

Chapter 20

Abnormal Involuntary Movement Disorders (Dyskinesias)

Abnormal involuntary movement disorders are defined as orofacial, lingual, head, trunk, and extremity movements that can be modified but not abolished by the patient. These are superimposed on normal motor activities and can interfere with coordinated voluntary motor activities and posture maintenance. Dyskinesias are usually classified as extrapyramidal mediated motor activities. In certain disorders, major biochemical and pathologic disturbances have been shown to occur in the basal ganglia; however, despite recent advances, exact pathophysiology and neuropharmacology of dyskinesias remain incompletely understood.

Evaluation

The patient's motor function should be carefully characterized upon walking into the room, sitting and rising from the chair, and talking to the examiner. Special attention should be directed towards:

- Body and neck posture
- Gait
- Facial expression
- Speech
- Handwriting and ability to draw Archimedes spiral (circle of progressively increasing diameter)
- Muscle tone
- Posture of outstretched hands
- Performance of rapid successive and alternating movements
- Speed and dexterity of finger to nose, heel to shin, and finger movement

The dyskinesias are carefully analyzed for the following:

Occurrence. Resting state, posture maintenance, voluntary movements.

Morphology. Rhythmic or nonrhythmic, stereotyped or random, simple or complex, nonpurposeful or semipurposeful.

Distribution. Trunk, neck, face, extremities (proximal or distal, unilateral or bilateral).

Velocity and Duration. Rapid or slow, brief or prolonged, intermittent or persistent.

Relation to and possible interference with purposeful motor activities.

Modifying Factors. Sleep, distraction, anxiety, alcohol, medications.

In assessing possible causes, it is important to determine age of onset, rate of progression, family history, prior medication history, possible toxic exposure, and associated medical, neurological, psychiatric illnesses. Onset in infancy is suggestive of cerebral palsy, and those disorders initially developing in childhood or adolescence can be related to rheumatic fever, Wilson's disease, primary dystonias. Dyskinesias developing later in life can be of degenerative (Huntington's disease, Parkinson's disease), vascular, neoplastic, or drug-induced etiology.

Movement disorders related to vascular disease, rheumatic fever, or medications develop rapidly, and those caused by degenerative disorders or neoplasms develop more slowly. Some disorders show specific genetic pattern, for example, Huntington's disease, primary dystonias. Because certain patients are not aware of the dyskinesias, clinical examination of the entire family is necessary before accepting negative family history. Patients should be questioned for use of medications that can induce dyskinesias (e.g., antipsychotics, phenytoin, lithium, valproic acid, oral contraceptives) or possibility of toxic exposure (e.g., manganese as occurs with welders). Certain medical conditions can be associated with dyskinesias (e.g., rheumatic fever, systemic lupus erythematosus, liver disease).

The characteristics of certain abnormal involuntary movements are listed by heading type. Although fasciculations are more completely discussed with motor neuron disease and myoclonus with epilepsy, both fasciculations and myoclonus clinically represent abnormal involuntary muscle activity and are described in this section, although they are not extrapyramidal in type.

FASCICULATIONS

Occurrence. Observed at rest or following extended muscle contraction.

Modifying Factors. Exacerbated by anxiety, caffeine, amphetamine, prolonged muscle activity; reduced by rest and sleep.

Characteristics. Rapid, brief, twitch-like muscle contractions of low amplitude and not sufficient to move the joint. No interference with purposeful activity.

Associated Findings. "Benign" fasciculations are quite common in normal persons and are most common following extended muscle contraction or during rest. Those caused by motor neuron disease are more prolonged, spread across large portions of the muscle, and can involve the tongue; most important, muscle weakness and wasting accompany fasciculations due to motor neuron disease.

Etiological Conditions. Motor neuron disease or physiological state caused by motor neuron fatigue in normal persons.

Biochemical Abnormality. Metabolic imbalance of motor neuron.

Treatment. None; allay anxiety that fasciculations do not represent amyotrophic lateral sclerosis and are benign.

MYOCLONUS

Occurrence. Random jerking movements observed in sleep and anxiety states; occur at rest or with voluntary activity in pathologic states including metabolic-electrolyte imbalances.

Modifying Factors. Action myoclonus exacerbated by voluntary movement; can persist with sleep.

Characteristics. Rapid coarse contraction of groups of muscles which may move the joint. There can be nonrhythmic isolated jerking or twitching of portion of extremity (finger, wrist, or shoulder), head, trunk, or neck. There can also be prolonged, continuous rhythmic contraction of isolated muscle groups (e.g., palatal myoclonus) with brain stem lesions.

Associated Findings. Can be seen in patients with epilepsy. Dementia develops in patients with Creutzfeldt-Jakob disease; spasticity and dementia develop in subacute sclerosing panencephalitis. In postanoxic myoclonus, cerebellar and corticospinal tract signs can be present.

Etiology. Metabolic and toxic encephalopathies (most frequently caused by cerebral hypoxia), Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, and epilepsy.

Biochemical Abnormality. Reduced cerebrospinal fluid levels of hydroxyindoleacetic acid (serotonin) has been reported in postanoxic myoclonus.

Treatment. Clonazepam, valproic acid (Depakote), and L-tryptophan (amino acid serotonin precursor).

TIC (HABIT SPASM)

Occurrence. Resting state causing no interference with voluntary movement.

Modifying Factors. Exacerbated by anxiety; decreased by sleep and distraction; can be voluntarily suppressed for short time periods.

Characteristics. Rapid, stereotyped, random, spasmodic, nonpurposeful movements. These include blinking, shoulder shrugging, facial grimacing, tongue darting or protrusion, coughing, or grunting.

Associated Findings. Tics can be single or multiple. Coprolalia (obscene language) or echolalia (repeating words and sounds made by the examiner) may occur in Tourette's syndrome.

Etiology. Can be of psychogenic origin; multiple tics with forced vocalization characterize Tourette's syndrome.

Biochemical Abnormality. None known.

Treatment. Good clinical response in Tourette's syndrome to haloperidol, clonazepam, and clonidine; isolated or multiple tics do not usually require treatment.

CHOREA

Occurrence. Resting state with no interference with voluntary activity; movements can appear to simulate semipurposeful activity.

Modifying Factors. Exacerbated by anxiety; disappear in sleep.

Characteristics. Rapid coarse, semipurposeful, random, nonrhythmic movements of extremities, trunk, and face.

Associated Findings. Dementia in Huntington's disease, carditis in Sydenham's chorea, facial rash in systemic lupus erythematosus, Kayser-Fleischer ring in Wilson's disease.

Etiology. Rheumatic fever, Huntington's disease, drug induced, aging, pregnancy, Wilson's disease, systemic lupus erythematosus.

Biochemical Abnormality. In Huntington's disease, there is reduced glutamic acid decarboxylase and gamma-aminobutyric acid (GABA) in neostriatum.

Treatment. Dopaminergic blocking agents (e.g., haloperidol) or presynaptic dopamine depleters (e.g., reserpine).

BALLISM

Occurrence. Resting state; can interfere with voluntary movement.

Characteristics. Irregular random and nonrhythmic violent flinging (flail-like) movements usually involving arm, usually unilateral.

Associated Findings. Can occur as isolated finding or as part of subthalamic syndrome.

Etiology. Focal lesion of the subthalamus (hemorrhage, tumor, infarction).

Biochemical Abnormality. None known.

Treatment. Haloperidol and phenazine, ventrolateral thalamotomy.

ATHETOSIS

Occurrence. Resting state or posture maintenance; can be severe enough to interfere with voluntary movements.

Modifying Factors. Same as chorea.

Characteristics. Slow, coarse, irregular, and nonrhythmic writhing movements of hands, feet, facial, and neck muscles.

Associated Findings. Choreiform and dystonic movements.

Etiology. Usually results from perinatal hypoxic-ischemic injury.

Biochemical Abnormality. None known.

Treatment. Dopaminergic agents can be effective.

DYSTONIA

Occurrence. At rest and posture maintenance.

Modifying Factors. Exacerbated by anxiety states and disappears during sleep.

Characteristics. Usually slow, but can be more rapid. Coarse, sustained muscle contraction leads to abnormal turning or twisting postures including torticollis (wry neck), writer's cramp (contraction of muscles of fingers and forearm), blepharospasm, or inward turning of foot (equinovarus deformity).

Associated Findings. Contracture of the limb as a result of sustained muscle contraction.

Etiology. Drug induced (antipsychotics, dopaminergic agents), primary dystonias, psychogenic conditions.

Biochemical Abnormalities. None known.

Treatment. Sedation with diazepam or haloperidol; dopaminergic agents have rarely been effective; high-dose anticholinergic agents; anterior cervical root or spinal accessory nerve denervation; local injection with botulinum toxin for spasmodic torticollis.

AKATHISIA

Occurrence. At rest and posture maintenance.

Modifying Factors. Exacerbated by anxiety or prolonged immobility.

Characteristics. Inability to sit still with constant body and limb motion.

Associated Findings. Bradykinesia and rigidity can be present in parkinsonism. Part of restless leg syndrome in patients on neuroleptic therapy.

Etiology. Antipsychotic drugs.

Biochemical Abnormality. Dopamine receptor blockade.

Treatment. Anticholinergics; clonazepam; benzodiazepines; beta-adrenergic antagonists.

TREMOR

Occurrence and Characteristics. Rhythmic, stereotyped, nonpurposeful movement of groups of muscles around specific axis at equal velocity and amplitude.

- Slow and coarse pill-rolling *resting* tremor of parkinsonism (3 cycles per second)
- Rapid and fine lower amplitude *postural* tremor caused by anxiety, metabolic disorders (thyrotoxicosis, alcoholism), and benign essential tremor
- Coarse *intention* tremor of cerebellar disorders

Modifying Factors. Exacerbated by anxiety and disappears in sleep; benign essential tremor reduced by alcohol.

Etiology. *Resting* tremor: parkinsonism. *Postural* tremor: anxiety, thyrotoxicosis, alcoholism, benign essential tremor, cerebellar disease. *Intention* tremor: Wilson's disease, cerebellar disease, medication effect (lithium, valproic acid).

Biochemical Abnormality. *Resting* tremor: dopamine insufficiency in parkinsonism. Not known in other types.

Treatment. *Resting* tremor: anticholinergic and dopaminergic drugs. *Postural and intention* tremor: diazepam, primidone, and propranolol. Ethanol reduces amplitude of tremor. Use of weights on wrist may dampen amplitude of hand tremor to improve motor coordination.

CLINICAL SYNDROMES

Parkinson's Disease (PD)

The cardinal findings of parkinsonism include the following:

- Resting tremor, slow (3-5 cps) in velocity and coarse in amplitude; initially involves thumb, index, and middle fingers to cause pill-rolling movement
- Rigidity involving extremities, trunk, and neck; there may be superimposed cogwheel quality, which can represent superimposed tremor
- Freezing in which there is brief inability to form voluntary motor activities. The feet seem stuck, there is hesitation when patient tries to initiate walking or turning
- Bradykinesia or hypokinesia, which is most prominent on initiation of motor activity
- Impairment of postural reflexes
- Lack of facial animation or emotion (hypomimia) which is referred to as mask-like facies

This clinical constellation can be due to many different diseases; however, PD is the most common cause of parkinsonism. PD refers to chronic progressive neurological disorder caused by dopamine deficiency and associated with depigmentation within zona compacta of substantia nigra. Reduced dopamine transmission in the striatum causes disinhibitory activity in the subthalamus and medial globus pallidus.

Initial symptoms of PD include insidious onset of tremor, clumsiness, stiffness, or frequent falls. Motor dysfunction can initially be unilateral or more commonly bilateral and asymmetrical. Rarely, patients show gait unsteadiness with no signs of parkinsonism in arms (lower-half syndrome). When only legs are involved and no tremor is present, this clinical pattern can cause diagnostic confusion with other neurological disorders such as progressive supranuclear palsy, normal pressure hydrocephalus or vascular disorders.

Some patients with PD seek treatment because of tremor. Tremor can be the source of embarrassment but not functional disability because it is maximal at rest and disappears with limb movement. It is therefore a manifestation that the patient is not well. Other symptoms include poor balance, frequent falls, weakness, aching pains, stiffness (especially in shoulder, neck, and extremities), seborrhea, and sialorrhea. Some PD patients have limb pain that simulates arthritis (e.g., morning stiffness, frozen shoulder) or peripheral vascular disease; however, careful examination of these patients may show other parkinsonism features to permit differentiation from these non-neurological conditions.

When PD patient is asked to arise from a chair, there is initial hesitation and delay. The patient walks stiffly, has stooped posture, takes small shuffling steps that progressively accelerate to running pace (festinating gait). Associated swinging arm movements that

accompany normal gait are decreased in PD patients. Impaired postural reflexes can be demonstrated by asking patient to stand with feet together, then applying sudden force to sternum; patient falls backward en bloc (retropulsion) rather than having normal response of broadening base to regain balance. When trunk or extremities are passively moved, increased resistance (rigidity) is detected. This can be accentuated by having patient perform rapid successive movements (e.g., opening and closing fists) with one extremity while physician tests tone in trunk or other limbs. Handwriting shows tremor, is small in size (micrographia) and is performed slowly. The face lacks animated emotional expression (mask-like facies), blink rate is decreased, and drooling is common. Skin is oily due to seborrhea. Tapping over glabella (bridge of nose) produces sustained blinking (Myerson sign). Impairment of intellectual capabilities or dementia are uncommon in initial stages of PD; however, mental disturbances simulating frontal lobe dysfunction (slowness to initiate mental tasks) are common. Prominent cognitive impairment suggests alternative diagnoses (e.g., Lewy body dementia, corticobasal degeneration), conditions unlikely to respond to dopaminergic medication.

If parkinsonism occurs in young patient, Wilson's disease or drug use may be considered although juvenile form of PD exists. Manganese and N-methyl-4-phenyltetrahydro-pyridine (MPTP), which is synthetic meperidine produced by "street chemists" and toxic to striatal dopaminergic cells, can cause parkinsonian syndrome. Parkinsonism can start unilaterally, then later generalize, but in unilateral cases focal e.g., tumor, vascular lesion must be excluded. Patients with benign essential tremor are sometimes initially diagnosed as having parkinsonism; however, the tremor is postural and there is no rigidity or bradykinesia. Not all patients who shake as result of tremor suffer from parkinsonism; conversely not all PD patients have tremor. The diagnostic error is greatest in those patient who have PD but no tremor. The diagnosis of PD is clinical and important to establish, as only PD patients respond to dopaminergic medication.

Neurologic deficit as result of PD can remain stable for many years or progress rapidly; most frequently there is slow deterioration over one decade. The initial symptoms are usually unilateral hand tremor with difficulty using limbs as a result of rigidity and bradykinesia. Later these symptoms become generalized. Rigidity and hypokinesia with loss of postural reflexes are major causes of functional disability; whereas tremor causes minimal interference with daily living activities. Symptoms can be ameliorated with medication, but eventually condition worsens as medication becomes less effective.

Treatment strategies for PD are directed at correcting striatal dopamine insufficiency. It is important to obtain a careful medical history, such as prior use of antipsychotic or antiemetic phenothiazine drugs, possible exposure to neurotoxins (MPTP), or prior viral encephalitis. The neurologic examination is directed toward excluding findings that suggest multisystem degenerative process such as olivopontocerebellar degeneration, progressive supranuclear palsy, striatonigral degeneration. CT/MRI excludes normal pressure hydrocephalus, cerebral infarct(s), basal ganglia neoplasm, or subdural hematoma as cause of parkinsonian syndrome. If diagnosis of PD is most likely, it should next be determined if the patient shows functional neurologic impairment. For example, moderate resting hand tremor can be embarrassing to patient but not interfere with hand dexterity, whereas mildly impaired postural reflexes and bradykinesia can cause patient to fall and be afraid to go out of the house. If there is functional impairment, treatment of PD should be initiated. Eighty to 90% of patients with PD respond to dopaminergic drugs; failure to respond should suggest an alternative diagnosis. The principle of therapy should be as follows: start low, go slow! (Table 20.1)

Dopaminergic medication is the most effective treatment. Levodopa in combination with decarboxylase inhibitor (Sinemet) is usually preferred because side effect incidence is low. Medication should be taken with food to avoid gastric irritation, nausea, and vomiting. The dosage is increased slowly, for example, once a week.

Because significant proportion of levodopa is enzymatically decarboxylated peripherally to dopamine (which does not effectively cross the blood-brain barrier) before it reaches CNS, it is possible to potentiate the effect using peripheral dopa decarboxylase inhibitor. The addition of dopa decarboxylase inhibitor has reduced incidence of nausea and vomiting and orthostatic hypotension, which were much more common with levodopa alone. It is possible to prolong duration of activity by adding catechol-O-methyl transferase inhibitor (COMT) to this combination. Available preparations of decarboxylase inhibitors with levodopa (Sinemet) include doses of 10/100, 25/100, or 25/250. Some patients require 1 to 3 g of levodopa with 100 to 200 mg of decarboxylase inhibitor; however, the dose of levodopa should be kept to 500 to 700 mg to minimize and delay onset of motor fluctuations that can complicate therapy (means without vomiting). Sinemet 25/100 causes minimal nausea and vomiting. If gastrointestinal symptoms persist, hydroxyzine (Vistaril) or trimethobenzamide (Tigan) can be used, but prochlorperazine (Compazine) should be avoided because of its potential to cause parkinsonian side effects. Sinemet is initiated at a low dosage and is increased slowly; it is initially administered twice per day and can later be increased to four or five times daily. When patients get into difficulty with dyskinesias, a smaller and more frequent dose administration schedule can help. Other medications that potentiate dopamine effect include monoamine oxidase B-inhibitor (selegiline) and catechol O-methyl transferase inhibitor (entacapone). Dopamine receptor agonists can be divided into ergot derived (bromocriptine, pergolide, cabergoline) and non-ergot derived (ropinirole, pramipexole). Dopamine agonists are somewhat less effective than Sinemet but less likely to cause dyskinesias as side effects, because their longer sustained effect simulates the natural tonic release of dopamine from nigral neurons, as contrasted with pulsatile stimulation of receptors caused by Sinemet.

Potential complications of dopaminergic agents are listed in Box 20-1.

Although peripheral untoward effects are reduced by Sinemet, central untoward effects are not modified. Dyskinesias are initially dose dependent and can be avoided by low doses. With chronic dopaminergic therapy, dyskinesias occur at progressively lower doses. Delirium, confusion, and hallucinations can develop acutely, and their occurrence can require medication discontinuation; clozapine (Clozaril), olanzapine, (Zyprexa), ziprasidone (Geodon) should be used because other antipsychotic agents can worsen parkinsonism. The on-off phenomenon is characterized by abrupt change from good control, alternating with sudden unexpected return of maximal symptoms, then return to good control-all within several-minute interval. It occurs in PD patients receiving long-standing Sinemet therapy who have rapidly fluctuating levodopa blood levels. Motor fluctuations can become more frequent and incapacitating as a result of the medication effect or disease progression. Several strategies have been used to reduce motor fluctuations. These include low protein diet (especially limiting protein which patient eats early in day), use of controlled or sustained release dopaminergic medication (Sinemet CR), shortening the interval between Sinemet doses, and the use of dopamine receptor ergot derived agonists bromocriptine (Parlodel), pergolide (Permax) or non-ergot derived agonists, e.g. pramipexole (Mirapex), ropinirole (Requip).

BOX 20-1

1. Nausea and vomiting
2. Orthostatic hypotension
3. Cardiac arrhythmias
4. Mental change (e.g., confusion, psychoses, hallucinations, depression)
5. Dyskinesias (chorea, dystonia, buccal-lingual-facial movements)
6. Clinical fluctuations (e.g., early wearing off effect, early morning akinesia, freezing episodes in which the patient suddenly becomes immobile, on-off phenomena that are random, sudden, and unexpected motor fluctuations of good control alternating with sudden development of an inadequate effect)

Anticholinergic drugs are effective in treating parkinsonism by reducing striatal cholinergic effect or increasing dopaminergic concentration; however, they are less effective than other dopaminergic enhancing medications. Benztropine mesylate (Cogentin) is supplied as 0.5-, 1-, or 2-mg tablets. It has long half-life and is administered once or twice daily. The starting dosage is 0.5 mg daily; this can be increased to maximal dose of 4 mg twice daily. Biperiden (Akineton) is supplied in 2-mg tablets; has shorter half-life, and therapy is usually started at 1 mg and increased to 2 mg three times daily. Trihexyphenidyl (Artane) is supplied in 2- and 5-mg tablets; therapeutic range is quite variable; dosage ranging from 1 to 5 mg three times daily. These agents are initiated at low dosages and gradually increased. These drugs do not improve akinesia or impaired postural reflexes. Side effects include dry mouth, visual blurring, glaucoma, constipation, urinary retention, delirium, and hallucinations and it is these side effects which limit their use. These drugs have been reported to decrease tremor with less effect on rigidity or bradykinesia.

Amantadine (Symmetrel) can have dopamine releasing effect or effect on alternative neurotransmitter such as glutamate. It is usually used in combination with dopaminergic drugs to potentiate their effect, but it has little activity when used alone. When effective, this improvement is seen very rapidly. It appears to enhance dopamine production and release. Toxicity includes depression, delirium, congestive heart failure, orthostatic hypotension, skin lesion (livedo reticularis). The dosage is usually 100 mg, two or three times daily. It may initially be effective, but with time it becomes less effective.

Initiate treatment with Sinemet using 100 mg of levodopa and 25 mg of decarboxylase inhibitor once daily. The dosage is increased slowly every seven days by one-half tablet. Increments should continue until adequate functional improvement occurs or signs of toxicity develop. Maximal improvement with minimal toxicity occurs within the early years of therapy; however, with increasing time, drug effectiveness diminishes and drug toxicity increases. As drug becomes less effective, there are clinical fluctuations in motor function. These include akinetic periods alternating with dyskinesias. Certain fluctuations are related to less effect obtained with same drug amount. These fluctuations include end-of-dose, morning time akinesia, and wearing-off effect; these can be managed by more frequent drug administration. Increasing sensitivity to the dopaminergic medication may cause peak-dose dyskinesia or dystonia. Less predictable and more dangerous to the patient are "on-off" effect and paroxysmal dyskinesia; these have no relation to drug administration schedule. These effects can occur without warning and are managed by a lower dose that is administered at more frequent intervals or by addition of dopamine agonists. Controlled-release (CR) levodopa preparations are believed to achieve even distributions (less fluctuating) of dopamine levels and this reduces

frequency or severity of motor fluctuations. There is longer half-life and lower peak plasma level of levodopa. Sinemet CR (50/200) is usually initiated at a dosage of one-half tablet twice per day. There is less bioavailable levodopa in a controlled-release tablet, and if patient is switched from regular to Sinemet CR, levodopa amount should be increased by 33%. Sinemet CR is believed to delay motor fluctuations. Also with Sinemet CR it takes longer time for patient to achieve mobility in the morning and sometimes regular Sinemet is given as morning dose supplementing Sinemet CR tablet.

When levodopa therapy is initiated, there is usually sustained benefit in motoric dysfunction. There are no motor fluctuations. After several years, patients begin to experience fluctuations and early "wearing off" of medication effect. Duration of motor improvement shortens and patient develops dyskinesias (chorea, dystonia). The precise mechanism is not known but may relate to disease progression or levodopa effect on the dopamine receptor; therefore substituting dopamine agonist for levodopa may be helpful. Dyskinesias become more severe and disabling with increased duration and dose of levodopa. There is no evidence that levodopa is "toxic" to PD patients; however, management with dopaminergic medication becomes more difficult with advanced disease state.

Dopamine agonists directly act on dopamine receptor. The ergot derived bromocriptine (Parlodel) and pergolide (Permax) and new non-ergot derived pramipexole (Mirapex), and ropinirole (Requip) are available for clinical use. These drugs produce fewer dyskinesias than levodopa and have more prolonged therapeutic effect than Sinemet. The latter effect is useful in combating wearing-off effects; however, neurobehavioral side effects are more common with the dopamine agonists than with Sinemet. Ergot-derived dopamine agonists have prominent skin vascular effects to cause red inflamed skin and rarely cause retroperitoneal fibrosis. Non-ergot dopamine agonists may cause sleep-wake cycle disturbances such as sudden falling asleep. This may be serious problem if patient drives or works. Dopamine agonists are less likely to cause dyskinesias than Sinemet and have longer time effective period but are less effective. There is controversy as to whether they should be used early in course of PD; however, it is best to use Sinemet initially. Later it is feasible to combine Sinemet with dopamine agonists or use these agents only when clinical fluctuations occur.

Treatment with anticholinergic, dopaminergic, or dopamine receptor agonist medication provides symptomatic improvement. Selegiline (Deprenyl, Eldepryl) is selective monoamine oxidase (MAO) inhibitor that can act as neuroprotective agent to slow actual pathologic progression of PD by reducing oxidative stress (antioxidant therapy) within CNS. Selegiline can reduce levodopa metabolism, increase synaptic dopamine, and prevent free radical formation in brain. The initial dosage is 2.5 mg daily, and this is usually increased to a maximum dosage of 5 mg twice daily. Untoward effects include sleep disturbances, dyskinesias, behavioral disorders. Because dopamine levels are reduced by 80% when PD patients become initially symptomatic, dopamine system has already suffered severe damage; therefore Deprenyl can be more effective if preclinical (before motor dysfunction occurs) diagnosis is possible. Unfortunately it is not possible to identify these asymptomatic patients at risk for PD at the present time. Deprenyl should be maximally effective in patients with early parkinsonism. There is some weak evidence that Deprenyl slows disease progression but it also can have a symptomatic effect on motor dysfunction.

Functional neurosurgical procedures have been utilized to inhibit neuronal activity when medication effect is reduced or side effects occur. The target is the dysfunctional activities in the motor portion of the thalamus, internal segment of globus pallidus, and subthalamus. Improved

stereotactic techniques that are neuroablative and stimulatory procedures (deep brain stimulation) still carry risk of neurological complications, especially if bilateral **lesions** are made. Surgical reduction of excessive inhibitory activity of internal segment of globus pallidus to thalamus or reduction of firing rate of subthalamus to internal segment of globus pallidus and pars reticularis of substantia nigra can enhance activity of premotor cortex and supplementary motor cortex. This can be achieved with pallidotomy or deep brain stimulation of globus pallidus or subthalamus. Transplantation procedures to the striatum that serve to enhance deficient striatal dopamine have been mostly abandoned due to poor effectiveness.

Progressive Supranuclear Palsy (PSP)

This disorder resembles PD; however, there are additional features. Diagnosis of PSP is established by these features: parkinsonian signs including impaired postural reflexes causing frequent falls, bradykinesia, rigidity; resting tremor is *not* usually present; slow vertical rapid eye-movements especially with impaired downward but intact (oculocephalic) reflex; rigidity affecting axial more than appendicular muscles; dysarthria; dysphagia; dysphonia; blepharospasm; eyelid opening apraxia; dementia; and bilateral corticobulbar and corticospinal signs (Babinski signs). Compared with PD, PSP patients have no tremor; impaired balance is prominent, and this leads to sudden frequent falls (the patient stumbles backward as compared with PD patients who usually fall forward). Pathological changes include neurofibrillary tangles in midbrain, globus pallidus, subthalamus, substantia nigra. The course of PSP is relentless progression. Treatment with dopaminergic medication is less effective than in PD patients, and much higher doses of levodopa have been utilized in PSP patients, but usually with minimal success. The lack of response to dopaminergic agents differentiates PD from PSP.

Benign Essential Tremor

Benign essential tremor is often familial and transmitted as an autosomal dominant trait with variable penetrance. Tremor usually develops in childhood and adolescence but becomes clinically evident and functionally disabling in adult life. Tremor amplitude and occurrence increase with age, for example, senile tremor. Tremor is postural and intentional at a rate of 8 to 12 Hz. Initially it involves hands; it causes difficulty writing and shaving. Also, patient is clumsy holding drinking cup, combing hair, or using food utensils. The tremor is bilateral and asymmetrical, frequently beginning in the dominant hand. Later, head or voice tremor can develop. There is no gait disturbance, mental change, rigidity, or hypokinesia; absence of these findings permits differentiation from parkinsonism. The condition is defined as "benign"; however, the tremor can be very disabling by interfering with writing, shaving, grooming, dressing, feeding. If tremor develops late in life, it is called "senile tremor."

The condition remains relatively unchanged throughout life. Tremor is ameliorated by alcohol and exacerbated by anxiety, caffeine, fatigue, and exercise. It can be precipitated by theophylline, lithium, valproic acid, or hyperthyroidism. Frequency and amplitude of tremor are reduced by diazepam (Valium), primidone (Mysoline), or propranolol (Inderal). Because tremor may not interfere with activities of daily living, risks of drug addiction (diazepam) and cardiac (propranolol) complications must be considered relative to potential benefits of treatment. The patient can use drugs to reduce dysfunction caused by tremor as indicated by lifestyle pattern. For example, a professor with voice tremor may use medication only when giving speech in public. The most effective drugs to reduce tremor amplitude are primidone and propranolol. Initiate treatment with primidone in the smallest possible dose (50 mg daily) and gradually

increase until tremor reduction is achieved or side effects occur. Other beta-adrenergic antagonists such as metoprolol may be used in patients with asthma or cardiovascular disease, in cases when propranolol is contraindicated.

Huntington's Disease

The cardinal features of Huntington's disease (HD) are choreiform movements and progressive cognitive and behavioral deterioration. This disorder usually becomes evident in third or fourth decade. It is transmitted as an autosomal dominant trait with complete penetrance such that each patient likely has an affected parent. There are areas of high prevalence (western Scotland, Lake Maracaibo region of Venezuela). This disorder results from genetic expression (DNA expansion syndrome) involving chromosome 4. With improving DNA technology it is becoming possible to predict which family members will become symptomatic.

The earliest symptoms are usually stereotyped tics (shoulder or face), generalized motor restlessness, clumsiness, awkwardness, or frequent falls. Motor impersistence or inhibition during performance of voluntary motor activity such as protruding the tongue may lead to "tongue darting" or during squeezing the examiner's hand may lead to relaxation of the grip (milkmaid grip) and cause the patient to drop objects. With progression of the illness, muscle rigidity develops.

The patient may be unaware of dyskinesias, which can be initially reported by family members or friends; however, certain families go to fantastic extremes to hide family evidence of HD. Onset can be quite insidious with initial psychiatric symptoms including affective disorder, obsessions and compulsions, irritability, and aggressive behavior. Some patients have dementia or acute psychoses; more commonly these symptoms develop after the onset of dyskinesias. In later stage of HD, dementia becomes prominent, and speech is slurred almost to becoming incomprehensible. There is a juvenile form of HD characterized by dystonia, rigidity, dementia, and seizures as well as chorea.

Certain potentially treatable conditions should be considered in suspected HD patients. In children and young adults chorea can appear as a major manifestation of rheumatic fever or postencephalitic syndrome. In Sydenham's chorea, dyskinesia develops acutely. It usually persists for 2 to 6 months and spontaneously remits but can subsequently recur. Chorea can develop in women during pregnancy or with oral contraceptive use. In adults, neuroacanthocytosis may present with chorea, tics and dystonia, and patients also show evidence of peripheral neuropathy. There may also be behavioral and cognitive disorders. MRI shows caudate atrophy similar to that seen in HD. Fresh blood smear shows acanthocytes (spike-shaped red blood cells); lipid profile and lipoproteins are normal. Dyskinesias which develop in psychiatric patient who have received anti-psychotic medications is more likely tardive dyskinesias than HD, especially if movements are more oral-facial lingual in distribution and gait is normal; however, family history and genetic testing may be required. Benign nonprogressive chorea is not associated with cognitive or behavioral disorder. Other etiologic considerations for chorea include systemic lupus erythematosus, Wilson's disease, neurosyphilis, thyroid disorders, parathyroid disorders.

Biochemical analysis of brains of patients who have died of HD shows abnormalities of several neurotransmitter types; however, most striking is the decreased level of gamma-aminobutyric acid and enzyme glutamic acid decarboxylase in the caudate nucleus, putamen, and cerebral cortex (especially frontal lobes). CT/MRI can show characteristic "squared-out" appearance of anterior frontal horns of lateral ventricles as result of caudate atrophy. Positron

emission tomography can show decreased oxygen and glucose utilization within striatum; this can be even detected in asymptomatic HD patients. No treatment halts progressive nature of HD. Dopamine antagonist drugs may treat psychoses and chorea. Dopaminergic blocking agents (e.g., haloperidol, perphenazine) are used to reduce choreiform movements but do not alter progression of cognitive-intellectual (dementia) symptoms. If active rheumatic fever or systemic lupus erythematosus is the cause of chorea (Sydenham's chorea), antibiotics or corticosteroids are also administered.

Gilles de la Tourette Syndrome (TS)

TS begins in childhood or adolescence, and is more common in boys. Initial symptoms include hyperactive motor behavior (face and eye twitching or facial grimacing). Tics spread to neck and shoulder and later involve extremities. Repetitive stereotyped vocal involuntary movements (grunting, coughing, spitting) can develop several years later; this is followed by involuntary vocalization of obscene language in 50% of patients. There are multiple motoric and phonation tics. Tics disappear with sleep and decrease with distraction; they are worsened by anxiety. They can be suppressed for short periods of time but then recur. Tics can change in pattern and location, and they frequently undergo remissions, but later tics can exacerbate. TS is chronic disorder with maximal frequency in adolescence and early adulthood, then tics diminish as the patient gets older. Tic occurrence can cause psychological problems and social isolation.

In TS, behavioral features include obsessive-compulsive disorder and attention deficit-hyperactivity syndrome. TS is hereditary condition with the following diagnostic criteria: multiple motor tics; the presence of one or more vocal tics; initial presentation of symptoms before 21 years of age; and symptom duration exceeding one year. Chronic tic disorder that is *not* TS has motor or vocal tics, but *not* both disorders. Transient tic disorder differs from TS in that symptoms last less than one year.

Treatment consists of haloperidol, but this can require extremely high doses (30-100 mg/day). Haloperidol has benefited certain patients; however, sedative effect limits maximal dosage. The physician should be concerned about tardive dyskinesias with prolonged haloperidol use, and there should be drug-free periods. Clonazepam (Clonopin) or pimozide (Orap) are alternative drugs, less likely to cause side effects. Pimozide is as effective as Haldol in tic suppression, has less sedative effect, and is less likely to cause dyskinesias; however, electrocardiogram monitoring is warranted because of risk of cardiovascular complications. If tics are mild, they need not always be treated.

Wilson's Disease (Hepatolenticular Degeneration)

This is autosomal recessive genetic disorder of copper metabolism that causes pigmentation of cornea, pathological damage of liver and brain, damage to kidney tubular system and red blood cells (hemolytic anemia). The majority of body copper is bound to plasma protein (ceruloplasmin). The major abnormality in Wilson's disease is low ceruloplasmin level, but this is not the primary abnormality. Because copper is not bound to ceruloplasmin, it is free in plasma, and copper urinary excretion is increased. Copper is deposited in brain, liver, kidney, and red blood cells to cause pathological damage to these organs. Major neuropathological disturbances are located in putamen and globus pallidus.

Tremor (resting, postural, intention) is major dyskinesia; however, choreoathetosis, dystonia and parkinsonism symptoms can develop. Parkinsonism that develops in young person without known etiology should be considered to be Wilson's disease until proven otherwise.

Postural tremor is most characteristic; if it is present at the shoulders, this tremor can have "wing-beating" quality. Tremor is brought out by having patient hold out the arms in abducted position and bend the elbows to touch fingertips. The patient is uncoordinated using hands and frequently falls because of ataxia. The face has fixed smile and constant drooling. In children, initial symptoms can be deterioration in school performance and behavioral changes with characteristic rapid outbursts of anger or crying. An examination shows muscular rigidity, bradykinesia, poor postural control, dysarthria, and ataxia. The eyes must be examined with slit lamp for presence of green-yellow corneal rim (Kayser-Fleischer ring); this feature is invariably seen in patients with CNS manifestations. Wilson's disease should be suspected in children and young adults with unexplained hepatic disease or hemolytic anemia.

Laboratory studies are necessary to confirm the diagnosis (Box 20-2).

Wilson's disease is a chronic and progressive disorder, and without treatment there is severe disability. The goal of therapy is to remove copper from tissues by reducing copper intake and increasing excretion and to prevent reaccumulation of copper in tissues. Treatment strategies include reducing dietary copper, potassium sulfide to reduce copper absorption, and penicillamine. Penicillamine (250 to 500 mg four times daily) is a chelating agent; it rapidly binds copper, removes it from tissues, and facilitates excretion. It is effective in enhancing excretion of copper in the urine but high percent of patient have untoward effects including leukopenia, optic neuritis, myasthenic syndrome, aplastic anemia, thrombocytopenia, polyneuropathy, nephropathy, and polymyositis. Also worsening of neurological dysfunction can occur with initial stage of therapy. Alternate therapies include ammonium tetrathiomolybdate which may block copper absorption and triethylene tetramine dihydrochloride (trientine), which acts as chelator, and zinc acetate, which acts to prevent copper entry into the bloodstream. Liver transplantation can be utilized in patients with liver failure.

BOX 20-2

1. Decreased serum ceruloplasmin levels (less than 20 mg/dl)
2. Serum copper levels decreased to 100 µg/ml
3. Urine copper excretion is markedly elevated (most reliable parameter to establish diagnosis)
4. Impaired hepatic function
5. Elevated liver copper content

Myoclonus

Myoclonus refers to sudden brief shock-like muscular contractions (single or multiple), confined to individual muscle groups (face, tongue, extremity) or widespread in distribution. The movements are rapid and irregular in rate and amplitude. They cannot be controlled voluntarily. Brief rapid irregular muscle contractions of myoclonus are different from dystonic movements, which consist of more sustained muscular contractions. Rhythmic myoclonus (as seen in palatal myoclonus) can resemble intention tremor. In myoclonus there is repetitive character to movements in contrast to chorea in which movements are random and unpredictable in distribution. Myoclonus is due to abnormal neuronal excitability at cerebral cortex, brain stem, or spinal cord levels.

Myoclonus can be seen in normal persons (physiologic) as manifested by sleep jerks and anxiety- or exercise-induced movements and can be suppressed by alcohol. Hypnagogic myoclonus are single or bursts of jerks experienced by patients as they fall asleep or can occur

when patients are in light sleep stage. Other patients develop rapid and frequent myoclonic jerks during sleep; these are noted by bed partner and can prevent sleep. Myoclonus caused by abnormal cerebral neuronal excitability can be associated with seizures and EEG abnormalities. Myoclonic jerks can be triggered by stimulus-sensitive conditions (lights flashing, limb movement). Palatal myoclonus is rhythmic rapid movement of palate and pharynx, facial, neck, and diaphragmatic muscles. This condition is due to lesions interrupting central tegmental tract, inferior olivary nucleus, brachium conjunctivum, and dentate nucleus. Intention (action) myoclonus is myoclonus resulting from hypoxic-ischemic brain injury. In action myoclonus, jerks may be so frequent and of such high amplitude as to interfere with purposeful limb movements. There are usually associated gait ataxia, dysarthria, and intention tremor. Also immediately after cardiopulmonary arrest, transient myoclonus may occur as a result of cortical irritability, and these are usually self-limited.

Myoclonus can be one manifestation of generalized encephalopathy. When it occurs in young patients, complete evaluation for metabolic storage disease is indicated (see Chapter 13) as well as an EEG to exclude epileptic myoclonus or Creutzfeldt-Jakob disease. In adult patients structural CNS (cerebral cortex, brain stem, spinal cord) disease should be excluded and metabolic studies including investigation for toxic substances (bismuth, heavy metals, methyl bromide) should be performed. Viral encephalitis can cause myoclonus, and CSF examination should be performed. Treatment of myoclonus includes valproic acid (Depakote) or clonazepam. The prognosis depends on underlying cause.

Blepharospasm and Hemifacial Spasm

This results in constant blinking and closing of the eyes. It can occur so frequently to interfere with ability to read or drive. There can be ocular discomfort and photophobia caused by repeated blinking. Because of ocular symptoms, patients may be initially seen by ophthalmologist. Blepharospasm can be an isolated finding or can be associated with oral, jaw, neck spasms (Meige syndrome). It is believed that blepharospasm is due to hyperirritability of the facial nucleus in pons. An underlying structural lesion is almost never identified as the cause of blepharospasm. This should be contrasted with hemifacial spasm in which patient reports difficulty in opening eyes and has frontalis muscle spasm with elevated eyebrows. For patients with hemifacial spasm, MRI is warranted to exclude cerebellopontine or posterior fossa lesion. Treatment of blepharospasm and hemifacial spasm should be botulinum toxin injection.

Torsion Dystonias

These can be classified by age at onset of symptom (childhood, zero to 12 years; adolescent, 13 to 20 years; adult, older than 20 years), by distribution (focal, segmental generalized) or by etiology (primary familial, secondary dystonia plus other neurological disorders). The term torsion emphasizes the twisting nature of the dystonic state. In the primary torsion dystonia, the disorder begins in the leg and then generalizes. This disorder was previously called dystonia musculorum deformans and is most likely to spread to multiple body regions and be severe to interfere with motoric functioning. The gene responsible for familial cases is DYT 1, DYT 6 or DYT 7. The majority of adult cases are sporadic and are focal in type (e.g., neck dystonia).

In children, dystonia is characterized by slow inversion and plantar flexion of foot (equinovarus). It may later involve upper extremities (writer's cramp, athetoid writhing of hands). If head, neck, and axial muscles are involved, this can result in torticollis, retrocollis, or spinal deformity (e.g., kyphoscoliosis). Dystonic movements are initially intermittent and

nonpurposeful and interfere with voluntary motor activities. They are frequently painful. Postures subsequently become fixed. This can lead to development of contractures, muscular hypertrophy, skeletal deformities, osteoarthritic changes. There is progressive impairment of gait, speech, and extremity movements. The patient becomes disabled and bedridden because of skeletal and joint deformities.

The autosomal dominant type of primary torsion dystonia most commonly occurs in patients of Jewish origin, has onset between 4 and 15 years of age, initially involves lower extremities. It is associated with DYT 1 gene. The disorder rapidly progresses, and patient is soon reduced to a bedridden state with deforming contractures.

In the adult onset dystonia, there is focal onset, usually beginning in neck (spasmodic torticollis), face (blepharospasm), jaw (oromandibular dystonia), arm (writer's cramp), vocal cords (spastic dystonia), and remains localized. There is usually no family history. Onset is variable and can occur as late as age 40. Axial muscles (torticollis, retrocollis) are most frequently initially involved. The course is static or slowly progressive and the cranial-cervical type of adult onset dystonia remains localized. Clinical features include cervical dystonia, blepharospasm, oral-mandibular dystonia, spastic dysphonia, and writer's cramp. No drug has been proved beneficial to control dystonia and slow disease progression; however, high-dosage anticholinergics (baclofen, benzodiazepam, and antidopaminergic) medications have shown variable success. Certain dystonias are levodopa responsive, and this responds to Sinemet or anticholinergic medication. For focal dystonias, instillation of botulinum toxin is effective. Thalamotomy and pallidotomy have been effective in selected patients. No characteristic pathological substrate has been identified by autopsy examination of these patients.

Spasmodic Torticollis

Torticollis (wry neck) is characterized by sustained contraction of trapezius and sternocleidomastoid muscles. This results in lateral deviation of neck. Other patients have neck flexion (anterocollis), extension (retrocollis), and head tilt (laterocollis). Movements can be sustained and *not* always spasmodic. Dystonic movements become more frequent and severe with fatigue and emotional stress; they disappear with sleep and biofeedback. They can be suppressed by tactile and proprioceptive input, for example, torticollis may be suppressed as patient places the hand under the chin or touches the face. Dystonia can result from acute phenothiazine or dopaminergic toxicity. If drug induced, treatment with 50 mg of diphenhydramine (Benadryl) causes immediate and dramatic reversal. Multiple therapies (e.g., dopaminergic agents, anticholinergic medication, muscle relaxant medication, haloperidol, cervical rhizotomy, and biofeedback techniques) have been tried in chronic disorders but are of questionable value. The high dose of medication used to control dystonia usually cause unacceptable side effects. Recently local injection of botulinum toxin (Botox) into spasmodic contracted dystonic muscles has been used successfully. This is relatively safe procedure and almost no botulinum toxin enters systemic circulation. Rarely weakness may result from toxicity relating to impaired neuromuscular transmission. With repeated use, antibodies may develop, and this reduces effectiveness of Botox therapy.

Drug-Induced Dyskinesias

Several types of disorders result from antipsychotic and antiemetic medications which block dopamine D-2 receptors. The atypical neuroleptic drugs such as clozapine (Clozaril), olanzapine (Zyprexa), ziprasidone (Geodon), and quetiapine (Seroquel) block the D-4 receptor and do not

cause these dyskinesias. Four dyskinetic patterns have been described. These include acute dyskinesias, akathisia, parkinsonism, and tardive dyskinesias. They are more common with high-potency antipsychotics (e.g., fluphenazine [Prolixin], haloperidol [Haldol]). Acute dyskinesias include dystonic neck posturing, oral-facial-tongue spasms or grimacing, and oculogyric crisis (sustained upward eye deviation). These usually occur in children and young adults. They can appear within several hours after the initial dose. Resolution can be spontaneous, or patients respond to diphenhydramine (Benadryl) in a dose of 50 mg (intravenously or intramuscularly) or benzotropine (Cogentin) (one mg intravenously). Once acute reaction is controlled, antipsychotic medication can be restarted, preferably on a different antipsychotic medication and patient is concurrently treated with anticholinergic medication.

Akathisia (motor restlessness) is characterized by the patient being in constant motion. These usually begin with few weeks to months of initiating therapy. Patient feels unable to stay in one place and carries out motor activities to satisfy inner feeling of motor restlessness. Patterns include tapping of feet, leg shifting, body rocking or swaying, aimless pacing, and airplane-like swinging arm movements. It is important to differentiate akathisia caused by antipsychotic medication from behavior related to psychoses. Akathisia is sometimes associated with parkinsonian features (e.g., bradykinesia, rigidity). Akathisia does not usually remit spontaneously but can disappear after discontinuation of antipsychotic drug. Akathisia is due to dopamine receptor blockade. Treatment consists of lowering medication dose or switching to lower-potency neuroleptic drug. Medications that have been utilized include clonazepam, benzodiazepine, and beta-adrenergic antagonists.

Parkinsonism that is drug induced (e.g., antipsychotics, reserpine) most commonly affects elderly patients, but it may also be seen in young adults. Rigidity and hypokinesia are most common clinical abnormalities; resting tremor occurs in only 50% of cases and develops several weeks to months after initiation of antipsychotic medication. Drug-induced parkinsonism rarely causes significant functional disability. It is usually self-limited, and findings can disappear within several months even without treatment. Resolution occurs after antipsychotic medication is discontinued; however, switching the patient to another antipsychotic drug does not usually avoid recurrence of parkinsonism. It is therefore usually necessary to treat these patients with anticholinergic drugs or amantadine (Symmetrel) if symptoms are severe enough to interfere with motor function.

Tardive dyskinesia consists of stereotyped pattern of oral-facial-lingual movements. These include tongue darting, lip smacking, lip pursing, eye blinking, and rhythmic jaw opening and closing. Movements resemble chorea. They can become severe enough to interfere with speaking, swallowing, and breathing (as a result of diaphragmatic involvement). Also, tardive dystonia and tardive myoclonus can be manifestations of neuroleptic-induced movement disorders. Fine, rhythmical lip and oral movements (rabbit syndrome) can develop. It is most important to differentiate parkinsonian syndrome from tardive dyskinesia because latter condition requires change in neuroleptic drugs. Tardive dyskinesias are caused by high-potency antipsychotics. There is increased risk of this complication in certain patient populations (e.g., schizophrenics, women, and elderly patients and those with preexisting organic brain damage). There is some evidence that prophylactic treatment with anticholinergic drugs increases risk of tardive dyskinesia. Dyskinesias usually occur after years of treatment, although they may be precipitated by sudden drug withdrawal after long-term use.

If tardive dyskinesia is detected at early stage, immediate reduction and discontinuation of antipsychotic drug causes movements to disappear; however, dyskinesia is not usually

reversible if disorder has been present for prolonged time. It is believed that early detection with rapid reduction in drug dose can be the most important preventive measure. Dyskinesia can be initially detected or exacerbated when the antipsychotic drug is discontinued for drug holiday. Dyskinesia can be suppressed by reinstating drug at previous dose. If patient is kept off the drug, there is gradual decrease in dyskinesia over several months. If tardive dyskinesia persists, drug treatment is unrewarding in most cases. Treatment strategies include antidopaminergic agents (e.g., haloperidol, reserpine), cholinomimetic drugs (e.g., choline [deanol], lecithin, physostigmine, or gamma-aminobutyric acid blocking agents (e.g., benzodiazepines [diazepam, clonazepam])). Reserpine (1-5 mg/day) is believed the most effective treatment.

The link between increased dopamine blockage which reduces psychotic symptoms but leads to a state of denervation hypersensitivity of D-2 dopamine receptor. Dopaminergic hyperactivity predisposes patient to the development of tardive dyskinesias. By increasing dosage of antipsychotic drug, it is possible to abolish movements temporarily, but this strategy eventually worsens dyskinesias. The best treatment is judicious and limited use of antipsychotics at the lowest possible dose to control psychotic symptoms with appropriate drug-free intervals. It is a tragic situation in which tardive dyskinesia disables patient who has received antipsychotic inappropriately (e.g., anxiety states, neurosis).

Neuroleptic Malignant Syndrome (NMS)

This disorder is precipitated by dopamine blocking medication, for example, haloperidol. It can occur at any point of time during therapy. Findings include severe hyperthermia, muscular rigidity, autonomic instability (tachycardia, hypertension, diaphoresis), and elevation of creatine phosphokinase. Because of intense muscular rigidity, rhabdomyolysis can occur to cause renal dysfunction. Treatment includes immediate cessation of the neuroleptic drug, hydration of the patient, reduction of elevated temperature, and cardiopulmonary support. Bromocriptine, which is specific dopamine receptor agonist, and dantrolene, which is a muscle relaxant, can be used to reverse the condition.

Serotonin Syndrome

This occurs with initiation or increases in dosage of serotonergic medication. This can occur in patient taking selective serotonin reuptake inhibitors (SSRI) who also take triptans for migraine, parkinsonian medication, other antidepressant medication, or certain anti-epileptic medication. Symptoms include delirium, diaphoresis, fever, hyperreflexia, myoclonus, tremor, shivering, autonomic instability. Severe cases may be associated with rhabdomyolysis, disseminated coagulation, and renal failure. There are certain clinical similarities to NMS. Treatment includes discontinuation of all serotonergic medications, and control of systemic manifestations.

Stiff Man Syndrome

This consists of progressive muscular rigidity (stiffness) and painful muscle spasms, most prominent in the axial and proximal muscles. This resembles tetanus; jaw spasm (trismus) does not occur but facial and oropharyngeal muscles can be affected in this disorder. Movement and sensory stimulation may provoke stiffness and spasms. Spasms can lead to joint and bone injuries as well as muscle and tendon rupture. EMG shows continuous muscle discharges with normal potentials. Rigidity is reduced by spinal anesthesia or nerve block. There may be autoimmune pathogenesis and antibodies to glutamate decarboxylase are detected in blood and CSF. Treatment with diazepam, baclofen and tizanidine are effective.

SUMMARY

Dyskinesias are abnormal movements that are not under voluntary control. On the basis of observation of the patient with dyskinesias, clinical classification is usually possible. By specifically classifying the dyskinesia, potential causes and appropriate treatment are determined. Observation of the dyskinesia is crucial to establish correct diagnosis, and neuroimaging studies are not usually helpful in assessing dyskinesia patients. Hypokinetic movement disorders such as parkinsonism can be treated with dopaminergic medication, whereas hyperkinetic movement disorders such as chorea are treated with dopamine receptor blocking agents. The most common dyskinesia is tremor. The tremor that occurs with parkinsonism develops at rest and disappears with voluntary activity and is therefore not disabling. It is important to remember that shaking or trembling is now always due to parkinsonism. The most common and disabling dyskinesia is essential tremor in which the shaking movements interfere with activities of daily living, for example, holding a cup, using utensils, writing, shaving, and using a comb or toothbrush.

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Table 20.1
Drugs Utilized for Parkinson Disease

Category	Initial Dose-Frequency	Motor Adverse Effect
anticholinergics benztropine trihexyphenidyl	1 mg BID 2 mg BID	confusion; hallucinations; dry mouth; blurred vision; urinary hesitation
dopamine precursor levodopa		nausea; vomiting; hallucinations; motor fluctuations
dopamine enhancer levodopa plus peripheral decarboxylase inhibitor	25/100: 25/250; 10/100. Begin twice daily and increase dose and frequency. Avoid giving with meals	same as above
monoamine oxidase B inhibitor selegiline	5 mg BID	insomnia; confusion
catechol O-methyltransferase inhibitor entacapone	100 mg BID	accelerate dopamine effect; possible liver dysfunction
dopamine agonist ergot-type bromocriptine pergolide non-ergot ropinorile pramipexole	1.25 mg hs 0.05 mg hs 0.25 mg BID 0.125 mg BID	pedal edema; retroperitoneal fibrosis; vasoconstriction; enhanced dopamine effect enhanced dopamine effect; possible similar effect to dopamine effect
dopamine release enhancer amantadine	100 mg BID	skin-livedo reticularis; pedal edema