REVIEW ARTICLE

RECOGNIZING MOVEMENT DISORDER EMERGENCIES – A PRACTICAL REVIEW FOR NON-NEUROLOGIST

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Neurology still remains one of the most underserved specialties of medicine in Pakistan with roughly one neurologist per million people. Movement disorders (MD) are neurological problems that interfere with patient's motor abilities and diagnosis is typically clinical. In this review, we describe a practical approach to common MD emergencies that may be encountered by a non-neurologist physician, emphasizing on formulating a working diagnosis and their immediate management. Movement disorder emergencies can be classified based on MD phenomenology and we will provide a brief overview of dystonia including acute dystonic reaction, PAID syndrome and dystonic storm; chorea, myoclonus including serotonin syndrome and startle disease; and rigidity including neuroleptic malignant syndrome and malignant hyperthermia.

Keywords: Movement Disorders; Emergency; Neurology; Dystonia; Tardive; Serotonin Syndrome; Neuroleptic Malignant Syndrome

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INTRODUCTION

Neurology has evolved into a dynamic field with increasing role of neurologists in the emergency room setting.[1] Unfortunately, neurology still remains one of the most underserved specialties of medicine in Pakistan with roughly one neurologist per million people.[2] The bulk of neurological disorders thus have to be looked after by non-neurologists and they should be comfortable in recognizing and managing acute neurological problems.

Movement disorders (MD) are neurological problems that interfere with patient's motor abilities by either causing a lack of movements (called hypokinetic disorders such as rigidity, bradykinesia, stiffness) or increased involuntary movements (called hyperkinetic disorders such as dystonia, tremor, chorea, ballism, myoclonus, tics etc). Diagnosis typically relies on clinical observations as most conditions do not have diagnostic tests.[3]

Movements disorders emergency has been defined as 'as a movement disorder related neurological problem evolving acutely in which failure to accurately diagnose and manage the patient may result in significant morbidity or even mortality'.[4]

In this Practical review, we describe an approach to common MD emergencies that may be encountered by a non-neurologist physician, emphasizing on formulating a working diagnosis and their immediate management and management of delirium in a patient with Parkinson disease.

DISORDERS PRESENTING WITH DYSTONIA

Dystonia is an involuntary co-contraction of antagonistic muscles causing sustained abnormal postures or twisting and repetitive movements.[3] The key concept here is 'posturing' which means that the posture resulting from the abnormal contractions of a group of muscle is held in place for some time. Following are some of the MD emergencies with dystonia as the predominant phenomenology.

Acute Dystonic Reaction:

Acute dystonic reactions are commonly occurring MD emergencies. It may occur within hours to days of exposure to dopamine D2 receptor blocker drugs.[5] Commonly implicated drugs include antipsychotics like *haloperidol or risperidone* and antiemetics like *metoclopramide*.[6] Among the antipsychotics, quetiapine and clozapine are generally considered safer because of their effects on receptors other than D2. Acute dystonic reaction can take various forms such as sustained deviation of gaze to one side (oculogyric crisis), posturing of the neck (cervical dystonia), protrusion of the tongue or persistent opening or closure of the mouth (oromandibular dystonia). Sometimes, painful spasms and arching of the back (ophisthotonos) may be seen.[7] Consciousness usually remains intact and a sense of fear also accompanies these episodes.

Depending on the clinical presentation, differentials include partial seizures, tetanus, encephalitis and strychnine poisoning.[5] However, most of the times, the diagnosis is straight forward. Treatment response is usually prompt unless dystonic storm or status dystonicus has ensued (prolonged dystonic reaction for weeks or months). Therapeutic options include anticholinergics (*diphenhydramine*, *benztropine*, *trihexphenidyl, procyclidine*) and muscle relaxants (*diazepam*, *baclofen*).[8] If the clinical diagnosis is in doubt, benzodiazpines should not be instituted first as they would abort partial seizures and also help in relieving muscle spasms regardless of etiology.

PAID syndrome:

Paroxysmal autonomic instability with dystonia (PAID) syndrome is dysfunctional autonomic nervous system activity seen in patients with acquired cerebral insult such as traumatic brain injury, hypoxia or a space occupying lesion compressing the brainstem.[9] Other names for this condition in literature include sympathetic storm, paroxysmal sympathetic over activity and diencephalic storm.[10] The clinical symptoms include severe dystonia or extensor posturing with fever (temp >38.3 °C), tachycardia (heart rate >120 beats/min or >100 beats/min with β-blocker), hypertension (systolic blood pressure >160 mmHg or pulse pressure > 80 mmHg), tachypnea (respiratory rate > 30 breaths/min) and excessive diaphoresis.[11]

PAID syndrome is a diagnosis of exclusion and a seizure disorder has to be ruled out first. Infection workup should also be done before labelling hyperthermia to be due to dysautonomia. Once the diagnosis is established the treatment is symptomatic. IV fluids and cooling blankets may be used to counter diaphoresis and hyperthermia. Paracetamol is generally not very effective.[9] *Propranolol* (nonselective beta-adrenergic blocker) or *labetalol* (nonselective beta and selective alpha 1-adrenergic blockade) are effective in amelioration of sympathetic symptoms (such as hypertension and tachycardia). *Clonidine* (alpha 2-adrenergic agonist) controls hypertension as well as having a sedative and behaviour-stabilizing effect.[9,11]

Dystonic storm:

As the name implies, dystonic storm is a serious movement disorder emergency characterized by rapidly worsening sustained or non-sustained generalized dystonia that may require emergent airway protection.[12] Accompanying features include tachypnoea, tachycardia, excessive sweating and autonomic instability. Understandably, there is considerable overlap with PAID syndrome, neuroleptic malignant syndrome, serotonergic syndrome and encephalitis. Patients with dystonic storm usually have an underlying pre-existing condition such as idiopathic generalized dystonia, structural brain injury (cerebral palsy, traumatic brain injury), etc.[13] General management should focus on airway compromise, secondary renal injury due to rhabdomyolysis, dehydration and pain relief. Treatment is typically started with medications for acute dystonia noted above. However, elective anesthesia with IV *midazolam*, *propofol* and non-depolarizing neuromuscular blockers or barbiturates may be required depending on severity of symptoms. For prolonged resistant dystonic storm persists, deep brain stimulation (or pallidotomy) surgery have been performed.[14]

DISORDERS PRESENTING WITH CHOREA

Chorea is involuntary movements that are abrupt, unpredictable and nonrhythmic, resulting from a continuous random flow of muscle contractions described as 'dance like' (latin, chorea). An examiner may get an impression that the patient is not able to sit still and appears 'fidgety'. Sometimes, patients with chorea incorporate apparently goal directed movements on top of their involuntary movements called 'parakinesia'.[3] Ballism falls into the same spectrum as that of chorea albeit they are more forceful, large amplitude movements involving predominantly proximal muscle groups.[3]

Acute chorea can result from a variety of causes such as toxic, metabolic, vascular, autoimmune disorders and infections (Table-1).[15] Hemichorea of acute onset should be evaluated with brain imaging as it is mostly due to a structural cause.[16] Previous history of rheumatic fever should be sought in those presenting with generalized chorea in pregnancy or secondary to oral contraceptive use.[17] Symptomatic treatment options for chorea include VMAT inhibitors (*tetrabenazine*, *duetetrabenazine*), *valproate* (esp. for Sydenham's chorea), muscle relaxants (*baclofen*) and in very difficult cases careful use of dopaminergic blocking medications such as *Risperidone* (but with the risk of acute and tardive side effects).[17]

DISORDERS PRESENTING WITH MYOCLONUS

Myoclonus is involuntary, sudden, brief and 'shock like' movement. It may be due to sudden contraction of a muscle (positive myoclonus) or brief period of relaxation (negative myoclonus – asterixis).[3] Myoclonic jerks may be regular or irregular. Myoclonus may originate from the cortex (epileptic) or subcortical structures (sub cortex, spinal cord, peripheral nerve). Whenever in doubt, possibility of

epileptic myoclonus should be considered and an EEG preferably with a limb electrode obtained.[18]

Serotonin syndrome

Serotonin syndrome (SS) is a condition characterized by the presence of changes in mental status, agitation, myoclonus, hyperreflexia, and hyperthermia as a result of toxic and excessive serotoninergic stimulation. It usually occurs as a drug-drug interaction with concomitant use of two serotonergic agents but may also occur with monotherapy (Table-2).[19] A common scenario is prescribing serotonergic opioids (*fentanyl*, *methadone, meperidine, tramadol*) and morphine derivatives (*codeine, oxycodone*) for pain relief in ER to a patient already on selective serotonin reuptake inhibitors (SSRI) or monoamine oxidase inhibiters (MAOI) – a particularly high-risk combination) such as *Linezolid* for another indication.[9,20]

There is considerable overlap with neuroleptic malignant syndrome in terms of presentation and it can be mistaken as NMS (Table-3).[21] This may account for some reports in the literature that describe NMS as result of antidepressant treatment. An individual who presents with fever and muscle rigidity, and who has the antecedent of exposure to both antipsychotic and antidepressant drug treatment, poses a serious diagnostic challenge and a therapeutic dilemma. Myoclonus however is commonly seen in SS but not usually reported with NMS.

Management should be instituted immediately to prevent complications such as rhabdomyolysis, acute renal failure, seizures, metabolic acidosis, and even death. Offending agent should be stopped and specific antidote *cyproheptadine* (5 HT2a inhibiter) can be tried.[19]

Startle disease

This is a rare disorder characterized by hyperekplexia or exaggerated startle in a new born. These infants may develop repeated spasms on external stimulation and become apneic.[18] Diagnosis is clinical and is of paramount importance because the life-threatening manifestations can be avoided with the use clonazepam. Nose tapping test has been described. Normally, an infant would either blink or show no response. Patients with hyperekplexia do not habituate to this tactile stimulus and have repeated spasms in response.[22] Vigevano manoeuvre (flexion of infant's head and neck toward the trunk) has been described to abort life threatening attacks.[22] This manoeuvre is thought to activate a spinal reflex that aborts the spasm.[18]

Table-1: Causes of acute onset chorea. APLA; antiphospholipid antibody

Vascular	**Structural**	**Autoimmune**
Ischemic stroke	Basal ganglia mass lesion	Sydenham chorea
Haemorrhagic stroke	Post thalamotomy	Systemic lupus erythematosus
Arteriovenous malformations		APLA syndrome
Cerebral anoxia	**Inflammatory**	Chorea gravidarum
Cavernoma	Multiple sclerosis	Scleroderma
	Sarcoidosis	Behcet disease
Iatrogenic/Drugs		
Valproate	**Infectious**	**Metabolic**
Oral contraceptives	Tuberculoma	Non ketotic hyperglycemia
Levodopa	Cryptococcoccal granuloma	Hyperthyroidism
Cocaine	HIV encephalitis	Hyperparathyroidism
Alcohol intoxication and withdrawal	Toxoplasmosis	Uremic encephalopathy
Amphetamines		

Table-2: Common drugs related to Serotonin syndrome and particularly dangerous combinations to avoid. SSRI: selective serotonin reuptake inhibitor, MAO: monoamine oxidase inhibitor, TCA: tricyclic antidepressant.

Drugs related to Serotonin Syndrome			
Antidepressants		**OTC drugs**	**Analgesics**
SSRIs/SNRIs	MAOIs	Dextromethorphan	Tramadol
Fluoxetine	Selegeline	Supplements containing.	Fentanyl
Citalopram	Rasageline	tryptophan	Meperidine
Escitalopram	Phenelzine	Cough syrups	**Antiemetics**
Sertraline	TCAs	**Anticonvulsants**	Ondansetron
Mirtazapine	Imipramine	Valproate	Metoclopramide
Paroxetine	Amitriptyline	**Antibiotics**	**Antimigraine drugs**
Flucoxamine	Desipramine	Linezolid	Sumatriptan
			Zolmitriptan
Drug combinations to avoid			
All SSRIs in combination			
SSRI + Tramadol			
SSRI + Linezolid			
SSRI + MAOI			
Trazodone + Buspirone			
MAOI + Meperidine			

Table-3: Comparison between Neuroleptic malignant syndrome and Serotonin Syndrome.
SSRI: selective serotonin reuptake inhibitor, MAO: monoamine oxidase inhibitor

		Neuroleptic Malignant Syndrome	Serotonin Syndrome
Offending drugs		Dopamine antagonists Sudden withdrawal of dopaminergic agonists	SSRIs MAOIs Dopamine agonists
Time from onset to full blown clinical syndrome		Days to weeks	Hours
Identical features	**Vitals**	Hypertension Tachycardia Tachypnea Hyperthermia (>41.1C)	Hypertension Tachycardia Tachypnea Hyperthermia (>41.1C)
	Mucosa	Hypersalivation	Hypersalivation
Overlapping features	**Sensorium**	Variable; Alert, stuporous, comatose	Variable; Agitated, comatose
	Skin	Diaphoretic (Greasy quality)	Diaphoretic
	Rigidity	Lead pipe (involving all 4 limbs)	Lead pipe (involving lower limbs > upper limbs)
Distinctive features	**Pupils**	Normal	Mydriasis
	Bowel sounds	Normal to decreased	Hyperactive
	Reflexes	Normal to decreased	Hyperreflexia, clonus
	Myoclonus	Rare	Very common
Labs	**CK**	Moderate to marked increase	Normal to mild increase
	Leucocytosis	>90%	11%
Specific Drug Treatment		Bromocriptine Dantrolene Biperiden	Cyproheptadine

DISORDERS PRESENTING WITH RIGIDITY/STIFFNESS

Rigidity is the resistance felt on passively moving a joint independent of the speed of movement and is at times referred to as lead pipe rigidity.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome (NMS), was initially described by Delay and colleagues in 1960, is an infrequent yet life-threatening condition characterized by a tetrad of delirium, muscular rigidity, fever, and autonomic nervous system dysregulation.[23] NMS is frequently considered an idiosyncratic reaction to D2 blocker drugs but there are other recognized risk factors such as advanced age, multiple comorbidities, polypharmacy, parenteral administration of antipsychotics, application of physical restraints, underlying channelopathy or previous history of NMS.[24]

Delirium (fluctuating consciousness) is the hallmark symptom and psychomotor agitation may be seen. Fever is usually very high grade and responds poorly to antipyretics as autonomic instability has a contributory role. Rigidity is generalized and may result in abnormal postures such as opisthotonos (arching of the back). Focal dystonia may be seen in the form of blepharospasm, oculogyric crisis, or trismus. Nystagmus, dysphagia, dysarthria, or aphonia can also be a manifestation of increased muscular tone. Autonomic instability can manifest as heart rate variability, labile hypertension, and extreme diaphoresis.[23] A particularly 'greasy' quality to the sweat has been described in NMS.[23] Atypical cases have been described with the use of atypical antipsychotics such as clozapine and aripiprazole.[25]

Serum creatine phosphokinase (CPK) level may be as high as 10,000 IU/L.[23] Underlying infection should always be ruled out. These patients have impaired swallowing mechanism due to rigidity and are at risk of developing aspiration pneumonia. Differential diagnosis includes malignant hyperthermia, serotonin syndrome, CNS infection, and heat stroke (Table-3).[23]

Mortality rate can be as high as 10%[23,26] and emergent treatment is warranted. If there is suspicion of NMS, offending drug should be stopped even before confirmation of diagnosis. Replenishing fluid losses to maintain hydration and decreasing chance of renal injury due to myoglobinuria as well as controlling core body temperature is of paramount importance. Specific pharmacological management is anecdotal as there are no RCTs. *Bromocriptine, dantrolene* or *biperiden* may be used depending upon availability.[27]

Malignant hyperthermia

Malignant hyperthermia (MH) is an idiosyncratic drug reaction to potent inhalation agents (such as *halothane, isoflurane, sevoflurane*) and the depolarizing muscle relaxant *succinylcholine* in genetically susceptible individuals.[29] MH may occur during or in the first hour of post-operative period.[29] Earliest signs are masseter spasm, generalized muscular rigidity (50–80%), tachycardia, hypercapnia and hypoxia. Later hyperthermia,

rhabdomyolysis, acute renal failure, cardiac arrhythmia, hypotension and circulatory failure may ensue.[30] Temperature should be monitored in patients undergoing general anaesthesia.[29] Discontinuation of the offending agent and supportive care (temperature, fluid and electrolyte balance) are essential. *Dantrolene* is the only specific therapy available.[30] It is not possible to clinically determine this genetic susceptibility beforehand. Pre-op assessment should be carried out thoroughly inquiring family history of MH and/or muscle disease.[31]

MANAGING DELIRIUM IN A PATIENT WITH PARKINSON DISEASE

Delirium is an acute confessional state characterized by fluctuating level of consciousness and orientation. The clinical picture is characteristic and often the diagnosis can be confidently based on the clinical presentation alone.[32] If the diagnosis is in doubt, an EEG may be done to show evidence of diffuse cerebral dysfunction. Among hospitalized patients, prevalence ranges between 10% and 20% for medical inpatients. Risk factors for delirium include predisposing factors such as older age, male gender, dementia, visual and hearing impairment, alcoholism, hip fracture and metabolic derangements while immediate precipitating factors include multitude of drugs, occult infections, surgery, pain, physical restraints and ICU admission.[33] The general management for delirium revolves around identifying and addressing the precipitating factors while antipsychotics may be used to control an agitated delirious state.[32]

Parkinson disease is an independent risk factor for delirium.[34] Management of delirium in PD poses unique challenges. Antipsychotics are contraindicated for management of delirium in PD because apart from worsening parkinsonism, they also pose a risk of precipitating NMS. Short acting benzodiazepines may be used if required to control an agitated delirious state. Among the antipsychotics, quetiapine and clozapine are considered relatively safer to use in PD because of their effects on receptors other than D2.[35]

CONCLUSION

First responders to the bulk of Movement Disorder emergencies continue to be non-neurologists. Timely and appropriate management is of paramount importance to prevent morbidity and even mortality. It is imperative that all physicians are comfortable in recognizing as well as immediate management of these disorders.

AUTHORS' CONTRIBUTION

HH, MN, MFK, DEB: Conceptualization of design, literature search, write up, proof reading. NMS, MR, AA, MAJ: Literature search, write up, proof reading.

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