic attacks (2, 43). Potential triggers or aggravating factors include dopaminergic drug changes, the addition of antidopaminergic drugs to treatment, and concomitant infections (2). Severe prolonged OFF periods may lead to complications such as aspiration and deep venous thrombosis (43).

Treatment

Crushing L-dopa tablets in acidic liquid (e.g., by adding

vitamin C) or administering dispersible or controlled-release forms of L-dopa, dividing the daily dose of L-dopa, adding an MAO B inhibitor to L-dopa, and administering L-dopa with COMT inhibitor can shorten the off-time (2, 44). Subcutaneous injection of apomorphine or inhaled L-dopa powder without carbidopa (antiparkinsonian effect begins within 10-30 minutes) accelerates recovery (44). Prophylactic anticoagulants may be required. Stereotactic surgery can be considered as an additional alternative treatment (2).

Severe Dyskinesia

Clinical features

Severe generalized dyskinesia can cause rhabdomyolysis, hyperthermia, and dehydration (3). Dyspnea, tachypnea, dyskinesia of respiratory muscles (chest wall discomfort and involuntary grunting sounds) and anxiety may accompany (3).

Treatment

Reducing (or stopping) each levodopa dose is the first strategy in Peak-dose dyskinesias (44). Benzodiazepines can be given temporarily for accompanying anxiety (Neuroleptics should not be used) (3). Hydration and antipyretic approaches can be life-saving (3). An intermittent 'rescue' subcutaneous injection of apomorphine immediately before an on/off state transition may be a viable alternative in treating biphasic dyskinesias (43). Amantadine, DBS and LCIG are recommended for dyskinesia prophylaxis (3, 44).

3.4. Acute psychosis in Parkinson's disease

Clinical features

It has been reported that 8% of Parkinson's patients admitted to emergency departments have psychosis (29). Psychosis is the name of the clinical picture accompanied by hallucinations (visual>auditory), delusions (commonly paranoid) and agitation in addition to confusion, and it is seen in more than half of the cases (45-64%) during the course of the disease (3, 43). The most common triggers are the conditions associated with antiparkinsonian drugs (drug change, addition or dose increase), followed by acute clinical conditions (infection, metabolic disorders) or concomitant dementia (3, 43).

Treatment

After treating comorbidities, starting from anticholinergics, MAO-B inhibitors, DA agonists, amantadine, and COMT inhibitors should be gradually reduced or discontinued (3). If psychosis persists, antipsychotics (pimavanserin, a selective 5-HT2A receptor inverse agonist/antagonist, clozapine or quetiapine) may be required (3, 43, 45). Cholinesterase inhibitors such as rivastigmine and donepezil reduce hallucinations (43).

3.5. Fall in Parkinson's disease

Clinical features

It has been reported that 13-27% of PD patients admitted to the emergency department have a history of falling (29). As PD progresses, falls increase, and the frequency of falls is reported to be around 70% annually (46). Postural instability or freezing causes 80% of falls (29). Injuries (often hip fractures) occur in approximately 25% of falls (29). Severe dyskinesias and orthostatic hypotension can also cause falls (47).

Treatment

Although adjusting the levodopa dose in the treatment of falls (e.g., reducing the dose in the on-stage freezing and increasing the dose in the off-stage freezing) is the first strategy, freezing and postural instability are often not sensitive to levodopa (29, 48, 49). In levodopa-resistant freezing, the benefit of DBS [STN, globus pallidus internus (GPi) singly or combined with pedunculopontine nucleus] is controversial. However, high-frequency stimulation such as 130Hz in STN-off period freezes and low-frequency stimulation such as 60Hz in STN-on period freezes can be recommended (49, 50). Table 4 shows non-dopaminergic pharmacological treatment in freezing (49, 50). Exercise (reduces falls) and assistive devices (Walker, laser cane) can be preventative (49). Treatment of comorbidities that negatively affect mobility and may cause freezing can reduce falls (48). For example, SSRI or SNRI for depression and anxiety, rivastigmine for cognitive dysfunction, compression stockings and domperidone for orthostatic hypotension, and appropriate treatment for poor vision and musculoskeletal problems can be recommended. It has been reported that new non-drug treatment methods such as transcranial magnetic stimulation (TMS), noninvasive vagus nerve stimulation (VNS), and transcranial direct current stimulation (tDCS) are also effective in freezing (49). In addition, the treatment of possible complications is also critical.

Table 4. Non-dopaminergic pharmacological treatment in freezing

Drug	Group	Effect/Result
Rivastigmine	Ach-esterase inhibitor	Ineffective / Not recommended
Amantadine	Glutamate antagonist	Additional therapy in L-dopa-responsive freezing*
Methyl phenidate**	CNS stimulant	Freezing despite optimal L-dopa and STN DBS therapy*
Atomoxetine**	Strattera	Ineffective/ Not recommended
Droxidopa	Prodrug of norepinephrine	Combined with entecapone in DA resistant freezing*
Caffeine / Istradefylline	Adenosine antagonist	Recommended for research*
Botulinum toxin	Chemical denervation	Off period freezing*

* Not clear: There are positive and negative results; **It is used in the treatment of hyperactivity attention deficit syndrome; CNS, *Central nervous system;* STN-DBS, Subthalamic nucleus-*deep brain stimulation;* DA, dopamine

4. Conclusion

In summary, accurate diagnosis and early treatment can be life-saving in emergencies in movement disorders. Finally, complications related to device-aided therapies, including DBS, LCIG, and apomorphine subcutaneous infusion, may present extraordinary emergencies such as severe motor complications, psychosis and hyperpyrexia syndromes refractory to standard therapy (30, 38, 43). We discussed approaches to these complications in detail above.

Conflict of interest

None to declare.

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Authors' contributions

Concept: D.A., M.P., Design: D.A., M.P., Data Collection or Processing: D.A., M.P., Analysis or Interpretation: D.A., M.P., Literature Search: D.A., M.P., Writing: D.A., M.P.

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