Emergencies in movement disorders

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ABSTRACT:
Movement disorders constitute a large group of diseases that affect the control of voluntary motor activity without a direct impact on sensation and strength. Usual clinical course is slow, progressive and can be treated in an outpatient clinic. However, there are several emergencies regarding movement disorders that are serious medical conditions and may result in death if not recognized and treated promptly. Every neurologist should be aware of these states because they can develop during the course of a patient’s illness. The aim of this review is to provide key features of the most common emergencies in movement disorders, including drug-induced emergencies, emergencies in Parkinson’s disease, chorea and ballismus, tics, myoclonus and dystonia.

KEYWORDS: Emergencies; Movement Disorders; Parkinson’s disease

SAŽETAK:
Hitna stanja u poremećajima pokreta
Poremećaji kretanja čine veliku skupinu bolesti koje utječu na kontrolu dobrovoljne motoričke aktivnosti bez izravnog utjecaja na osjet i snagu. Obično su ti poremećaji spori, progresivni i mogu se lijeiti u ambulant. No, postoji nekoliko hitnih slučajeva u vezi s poremećajima kretanja koji su ozbiljna zdravstvena stanja i mogu dovesti do smrti ako ne prepoznaju i odmah ne liječe. Svaki bi neurolog trebao znati ove hitne slučajevi jer se mogu razviti tijekom pacijentove bolesti. Cilj ovog pregleda je pružiti ključne značajke najčešćih hitnih slučajeva kod poremećaja kretanja, a to uključuje hitne slučajevi izazvane lijekovima, hitne slučajevi kod Parkinsonove bolesti, koreu i ballizam, tikove, mioklonus i distoniju.

KLJUČNE RIJEČI: Hitni slučajevi; Poremećaji kretanja; Parkinsonova bolest
Introduction

Movement disorders affect the control of voluntary motor activity without a direct impact on sensation and strength. These disorders are traditionally described as slowly progressive chronic illnesses that are usually treated in outpatient clinics, but there are several acute and urgent conditions where movement disorders become the most prominent characteristic. These urgent conditions require a prompt response from the clinician otherwise they can lead to substantial morbidity and mortality (1). Some authors divide movement disorder emergencies into hypokinetic and hyperkinetic, but in this review, we divided them into drug-induced emergencies, emergencies in Parkinson's disease, chorea and ballismus, tics, myoclonus and dystonia. Under drug-induced emergencies we described neuroleptic malignant syndrome, serotonin syndrome, parkinsonism-hyperpyrexia syndrome and dyskinesia-hyperpyrexia syndrome, whilst under emergencies in Parkinson's disease we wrote about falls, acute psychosis, and motor fluctuations and severe dyskinesia.

Drug-Induced Emergencies

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare adverse drug effect, that can be lethal (2). NMS was first identified in the 1950s and 1960s, when it was observed that it can occur as a side effect of phenothiazine antipsychotics. Unfortunately, due to the large number of people taking these drugs, there were many cases of NMS. It is estimated that the prevalence of the syndrome is somewhere between 0.167 to 32.6 cases per thousand people (3). Although the specific pathophysiology of NMS is unknown, it is hypothesized that the mechanism includes a combination of dopaminergic hypofunction in the central nervous system and sympathetic hyperactivity in the peripheral nervous system (4). Conventional antipsychotics, like haloperidol, are linked with a higher incidence of NMS occurrence, but atypical antipsychotics, such as olanzapine, clozapine and risperidone can also cause the disorder (5). Certain symptoms of NMS could be the result of drugs disrupting central nervous pathways, such as the nigrostriatal pathway, the central thermoregulation pathway and the reticular activating system (4). Most often symptoms appear within the first two weeks of starting medication or changing the dosage. There are a lot of risk factors associated with the syndrome, such as male sex, young age, dehydration, high temperatures, hasty dosage increase in a short period of time, depot formulations and previous episodes of NMS (6). The typical symptoms include a clinical tetrad that is composed of hyperthermia, altered mental status, “lead pipe” rigidity and dysautonomia. The syndrome can be recognized by its early sign that include alterations in the mental state and muscular rigidity, usually accompanied by dysautonomia and high fever. Dysautonomia presents itself as tachycardia with fluctuating blood pressure (4). Elevated levels of creatine kinase (CK), often exceeding 600UI/L, and leukocytosis are common diagnostic findings. Some nonspecific inflammatory markers, such as fibrinogen, C-reactive protein and increased erythrocyte sedimentation rate, can also be present in laboratory findings (3). The first line of treatment, once NMS is recognized, is the stoppage of antipsychotic treatment. On the other hand, if NMS arises because of antipsychotic drug removal, then they should be reintroduced as soon as possible (2). Severe symptoms demand immediate medical attention and pharmacological treatment. The most used drugs are dantrolene sodium, bromocriptine and benzodiazepines. Dantrolene sodium is a muscle relaxant widely used in malignant hyperthermia and it may be helpful in patients with severe symptoms, which include rigidity and high temperature rises. Bromocriptine, a dopamine agonist, has been shown to alleviate parkinsonism and to reduce time to recovery and mortality rates in NMS patients. Benzodiazepines have been effective in patients with milder symptoms where they accelerate recovery and reduce symptoms (5).

Serotonin syndrome

Serotonin syndrome (SS) is a serious, potentially fatal neurological condition that is caused by high serotoninergic activity. The exact number of SS is hard to determine because as the number of individuals diagnosed with major depressive disorder increases, so does the number of individuals at risk for SS due to antidepressant medications (7). The risk for SS occurrence is higher when more serotonergic drugs are used at the same time (8). SS isn’t only caused by antidepressants, it is thought that it can be caused by several groups of drugs, like antibiotics, analgetics, antiemetics, drugs of abuse, antimigraine drugs, herbal supplements, monoamine oxidase inhibitors and over-the-counter drugs (9). Clinical symptoms of the syndrome match the role of central and peripheral serotonergic neurons which can be stimulated through several mechanisms, such as increased synthesis, increased release, direct agonism, inhibition of reuptake and decreased metabolism of serotonin (8). It is important to keep in mind that one mechanism is not limited to one drug, but one drug can act through multiple mechanisms. Cocaine can both operate as a serotonin agonist and also stimulate serotonin release (9). Typically, patients with SS present themselves with three main clinical features: (1) altered mental status, (2) autonomic dysfunction and (3) neuromuscular excitation. Under altered mental status we include confusion and agitation. Autonomic dysfunction is clinically presented as diaphoresis, tachycardia, nausea, vomiting and mydriasis. Neuromuscular excitation can be recognized by symptoms of myoclonus, hyperreflexia, hyperthermia, hypertonicity and rigidity (10). There are several diagnostic criteria used for SS diagnosis, but the Hunter Serotonin Toxicity Criteria are widely regarded as the gold standard. These criteria are composed of the three mains, earlier mentioned clinical features (altered mental status, autonomic dysfunction and neuromuscular excitation). In around 30% of patients the symptoms appear in the first hour,
Parkinsonism-hyperpyrexia syndrome
Parkinsonism-hyperpyrexia syndrome (PHS) is a serious, life-threatening condition that occurs in patients with Parkinson's disease (PD) when antiparkinsonian drugs are reduced or stopped. PHS is similar to NMS, but it occurs in individuals with previously diagnosed PD (1). PHS was first reported in 1981. when high doses of antiparkinsonian drugs were removed from a PD patient who hadn't previously been given neuroleptics. Furthermore, PHS isn't exclusive to PD, this condition can also develop in patients with different types of parkinsonism (11). As with NMS, it is considered that most NMS-like syndromes have the same main pathophysiological mechanisms which include impaired central dopamine and serotoninergic function, and peripheral noradrenergic function (4). PHS has a similar clinical presentation as NMS, but with more parkinsonian characteristics early and with a possible later start of symptoms (4). The typical symptoms of PHS include dysautonomia, hyperthermia, altered mental state, rigidity and elevated serum creatine kinase levels. Along with the removal of antiparkinsonian drugs, other potential risk factors are hot weather, infections and dehydration (6). Supportive therapy and the reintroduction of dopaminergic drugs are the first step in the treatment. The dosage of levodopa should be the same as before patients developed PHS. Further therapeutic measures, depending on the condition of the patient, may include bromocriptine and dantrolene. PHS is a serious condition, and as such patients frequently need intensive care, if needed, with respiration assistance and central venous pressure surveillance (11).

Dyskinesia-hyperpyrexia syndrome
Dyskinesia-hyperpyrexia syndrome (DHS) is a rare neurological emergency induced by increased dopaminergic activation in patients with PD (12). DHS has many similarities with PHS and SS, but it is primarily characterized with massive hyperkinesis. Although these syndromes look similar, they have different causes and therapies, and it isn't possible to provide prompt and appropriate care if the correct diagnosis isn't made (13). The first case of DHS was described in 2010 on a 68-year-old patient who had a 12-year history of PD with motor fluctuations, peak-off-dose and biphasic dyskinesia (14). Levodopa-induced dyskinesia is seen in 30–40% of PD patients who have been on the drug for longer than 5 years. Most of these cases are usually harmless and can be managed in an outpatient clinic, but every clinician must keep in mind that there is a possibility of patients developing significant complications. While levodopa-induced dyskinesia is quite common, dyskinesia coupled with hyperpyrexia is very rare and to date only 11 cases have been described (13). The exact pathophysiological mechanism is still unknown, but there are hypotheses about possible triggers and risk factors. Several triggers, such as antiparkinsonian drug treatment changes, infections, hot weather and dehydration, paired with risk factors, like higher levodopa equivalent dosage, continuous intraduodenal levodopa infusion and usage of dopamine agonists, could lead to the development of DHS (15). DHS is characterized by hyperpyrexia, extreme and generalized dyskinesia, altered mental state, autonomic dysfunction and CK increase. The two main symptoms, as the syndromes name indicates, are dyskinesia and hyperpyrexia, and they manifest in all patients. It is possible that in the early stage of the condition only dyskinesia is present, this is since hyperpyrexia usually occurs later. The most successful approach in management is to reduce dopaminergic drugs in the span of a few days to two weeks (13). If the patient with DHS has an implanted DBS device, it is recommended to lower both dopaminergic oral drugs and DBS stimulation settings. That way both possible dyskinetic causes are being addressed, while avoiding consequences from sudden dopaminergic discontinuation (16). Additionally, sedation has been proven to be helpful in patients suffering from resistant dyskinesia. Supportive therapy plays an essential role in the care of patients with DHS, and includes antipyretics, intravenous fluid resuscitation, antibiotics and electrolyte balance management (13).

Emergencies in Parkinson’s Disease
Falls in PD
Falls are a characteristic of PD progression and present a significant issue for PD patients. It is estimated that they occur in around 50-60% of patients, leading to decreased mobility and motor deterioration. The weakening of postural reflexes due to PD progression is considered to be an important factor in the pathogenesis. Also, conditions like gait freeze, dyskinesias and orthostatic hypotension may contribute to an increased risk of falls (17). Around 25% of falls result in injuries, with hip fractures being the most common one (1). In addition to injuries, falls can also lead to immobility, premature nursing home placement and increased mortality. Even without serious consequences, falls can significantly limit patients everyday lives by causing
fear of walking, and thus negatively affect their independence and quality of life (18). To prevent falls in patients who are at a greater risk, along with a greater degree of concern, some general measures can be applied. These measures include: (1) domestic measures, by what we consider removing obstacles at the patients home, (2) physical assistance, in the form of a walking cane, walking assistant or possibly a wheelchair, and (3) managing possible risk factors, like nocturia, orthostatic hypotension and dyskinesia (17).

Acute psychosis
Many studies have been undertaken to observe and determine the epidemiology of psychosis in PD, and they have concluded that PD patients have a higher prevalence of psychosis in the latter stages of the illness (19). PD patients who take dopaminergic therapy throughout a long period of time have a 30% chance of developing psychotic symptoms, while in dementia it can be as high as 45% to 64% of individuals (1,17). There is a strong link between the occurrence of psychosis during PD and higher morbidity and caregiver burden, and it has been linked to early mortality (19). Complex interactions between internal and external factors have been shown to influence psychosis in Parkinson’s (20). Infectious, metabolic, or neurological diseases may contribute alongside long-term antiparkinsonian therapy in the development of psychosis (6). Minor hallucinations and well-structured visual hallucinations are two of the most prevalent manifestations of psychosis in PD, which may be present together or individually. The main characteristics of minor hallucinations are a distorted feeling of presence, a distorted sense of passage, and illusions. In addition to these main characteristics, delusions and non-visual hallucinations may also be present, but are considered much rarer (21). When psychosis occurs, the first step must be removing the last introduced medication. The next step is to exclude other drugs in this exact order: anticholinergics, monoamine oxidase inhibitors, amantadine, dopamine agonists, catechol-O-methyltransferase inhibitors and lastly levodopa. It is further recommended to include atypical neuroleptics into the treatment regimen (20).

Motor fluctuations and severe dyskinesia
Over the past four decades, levodopa has been the principal therapy for the management PD. Patients in later stages may develop significant fluctuations between effective "on" states and times of inadequate disease control and severe PD symptoms, known as "off" states (22). Research on the pathophysiology of motor fluctuation indicates that stimulating dopamine receptors in a pulsatile manner might promote the development of motor fluctuations, but continuous stimulation may cause less motor fluctuations (23). It has been shown that half of all patients will suffer mild motor fluctuations in two years of using levodopa, and even 70% of all patients will experience them within 9 years of disease development (22). People with the disease can exhibit significant rigidity, bradykinesia, and postural instability in "off" states, rendering them unable to care for themselves or move. In addition to these symptoms, motor fluctuations can be further complicated with psychiatric symptoms (depression, anxiety and panic) and various problems with the autonomic nervous system (increase in heart rate, sweating, and fluctuations in blood pressure) (1). A variety of drugs should be considered to manage the symptoms, including subcutaneous dopamine agonists, monoamine oxidase B and catechol-O- methyltransferase. Other medical approaches, like careful medical management, controlled dosage and delivery methods of levodopa, and also stereotactic surgery, might prove useful (6).

Patients with PD who take levodopa for 5 to 10 years have around a 50% to 80% probability of developing dyskinesia. While there is variation in this estimate, it is common since it generally appears over the course of many years of therapy. Individuals typically develop levodopa induced dyskinesia in the later stages of PD, which is characterized with cyclical alternation between periods of improvement and worsening of dyskinesia (24). There are several types of levodopa induces dyskinesias: (1) peak-dose dyskinesia (the most common one; result of peak levels levodopa plasma levels), (2) diphasic dyskinesias (consequence of levodopa levels rising and falling), (3) off-state dystonia (due to low plasma levels of levodopa), (4) on-state dystonia (due to higher levodopa plasma levels) and (5) yo-yo dyskinesia (unpredictable pattern) (25). In most cases, these dyskinesias are non-life threatening and may be treated in an outpatient clinic. But in some cases, these dyskinesias can cause serious and potentially fatal complications, like rhabdomyolysis, dehydration and respiratory distress (20). Lowering levodopa doses should be the first line of treatment levodopa induced dyskinesia and amantadine hydrochloride should be introduced for longer-term treatment.

As states, both motor fluctuations and dyskinesias are hallmarks of advanced PD, where the main therapeutic challenge is improving "on" time, without increasing debilitating dyskinesias (26). Key treatment options in this case are deep brain stimulation (DBS) or levodopa/apomorphine pumps (27). There is a lack of randomized controlled studies comparing these therapeutic options head-to-head, although current research points out that both DBS and continuous pump treatment are better than best medical therapy, and are even more cost-effective in the long-term (27). Proper patient selection is key in determining the right procedure, which in turn leads to improved outcomes and quality of life (28).

Chorea and Ballismus
Chorea is a hyperkinetic movement disorder characterized by a continuous stream of involuntary muscular contractions that are random, short, and migratory (29). The development of acute chorea can be caused by a variety of factors, such as exposure to drugs, metabolic derangements, vascular illness, infectious/
postinfectious and autoimmune diseases. If it isn't recognized promptly and timely it can lead to rhabdomyolysis and hyperthermia (6). In children acute chorea most commonly presents itself during rheumatic fever caused by a streptococcal infection and is called Sydenham chorea. This type of chorea is additionally characterized by behavioral changes, hypotonia, and vocalizations. It was shown that carbamazepine or valproic acid may be utilized to help those suffering with Sydenham chorea, if medication is required (30). The most prevalent cause of acute chorea in adults is basal ganglia stroke (4). Chorea can also occur during pregnancy (chorea gravidarum), usually during the first or early in the second trimester. This type can affect one side of the body or both and sometimes involves the face and/or arms and legs. Chorea gravidarum is rarely an emergency and usually disappears in the third trimester or a few hours after delivery (30).

Ballism is a term for an advanced form of chorea that is characterized with high-amplitude, vigorous, rapid movements. Hemiballism, on the other hand is characterized by unilateral flinging movements of the limbs. Both of these conditions may in many cases be sufficiently strong enough to warrant immediate medical attention, with symptoms varying in their severity (31). Ballism/hemiballism is most commonly caused by an ischemic or hemorrhagic stroke, that causes lesions damaging the contralateral basal ganglia and the nearby white matter (6). Ballism typically occurs in hyperosmolar hyperglycemia crises, but can also develop, irregularly, in ketotic hyperglycemia. The underlying mechanism for this remains unknown. It has been shown that older women are more susceptible to this condition due to hyperosmolar hyperglycemia, and that the symptoms more frequently occur unilaterally (4). Anti-dopaminergic therapy, which includes either dopamine blockers or dopamine depleters, is essential to the treatment strategy. In the most severe instances, the most appropriate therapy is neurosurgery, either lesioning the globus pallidus (Gpi) or implanting Gpi DBS (31).

**Dystonia**

Dystonia is a hyperkinetic movement disorder characterized by continuing muscular contraction, repeating twisting motions, and abnormal body posture. Dystonia is the result of uncontrollable alternating contractions produced by agonist and antagonist muscles (35). While dystonia usually isn’t an emergency, in extreme circumstances, generalized dystonia can progress from mild to life-altering. This medical emergency is called dystonic storm or status dystonicus, and it is potentially fatal and urgent conditions that require immediate medical attention. When diagnosing dystonic status, it is important to consider other causes that may be bacterial meningitis, neuroleptic malignant syndrome, serotonin syndrome or malignant hyperthermia (31). Patients that develop status dystonicus typically have a previous history of dystonia. This emergency my potentially lead to hyperthermia, fluid loss, and respiratory compromise if not recognized on time. Every clinician must keep in mind that patients affected by this condition may be
resistant to drugs like anticholinergics, baclofen, benzodiazepines, dopamine blockers, or dopamine depleters. Therefore, in many cases sedation and paralysis may be the right choice of treatment (32). The other very effective treatment of status dystonicus is DBS (36). Researchers suggest that DBS might reduce dystonic crisis duration and also improve motor symptoms over a longer period of time, and can be considered as a disease-modifying therapy (37). There is still a need for further investigation for when the DBS device should be implanted in the course of status dystonicus, as well as to develop criteria for the optimal device settings (36). Another dystonic emergency is acute laryngeal dystonia. This is a condition that affects the vocal cords and laryngeal muscles and may even lead to upper airway obstruction and fatal suffocation. This condition relates to the usage of neuroleptics. Intravenous diphenhydramine has been documented to be effective in treating this emergency (31,32).

**Conclusion**

Although, movement disorders are typically slowly progressive, there are several movement disorder emergencies that can be fatal if not recognized and treated in timely and promptly. This review focuses on these emergencies and seeks to point out key data so that neurologists, as well as clinicians, can quickly identify these conditions. However, some of these emergencies are difficult to distinguish from each other and still have insufficiently clear diagnostic criteria. These conditions can cause confusion in the diagnosis and thus delay timely treatment which could result in unnecessary deaths. Therefore, in the future it is necessary to strengthen the diagnostic criteria in order to speed up the accurate diagnosis and achieve timely intervention, which would result in reduced mortality.

**References:**
