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447 Tremor, Chorea, and Other Movement Disorders

Parkinson’s disease Nonpharmacologic intervention Pharmacologic intervention Neuroprotection —? Rasagiline Functional disability No Yes PART 13 Neurologic Disorders Dopamine agonists MAO-B inhibitor Levodopa Combination therapy Levodopa/dopamine agonist/COMT Inhibitor/MAO-B Inhibitor Surgery/CDS FIGURE 446-7 Treatment options for the management of Parkinson’s disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: no drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: many experts favor starting with low doses of levodopa particularly in the elderly and those with more advanced disease. A monoamine oxidase type B (MAO-B) inhibitor may be preferred in mildly affected patients because of their good safety profile and the potential for a disease-modifying effect. Some prefer dopamine agonists for younger patients with functionally significant disability as they have a reduced risk of inducing motor complications. All patients eventually require levodopa, but it is generally recommended to employ polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent and minimize the risks of levodopa-induced motor complications. (4) Management of motor complications: motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the “on” time. When medical therapies cannot provide satisfactory control, surgical therapies such as deep brain stimulation (DBS) or continuous infusion of levodopa/carbidopa or apomorphine can be considered. (5) Nonpharmacologic approaches: interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-O-methyltransferase. (Reproduced with permission CW Olanow et al: Neurology 72:S1, 2009.) complications and avoid the need for

polypharmacy and surgical intervention. Treatment for the nonmotor features of PD should be instituted as deemed appropriate, and exercise therapy is recom mended for all patients. A decision tree that considers the various treatment options and decision points for the management of PD is provided in Fig. 446-7. ■ ■FURTHER READING Balestrino R, Schapira AHV: Parkinson disease. Eur J Neurol 27:27, 2020. Ben-Shlomo Y et al: The epidemiology of Parkinson's disease. Lancet 403:283, 2024. Berg D et al: MDS research criteria for prodromal Parkinson's disease. Mov Disord 12:1600, 2015. Blauwendraat C et al: The genetic architecture of Parkinson's disease. Lancet Neurol 19:170, 2020.

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Tremor, Chorea, and Other Movement Disorders C. Warren Olanow*, Christine Klein HYPERKINETIC MOVEMENT DISORDERS Hyperkinetic movement disorders are characterized by involuntary movements unaccompanied by weakness. The major clinical features are summarized in Table 447-1. The term is somewhat arbitrary and potentially misleading as hypokinetic disorders such as Parkinson's disease (PD) are often accompanied by tremor, while hyperkinetic disorders such as dystonia may be manifest as slow or restricted move ment because of severe muscle contractions. Nonetheless, the terms continue to be used by convention. The major hyperkinetic movement disorders and the diseases with which they are associated are consid ered in this section. TREMOR ■ ■CLINICAL FEATURES Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part with alternating contraction of agonist and antagonist muscles. It can be most prominent at rest (rest tremor), on assuming a posture (postural tremor), on actively reaching for a target (kinetic or intention tremor), or on carrying out a movement (action tremor). Tremor may also be characterized based on its distribution, frequency, amplitude, and related neurologic dysfunction. Tremor is classified along two axes: Axis 1 covers the clinical characteristics and histori cal features (age at onset, family history, temporal evolution), tremor characteristics (body distribution, activation condition), associated signs (systemic, neurologic), and laboratory tests (electrophysiology, imaging). Axis 2 relates to the etiology of the tremor and distinguishes genetic, secondary, or idiopathic origins. Essential tremor (ET) is characterized by a tremor that typically occurs while trying to sustain a posture and/or an action tremor that is noted when reaching toward a target. This contrasts with the resting tremor of PD (Chap. 446), which is characterized by a predominant resting tremor and is less pronounced with action. Cerebellar dys function is characterized by a kinetic tremor (brought out by trying to touch an object) and is usually associated with hypotonia and past pointing. Healthy individuals can have a physiologic tremor that typically manifests as a mild, high-frequency (10–12 Hz), postural, or *Deceased.

TABLE 447-1 Hyperkinetic Movement Disorders Tremor Rhythmic oscillation of a body part due to intermittent muscle contractions Dystonia Involuntary, patterned, sustained, or repeated muscle contractions often associated with twisting movements and abnormal posture Athetosis Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands (this represents a form of dystonia with increased mobility) Chorea Rapid, semi-purposeful, graceful, dance-like nonpatterned involuntary movements involving distal or proximal muscle groups. When the movements are of large amplitude and predominant proximal distribution, the term ballism is used. Myoclonus Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches Tic Brief, repeated, stereotyped muscle contractions that can often be suppressed for a short time. These can be simple and involve a single muscle group or complex and affect a range of motor activities. action tremor typically affecting the upper extremities. This tremor is usually of no clinical consequence and often is only appreciated with an accelerometer or under stress. An enhanced physiologic tremor (EPT) can be seen in up to 10% of the population and tends to occur in asso ciation with lifting a weight, anxiety, fatigue, a metabolic disturbance (e.g., hyperthyroidism, electrolyte abnormalities), drugs (e.g., valpro ate, lithium), or toxins (e.g., caffeine, smoking, alcohol). Treatment is initially directed at control of any underlying disorder, and if necessary, it can often be improved with a beta blocker. ■ ■ESSENTIAL TREMOR ET is the most common movement disorder, affecting ~1% of the population and 5% of those over 60 years (an estimated 5–10 million persons in the United States or Western Europe). It can present in childhood but dramatically increases in prevalence in those aged

> 70 years. ET is characterized by a high-frequency tremor (6–10 Hz) that predominantly affects the upper extremities. The tremor is most often manifest as a postural or action tremor and, in severe cases, can interfere with functions such as eating and drinking. It is typically bilat eral and symmetric but may begin on one side and remain asymmetric. Patients with severe ET can have an intention tremor with overshoot and slowness of movement, along with mild ataxia, suggesting the possibility of a cerebellar origin. Tremor involves the head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10%, and lower limbs in ~10%. Multiple body parts are involved in ~50% of cases. The tremor is characteristically improved by alcohol and worsened by stress. Usually, the neurologic examination is normal aside from tremor, but subtle impairment of coordination or tandem walking may be present, and disturbances of hearing, cognition, personality, mood, and olfaction have been described. The differential diagnosis includes dystonic tremor (see below) or PD. PD can usually be differentiated from ET because the former tends to be present primarily at rest and to be suppressed by a voluntary action. Further, PD is typically associated with bradykinesia with progressive slowing of sequential movements (sequence effect), rigidity, gait, postural instability, and other parkinso nian features. However, the examiner should be aware that PD patients may have a postural tremor and ET patients may develop a rest tremor, but these typically only begin after a latency of a few seconds (emergent tremor). In contrast to the micrographia of PD, ET patients have rela tively large handwriting with evidence of tremor in writing samples. The examiner must be careful to identify tremor

> when assessing tone in order to distinguish the interruption of movement associated with tremor from the cogwheel rigidity found in PD. ■ ■ETIOLOGY AND PATHOPHYSIOLOGY The etiology and pathophysiology of ET are not known. Approximately 50% of ET patients have a positive family history with an autosomal dominant pattern of inheritance. Linkage studies have detected pos sible loci in large ET families. Expansion of a GGC repeat in the

human-specific NOTCH2NLC gene has been found to be associated with ET, but no independently confirmed causative gene has been identified to date. It is likely that there are several as yet undiscovered genes underlying ET that have thus far escaped detection because of the heterogeneity of the syndrome and the high frequency of ET in the population, likely resulting in a large number of phenocopies (i.e., fam ily members with a similar clinical syndrome but not carrying the same causative mutation). The cerebellum and inferior olives have been implicated as possible sites of an altered “tremor pacemaker” based on the presence of cerebellar signs in ~10% of ET patients, as well as increased metabolic activity and blood flow in these regions in some patients. Some pathologic studies have described cerebellar pathology with a loss of Purkinje cells and axonal torpedoes, suggesting a neuro degenerative disease, but these findings remain controversial, and the precise pathologic correlate of ET remains to be defined. Interest has also focused on the possibility that ET is caused by degeneration of GABAergic cerebellar neurons with defects in neurotransmission. It is likely that multiple causes of ET will ultimately be identified.

CHAPTER 447 ■ ■TREATMENT Many cases are mild, do not cause any functional impairment, and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily living. This is more likely to occur as the patient ages and is often associated with a reduction in tremor frequency. Beta blockers and primidone are the standard drug therapies for ET and are useful in ~50% of cases. Propranolol (20–120 mg daily, given in divided doses) is usually effective at relatively low doses, but higher doses may be needed in some patients. The drug is contraindicated in patients with bradycardia or asthma. Hand tremor tends to be most improved, while head tremor is often refractory. Primidone can be helpful but should be started at low doses (12.5 mg) and gradually increased as necessary (125–250 mg three times daily) to avoid sedation, nausea, and dizzi ness. Benefits have also been reported with gabapentin and topiramate, but these drugs have not been widely employed. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with muscle weakness. Surgical therapies targeting the ventro-intermediate (VIM) nucleus of the thalamus can be very effec tive for severe and drug-resistant cases. More recently, focal ultrasound (a procedure that does not require surgery) has also been shown to be an effective therapy against tremor in some cases of ET. Tremor, Chorea, and Other Movement Disorders DYSTONIA ■ ■CLINICAL FEATURES Dystonia is a movement disorder characterized by sustained or inter mittent synchronous muscle contractions of agonist and antagonist muscles causing abnormal, often repetitive, painful movements and postures. Dystonic movements are typically patterned and twisting and may be associated with a “dystonic” tremor. This tremor can usu ally be distinguished from ET as the tremor is most pronounced when the body part is moved in the direction of the dystonia and relieved when the body part is moved in the direction opposite to the dysto nia. Dystonia can range from minor contractions affecting only an individual muscle group (focal) to

severe and disabling contractions with involvement of multiple muscle groups (i.e., multifocal, seg mental, or generalized). Nonmotor features such as pain, depression, anxiety, and impaired sleep can be associated with, or even precede onset of, the dystonia. The frequency of dystonia is estimated to be about 30 per 100,000 but is likely to be higher because many cases are not recognized or correctly diagnosed. Dystonia is often brought out by voluntary movements (action dystonia) and can extend to involve other muscle groups and body regions not required for the intended action (overflow contractions). Dystonia can be aggravated by stress and fatigue and attenuated by relaxation and sensory tricks such as touching the affected body part (geste antagoniste). Historically, dystonia has been described as primary or secondary. However, because of a confusing and not always congruent combina tion of phenotypic and etiologic features, the older terms are no longer

TABLE 447-2 Monogenic Forms of Isolated and Combined Dystonia DESIGNATION AND PHENOTYPIC SUBGROUP ADDITIONAL DISTINGUISHING FEATURES FORM OF DYSTONIA GENE TOR1A DYT-TOR1A Childhood or adolescent onset, generalized AD Isolateda KMT2B DYT-KMT2B Early onset, generalized, mild syndromic features AD THAP1 DYT-THAP1 Adolescent onset, cranial or generalized AD ANO3 DYT-ANO3 Adult onset, focal or segmental AD GNAL DYT-GNAL Mostly adult onset, focal or segmental AD VPS16 DYT-VPS16 Frequent cervical and laryngeal dystonia AD or AR EIF2AK2 DYT-EIF2AK2 Childhood or adolescent onset, focal to generalized AD or AR PRKRA DYT-PRKRA Generalized AR HPCA DYT-HPCA Childhood onset AR AOPEP DYT-AOPEP Frequent cervical and laryngeal dystonia AR Combinedb Dystonia plus parkinsonism GCH1 DYT-GCH1 Dopa-responsive AD TAF1 DYT-TAF1 Neurodegeneration XL PART 13 Neurologic Disorders ATP1A3 DYT-ATP1A3 Rapid onset AD Dystonia plus myoclonus SGCE DYT-SGCE Alcohol responsive AD KCTD17 DYT-KCTD17 Childhood onset AD aKMT2B pathogenic variants may present with mild syndromic features. bSelected examples. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked. recommended. A Movement Disorder Society Task Force recom mended classifying dystonia along the same axes as ET: clinical and etiologic. On clinical grounds, dystonia can be categorized by age of onset (infancy, childhood, adolescence, early and late adulthood), body distribution (focal, segmental, multifocal, and generalized), temporal pattern (static or progressive, action-specific [diurnal and paroxys mal]), and association with additional features. Clinical description along these lines enables formulating specific dystonia syndromes (e.g., early-onset generalized isolated dystonia). From an etiologic point of view, dystonia primarily reflects genetic abnormalities, although occasionally it may be secondary to other causes, such as trauma and stroke. Genetic features used for classification include mode of inheritance or identification of a specific pathogenic gene variant. More than 200 genes have been linked to different types of dystonia, primarily childhood-onset and generalized forms. These include forms in which dystonia is the only disease manifestation with the exception of tremor (“isolated dystonia”) and forms in which dystonia co-occurs with another movement disorder such as parkinsonism, myoclonus, or other neurologic and/or nonneurologic manifestations (“combined dystonia”) and may not even be the dominant clinical feature. This group represents the most heterogeneous class in terms of clinical expression. A list of confirmed monogenic mutations associated with isolated or combined dystonias is provided in Table 447-2. ■ ■ISOLATED DYSTONIAS Focal, Multifocal, and Segmental Dystonia Adult-onset, focal dystonia is by far the most frequent form of isolated dystonia. Women are affected about twice as often as men, with the exception of writer’s cramp, which occurs more frequently in men than in women. Focal dystonia typically presents in the fourth to sixth decade. The major clinical phenotypes are: (1) Cervical dystonia—dystonic contractions of neck muscles

causing the head to deviate to one side (laterocollis), twist (torticollis), move in a forward direction (anterocollis), or move in a backward direction (retrocollis). Muscle contractions can be painful and occasionally can be complicated by a secondary cervical radicu lopathy and even myelopathy. (2) Blepharospasm—dystonic contrac tion of the eyelids resulting in increased blinking and eye closure that can interfere with reading, watching television, working on a com puter, and driving. This can sometimes be so severe as to cause func tional blindness. (3) Oromandibular dystonia (OMD)—contractions of muscles of the lower face, lips, tongue, and jaw (opening or clos ing). Meige's syndrome is a combination of OMD and blepharospasm that predominantly affects women aged >60 years. (4) Spasmodic

MODE OF INHERITANCE dysphonia—dystonic contractions of the vocal cords during phonation, causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly, the abductors are affected, leading to speech with a breathy or whispering quality. (5) Limb dystonias—these can be present in either arms or legs and are often brought out by task-specific activities such as handwrit ing (writer's cramp), playing a musical instrument (musician's cramp), or putting in golf (the yips). The vast majority of patients with focal dystonia have cervical dystonia (~40%) or blepharospasm (~15%). Focal hand or leg dystonia (~10%), musician's dystonia (~3%), spas modic dysphonia (~2%), and OMD (~1%) are much less common. Focal dystonias can extend to involve other body regions (~30% of cases) and are frequently misdiagnosed as psychiatric or orthopedic in origin. Their cause is usually not known. They are rarely mono genic (~1%); autoimmunity and trauma have been suggested as other possible etiologies. Focal dystonias are often associated with a highfrequency tremor that can resemble ET. Dystonic tremor can usually be distinguished from ET because it tends to occur in the direction of the dystonic contraction and disappears when the dystonia is relieved (i.e., turning the head in the opposite direction of the dystonia). Generalized Dystonia Generalized dystonia is often hereditary and, unlike focal dystonia, typically has an age of onset in childhood or adolescence. There are currently at least 10 well-established genes that, when mutated, can cause mostly isolated, segmental or generalized dystonia: ANO3, AOPEP, EIF2AK2, GNAL, HPCA, KMT2B, PRKRA, THAP1, TOR1A, and VPS16. The AOPEP, HPCA, and PRKRA patho genic mutations are recessively inherited, while others (e.g., EIF2AK2 and VPS16) can be either dominantly or recessively inherited. Accord ing to the recommendations of the International Parkinson's Disease and Movement Disorder Society, monogenic forms of dystonia are classified according to the absence or presence of accompanying additional clinical features and preceded by a "DYT" prefix, e.g., DYT-TOR1A. Mutations in the TOR1A gene (torsin family 1 member A—formerly known as the DYT1 gene) are the most common cause of early-onset generalized dystonia. The first, and currently the only, clearly estab lished mutation is a 3-base pair deletion in the TOR1A gene. The mutation is frequently found among Ashkenazi Jewish patients due to a founder effect. Mutation carriers usually present with dystonia in an extremity in childhood that later progresses to affect other body parts, but the face and neck are typically spared. Rare carriers of two mutated alleles have been described and are characterized by a severe neurode velopmental syndrome and arthrogryposis.

Missense mutations in KMT2B (lysine methyltransferase 2B) are another relatively frequent cause of early-onset generalized dystonia, which may be accompanied by other syndromic features, including intellectual disability, microcephaly, psychiatric features, dysmorphia, or skin lesions. The majority of the mutations occur de novo. KMT2B mutations may account for up to 10% of early-

onset generalized dysto nia, but further validation is warranted, and placement into the group of isolated versus complex dystonias is currently under debate. Mutations in the THAP1 gene (THAP domain containing apoptosisassociated protein 1) have been linked to adolescent-onset dystonia with mixed phenotype. About 100 different mutations have been reported in THAP1. Mutations typically manifest with dysphonia or writer's cramp beginning in late childhood or adolescence. Over the course of the disease, dystonia can spread to other body parts with prominent craniocervical involvement. While DYT-Tor1A and DYTKMT2B typically respond well to deep brain stimulation (DBS) of the globus pallidus internus bilaterally, the DBS response is much more variable in carriers of pathogenic variants in the THAP1 gene. Mutations in the ANO3 gene (anoctamin 3) were first reported in patients with predominantly craniocervical dystonia with a broad range of ages of onset. While a large number of missense variants can be found in healthy individuals, a pathogenic role of ANO3 mutations has been confirmed by the description of additional families with dys tonia and myoclonic jerks. Mutations in the GNAL gene (guanine nucleotide-binding protein subunit alpha L) are a rare cause of cervical or cranial dystonia, with a few patients developing generalized dystonia. The mean age of onset is in the thirties. Pathogenic variants in the VPS16 gene can be inherited in a recessive or dominant fashion, with the latter mode of inheritance being more common. Currently, >30 carriers of ~20 different, often truncating, heterozygous pathogenic variants have been described. The median age of onset is 14 years. Dystonia tends to generalize and is typically isolated, although more complex phenotypes have also been described. Pathogenic missense variants in EIF2AK2, coding for the eukaryotic translation initiation factor 2-alpha kinase 2, cause dystonia with a median age at onset of 6 years and onset often in the limbs followed by generalization. There is a recurrent missense variant (p.Gly130Arg) in most patients. The EIF2AK2 protein is one of the kinases responsible for eIF2a phosphorylation and is thus linked to the same pathway as PRKRA. The vast majority of PRKRA mutation carriers develop a generalized dystonia, frequently with laryngeal involvement. Likewise, all patients described to carry HPCA mutations are characterized by generalized dystonia with childhood onset. The median age at onset of carriers of recessively inherited, bial lelic, and typically truncating pathogenic variants in the AOPEP gene is 20 years, with frequent onset in the hands. Most patients progress to isolated, generalized dystonia. ■ ■COMBINED DYSTONIAS A number of other well-established genes have been described that are associated with combined forms of dystonia in which dystonia occurs in conjunction with a different movement disorder (e.g., parkinsonism or myoclonus) or with other neurologic and/or nonneurologic features. Dopa-responsive dystonia (DRD; also known as Segawa syndrome) is caused by mutations in the GCH1 gene (GTP cyclohydrolase-1) that encodes for the rate-limiting enzyme in the biosynthesis of dopamine via the biopterin pathway. It manifests as a childhood-onset form of dystonia with diurnal fluctuations, and it is important to recognize as the condition dramatically responds to low doses of levodopa. Parkinsonism can be a major or even the only finding, and there may be a presynaptic dopaminergic deficit as evidenced by single-photon emission computed tomography. Younger patients are frequently misdiagnosed as having cerebral palsy, mistaking dystonia for spastic ity, and it is important that young-onset forms of dystonia should be tested with levodopa to exclude the possibility of DRD. To date, >100 different mutations have been reported with a penetrance of ~50% and incidence considerably higher in women compared to men. Recessively

inherited (biallelic) mutations in GCH1 result in a much more severe clinical phenotype with developmental delay and infantile onset. Due to the enzymatic defect in the levodopa biosynthesis, there is a life long and dramatic response to levodopa therapy. Importantly, since dopamine

terminals do not degenerate and the dopamine neuronal network is anatomically preserved, fluctuations in dopamine levels can be avoided, and accordingly, these patients do not develop dyskinesia with chronic levodopa treatment.

X-linked dystonia-parkinsonism (Lubag) presents with a combined form of dystonia and parkinsonism that is found exclusively in patients of Filipino origin due to a founder effect that seems to be fully pen etrant. The typical presentation is a focal (cranial) dystonia that rapidly generalizes and, after 5–10 years, is gradually replaced by a form of L-dopa-unresponsive parkinsonism. A retrotransposon insertion in the TAF1 (TATA-box binding protein associated factor 1) gene is the cause of the disease. Sixty-five percent of the age-at-onset variability is explained by the variable length of a hexameric repeat expansion within the retrotransposon and genotypes at three single-nucleotide polymorphisms in the MSH3 and PMS1 genes acting as age-at-onset modifiers. CHAPTER 447 Mutations in the ATP1A3 (ATPase Na+/K+ transporting subunit alpha 3) gene present with a characteristic, sudden-onset dystonia, usually in adolescence or young adulthood, often triggered by high fever, physi cal exertion, or emotional stress. Dystonic symptoms frequently show a rostrocaudal gradient with a strong involvement of the bulbar region, often accompanied by parkinsonian features such as bradykinesia. In addition, mutations in ATP1A3 have been linked to a variety of clini cal syndromes (pleiotropy), including epileptic or hemiplegic attacks, ataxia, cognitive decline, and other neurologic disorders, often with a more severe course and an earlier age at onset. Tremor, Chorea, and Other Movement Disorders Myoclonic-dystonia is characterized by action-induced, alcoholresponsive myoclonic jerks predominantly involving the upper body half. Onset is usually in childhood or adolescence. Many individuals also develop psychiatric features such as depression, anxiety-related disorders, and alcohol dependence. The disorder is primarily related to mutations in the SGCE gene (sarcoglycan epsilon), which codes for the ε member of the sarcoglycan family. About 80 different mutations have been reported in SGCE, including deletions of the entire gene. The latter type of mutation often also involves loss of adjacent genes, leading to additional clinical features such as joint problems. SGCE mutations are incompletely penetrant and only manifest when inher ited from the father due to the epigenetic effect of maternal imprinting of SGCE. KCTD17 mutations are another recently identified cause of myoclonus-dystonia. A number of additional monogenic causes have been suggested for isolated and combined forms of dystonia but still await independent confirmation. Table 447-2 provides a list of the confirmed monogenic forms of isolated and combined dystonias. Diagnostic Considerations In the largest group of combined dystonias, dystonia is a part of a more complex syndrome that is char acterized by multiple different clinical manifestations of the disease. Most frequently, they are hereditary, such as Wilson’s disease (WD), Lesch-Nyhan syndrome, corticobasal ganglionic disorders, and a variety of other neurologic, neurometabolic, neurodevelopmental, and mitochondrial disorders. Dystonia may also develop as a consequence of drugs or toxins. Drug-induced dystonia may be acute or chronic and is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients. Dystonia can also be observed following discrete lesions in the striatum (e.g., caudate/putamen) and occasionally in the globus pallidus, thalamus, cortex, or brainstem due to infarction, hemorrhage anoxia, trauma, tumor, infection, or toxins such as manganese or carbon monoxide. In these cases, dystonia often assumes a segmental distribution but may be generalized when lesions are bilateral or widespread. More rarely, dystonia can develop follow ing peripheral nerve injury and be associated with features of complex regional pain syndrome (Chap. 19). A psychogenic origin is respon sible for some cases of dystonia; these typically present with fixed, immobile dystonic

postures (see below).

■ ■PATHOPHYSIOLOGY OF DYSTONIA Even in cases with a known dystonia gene mutation, the pathophysi ologic basis of dystonia is not completely known. Physiologically, dys tonia is characterized by co-contracting synchronous bursts of agonist and antagonist muscle groups with recruitment of muscle groups that are not required for a given movement (overflow). Dystonia is char acterized by derangement of the basic physiologic principle of action selection, leading to abnormal recruitment of inappropriate muscles for a given action with inadequate inhibition of this undesired motor activity. Loss of surround inhibition is observed at multiple levels of the motor system (e.g., cortex, brainstem, spinal cord), accompanied by increased cortical excitability and reorganization. Attention has focused on the basal ganglia as the site of origin of most types of dystonia, as there are alterations in blood flow and metabolism in these structures. Further, lesions of the basal ganglia (particularly the putamen) can induce dystonia, and surgical ablation or DBS of specific regions of the globus pallidus may ameliorate dystonia. The dopa mine system has been specifically implicated because dopaminergic therapies can both induce and treat some forms of dystonia in different circumstances. However, no specific pathology has been consistently identified that underlies dystonia.

PART 13 Neurologic Disorders TREATMENT Dystonia Treatment of acute dystonia should include the immediate with drawal of any precipitating agent. A variety of drug therapies may be beneficial including diphenhydramine, benztropine, benzodiaz epines, or dopamine agonists. Treatment of chronic dystonia is for the most part symptomatic except in rare cases where correction of a primary underlying con dition is possible. WD should be ruled out, particularly in young patients with dystonia. Levodopa should be tried in all cases of childhood-onset dystonia to test for DRD. High-dose anticholin ergics (e.g., trihexyphenidyl 20–120 mg/d) may be beneficial in children, but adults can rarely tolerate high doses because of side effects related to cognitive impairment and hallucinations. Oral baclofen (20–120 mg) may also be helpful, but benefits, if present at all, are usually modest, and side effects of sedation, weakness, and memory loss can be problematic. Intrathecal infusion of baclofen is more likely to be useful, particularly for leg and trunk dystonia, but benefits are frequently not sustained, and complications can be serious and include infection, seizures, and coma. Tetrabenazine is another consideration; the usual starting dose is 12.5 mg/d and the average treating dose is 25–75 mg/d, but its use may be limited by sedation and the development of parkinsonism. Parkinsonian side effects can be minimized with deuterated tetrabenazine (discussed below). Neuroleptics can both improve and induce dystonia, but they are typically not recommended because of their potential to induce parkinsonism and other movement disorders, including tar dive dystonia. Clonazepam and diazepam are sometimes effective. Botulinum toxin is the preferred treatment for patients with focal and segmental dystonia, particularly where involvement is limited to small muscle groups such as in blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction, leading to reduced dystonic muscle contractions. However, treatment with botulinum toxin can be complicated by excessive weakness that can be trouble some, particularly if injections involve the neck and swallowing muscles. No systemic side effects are encountered with the doses typically used, but benefits are transient, and repeat injections are typically required at 2- to 4-month intervals. Some patients fail to respond after having experienced an initial benefit. This has been attributed to the development of neutralizing antibodies, but improper muscle selection, injection technique, and inadequate dose should be

excluded. A new long-acting formulation of botu linum toxin (daxibotulinumtoxinA-l) that provides benefits for up to 6 months has recently been approved in the United States for the treatment of cervical dystonia.

Surgical therapy is a consideration for patients with severe gener alized dystonia who are not responsive to other treatments. Periph eral procedures such as rhizotomy and myotomy were used in the past to treat cervical dystonia but are now rarely employed. DBS of the pallidum can provide dramatic benefits for some patients with various forms of hereditary and nonhereditary generalized dysto nia. This represents a major therapeutic advance because previously there was no consistently effective therapy, especially for patients with generalized dystonia and severe disability. Benefits tend to be obtained with a lower frequency of stimulation than used in PD or ET and often occur only after a relatively long latency (weeks to months). Better results are typically obtained in younger patients with shorter disease duration and in those with certain monogenic forms, such as DYT-Tor1A. DBS may also be valuable for patients with focal and secondary dystonias, although results are less consis tent. Neurophysiologic studies suggest that DBS acts by suppressing theta oscillations in the basal ganglia network that correlate with the dystonia. Adverse effects of DBS in dystonia patients include pares thesia, dysarthria, gait disturbance, and mood change. Dyskinesia can occur with stimulation of the subthalamic nucleus (STN), while bradykinesia and impaired coordination have been reported with stimulation of the globus pallidus pars interna (GPi). Focal ultra sound is being assessed as a possible alternative to surgical therapy. Supportive treatments such as physical therapy and education should be a part of the treatment regimen for all types of dystonia. Physicians should be aware of dystonic storm, a rare but poten tially fatal condition that can occur in response to a stress situation such as a surgical procedure or a systemic infection in patients with preexisting dystonia. It consists of the acute onset of generalized and persistent dystonic contractions that can involve the vocal cords or laryngeal muscles leading to airway obstruction. Patients may experience rhabdomyolysis with renal failure and should be managed in an intensive care unit with airway protection if required. Treatment can be instituted with one or a combination of anticholinergics, diphenhydramine, baclofen, benzodiazepines, and dopaminergic agents. In severe cases, anesthesia with muscle paralysis may be required. CHOREAS ■ ■HUNTINGTON’S DISEASE Huntington’s disease (HD) is a progressive, fatal, highly penetrant autosomal dominant disorder characterized by motor, behavioral, ocu lomotor, and cognitive dysfunction. The disease is named for George Huntington, a family physician who described cases on Long Island, New York, in the nineteenth century. Onset is typically between the ages of 25 and 45 years (range, 3–70 years) with a prevalence of 2–8 cases per 100,000 and an average age at death of 60 years. It is prevalent in Europe, North America, South America, and Australia but is rare in African blacks and Asians. HD is characterized by rapid, nonpat terned, semi-purposeful, involuntary choreiform movements, and for this reason was formerly referred to as Huntington’s chorea. However, dysarthria, gait disturbance, parkinsonism, oculomotor abnormalities, behavioral disturbance, and cognitive impairment with dementia are also common clinical features. Thus, the condition is currently referred to as Huntington’s disease. In the early stages, chorea tends to be focal or segmental but progresses over time to involve multiple body regions. With advancing disease, there tends to be a reduction in chorea and the emergence of dystonia, rigidity, bradykinesia, and myoclonus. Functional decline is often predicted by progressive weight loss despite adequate calorie intake. In younger patients (~10% of cases), HD can present as an akinetic-rigid parkinsonian syndrome known as the West phal variant. Eye movement abnormalities may be an early manifesta tion of HD. These include slowed and reduced

amplitude saccades with intrusions in smooth pursuit movements and impaired convergence. HD patients eventually develop behavioral and cognitive disturbances, and the majority progress to dementia. Depression with suicidal ten dencies, aggressive behavior, and psychosis can be prominent features. HD patients may also develop non-insulin-dependent diabetes mellitus

A B FIGURE 447-1 Huntington’s disease. A. Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging shows enlargement of the lateral ventricles reflecting typical atrophy (arrows). B. Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (arrows). and neuroendocrine abnormalities (e.g., hypothalamic dysfunction). A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history, but genetic testing provides the ultimate confirmation of the diagnosis. The disease predominantly affects the striatum but progresses to involve the cerebral cortex and other brain regions. Progressive atrophy of the head of the caudate nucleus, which forms the lateral margin of the lateral ventricles, can be readily visualized on magnetic resonance imaging (MRI) (Fig. 447-1), but the putamen can be equally or even more severely affected. More diffuse cortical atrophy can be seen in the middle and late stages of the disease. Supportive studies include reduced metabolic activity in the caudate nucleus and putamen and reduced brain metabolites on magnetic resonance spectroscopy. Genetic testing can be used to confirm the diagnosis and to detect atrisk individuals in the family, but it must be performed in conjunction with trained counselors because advising patients of positive results can worsen depression and even generate suicidal reactions. Indeed, genetic counseling is a requirement in some regions. The neuropa thology of HD consists of prominent neuronal loss and gliosis in the caudate nucleus and putamen; similar changes can also be widespread in the cerebral cortex. Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in the nuclei of some affected neurons. In anticipation of developing neuroprotective therapies, an inten sive effort has been made to define the earliest stage of HD. Subtle motor impairment, cognitive alterations, and imaging changes can be detected in at-risk individuals who later develop the manifest form of the disease. Defining the rate of progression of these features is paramount for future studies of putative disease-modifying therapies designed to slow the rate of disease progression and the development of cumulative disability. ■ ■ETIOLOGY HD is caused by a mutation in which there is an increase in the num ber of polyglutamine (CAG) repeats (>40) in the coding sequence of the Huntingtin gene located on the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest. Inter mediate forms of the disease with 36–39 repeats are described in some patients, typically with less severe clinical involvement and reduced penetrance (i.e., not every mutation carrier develops the disease). These clinic-genetic observations have recently been incorporated into a new research classification of HD. Carriers of a fully penetrant (>40 repeats) allele are defined as having stage 0 HD, irrespective of their affected status. These developments are meant to facilitate the inclu sion of at-risk individuals or those in the earliest disease stages into clinical trials.

 Expansion of repeat length tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. There is also evidence of postnatal somatic gene expansion that occurs over time as well as genetic modifiers of disease progression, for exam ple, in the FAN1 and MSH3 genes, the latter overlapping with X-linked dystonia-parkinsonism. New-onset gene expansion in patients with no family history is rare. The Huntingtin gene encodes the highly conserved cytoplasmic pro tein huntingtin (HTT), which is

widely distributed in neurons through out the central nervous system (CNS). Mutated HTT RNA is toxic and disrupts transcription, impairs immune and mitochondrial function, and is aberrantly modified posttranslationally. Genome-wide asso ciation studies have nominated DNA repair pathways as modifiers of somatic instability and disease course in HD. Fragments of the mutant HTT can also be toxic, possibly by translocating into the nucleus and interfering with transcriptional regulation of proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins. There is also interest in the possibility that the accumula tion and aggregation of toxic proteins in HD, like Alzheimer's disease (Chap. 442) and PD (Chap. 446), may be critical to the disease process and reflect a prion-like disorder (Chap. 449; see also Chap. 435). Models of HD with striatal pathology can be induced in multiple trans genic animals that express the mutant gene and by excitotoxic agents such as kainic acid and 3-nitropropionic acid, which promote calcium entry into the cell and cytotoxicity. These relevant animal models can be helpful in assessing potential therapeutic agents. Interestingly, when correcting the neurotransmitter deficit present in HD mice in the very first week of life, disease development can be prevented. TREATMENT Huntington's Disease Although the gene for HD was identified >30 years ago, there is still no disease-modifying therapy for this disorder, and clinically mean ingful symptomatic treatment is limited. Current treatment involves a multidisciplinary approach, with medical, neuropsychiatric, and social approaches, as well as genetic counseling for patients and their families. Dopamine-blocking agents such as tetrabenazine and val benazine have been approved to treat the choreiform movements but can be associated with secondary parkinsonism as an adverse event. Deuterated tetrabenazine (Austedo) and a long-acting version of deuterated tetrabenazine have also been approved as treatments for chorea in HD. Deuteration interferes with the metabolism of

tetrabenazine and avoids the high maximum concentration (Cmax), which is thought to contribute to adverse effects. In clinical trials, deuterated tetrabenazine has been shown to have fewer dose-related side effects and less parkinsonism than tetrabenazine and, therefore, can be administered in higher doses with potentially superior clini cal benefits. Neuroleptics are generally not recommended because of their potential to induce other troubling movement disorders and because HD chorea tends to be self-limited and is usually not disabling. These drugs may be used, however, in patients with severe and disabling chorea. There are currently no therapies approved for treating the more disabling motor features of HD, but large-scale platform studies are ongoing, which are assessing a variety of differ ent therapeutic approaches using a common placebo group. Depres sion and anxiety can be major problems, and patients should be treated with appropriate antidepressant and antianxiety drugs and monitored for mania and suicidal ideations. Psychosis can be treated with atypical antipsychotics such as clozapine (50–600 mg/d), que tiapine (50–600 mg/d), and risperidone (2–8 mg/d).

PART 13 Neurologic Disorders A neuroprotective therapy that slows or stops disease progres sion is the major unmet medical need. Some strategies are designed to reduce the formation or accumulation of mutant HTT. These largely focus on inhibiting mRNA synthesis either by blocking transcription (zinc finger motif protein), preventing posttranscrip tional processes, promoting early mRNA degradation (antisense oligonucleotides [ASO]), or inhibiting translation with short inter fering RNA. The most advanced of these experimental therapeu tic approaches investigated intrathecal administration of an ASO in patients with early HD in a randomized, placebo-controlled, double-blind clinical trial. While a dose-dependent reduction in concentrations of mutant HTT was

observed and there were no side effects, the study was terminated early because no clinical benefit was detected. Drugs that enhance mitochondrial func tion and increase the clearance of defective mitochondria are also being tested as possible disease-modifying therapies. Other inves tigative approaches include immunotherapy, dietary supplements (resveratrol), lipid-lowering medication (fenofibrate), anaplerotic therapy (triheptanoin), and DBS of the GPi. A promising therapy is the sigma 1 receptor agonist pridopidine. Various clinical trials have suggested that the drug may provide benefit with respect to total motor function and total functional capacity, particularly in patients with relatively mild disease. Double-blind studies are cur rently underway. Preliminary clinical trials testing cell-based thera pies (stem cells and fetal striatal cells) have been initiated, aimed at replacing damaged striatal neurons, but efficacy and safety of these procedures have not yet been determined. Experimentally, there is great interest in the potential of using CRISPR (gene editing) techniques to target and destroy or prevent the formation of mutant Huntingtin RNA and to reduce accumulation of the abnormal pro tein. Numerous other molecular and gene-based approaches are being evaluated to interfere with the formation and promote the clearance of the toxic protein, and many clinical studies are antici pated to begin within the next few years. HUNTINGTON’S DISEASE–LIKE DISORDERS A group of rare inherited conditions that can mimic HD, designated HD-like (HDL) disorders, have also been identified. HDL-1, -2, and -4 are autosomal dominant conditions that typically present in adult hood. HDL-3 is recessively inherited, presents in early childhood, and differs markedly from HD and the other HDLs. HDL-1 is due to expansion of an octapeptide repeat in PRNP, the gene encoding the prion protein (Chap. 449). Thus, HDL-1 is properly considered a prion disease. Patients exhibit onset of personality change in the third or fourth decade, followed by chorea, rigidity, myoclonus, ataxia, and epilepsy. HDL-2 manifests in the third or fourth decade with a variety of movement disorders, including chorea, dystonia, or parkinsonism, and dementia. Most patients are of African descent. Acanthocytosis can sometimes be seen in these patients, and this condition must be distinguished from neuroacanthocytosis (below). HDL-2 is caused by

an abnormally expanded CTG/CAG trinucleotide repeat expansion in the junctophilin-3 (JPH3) gene. The pathology of HDL-2 consists of intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats. HDL-4, the most common condition in this group, is caused by expansion of trinucleotide repeats in TBP, the gene that encodes the TATA box-binding protein involved in regulat ing transcription; this condition is identical to spinocerebellar ataxia (SCA) 17 (Chap. 450), and most patients present with ataxia rather than chorea. Like in HD, a certain range of repeat expansions in the TBP gene is associated with reduced penetrance, whereby penetrance was recently identified to be full when a variant in the Stub1 gene is present in conjunction with the repeat expansion. Mutations of the C9Orf72 gene associated with frontotemporal dementia and amyo trophic lateral sclerosis (Chaps. 443 and 448) have also been reported in some individuals with an HDL phenotype. ■ ■OTHER CHOREAS Chorea can be seen in a number of other disorders related to genetic mutations or other disease states. Among the hereditary forms of childhood-onset chorea, mutations in the NKX2-1 gene cause a benign hereditary chorea. Mutations in the ADCY5 (adenylate cyclase 5) gene are an increasingly recognized and relatively common cause of childhood-onset chorea, often in combina tion with dystonia and developmental delay. Characteristic perioral movements are a hallmark of the disorder. Notably, patients respond well to caffeine. Chorea-acanthocytosis (neuroacanthocytosis) is a progressive and typically fatal autosomal recessive disorder that is characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). The chorea can be severe and associated with

selfmutilating behavior, dystonia, tics, seizures, and a polyneuropathy. Mutations in the VPS13A gene encoding chorein have been described. A phenotypically similar X-linked form of the disorder has been described in older individuals who have reactivity with Kell blood group antigens (McLeod syndrome). A benign hereditary chorea of childhood (BHC1) due to mutations in the gene for thyroid transcrip tion factor 1 and a late-onset benign senile chorea (BHC2) have also been reported. It is important to do genetic testing in these patients to ensure that they do not have HD. Chorea may also occur in association with a variety of infections and degenerative disorders as well as vascular diseases and hypo- and hyperglycemia. Sydenham's chorea (originally called St. Vitus's dance) is more common in females and is typically seen in childhood (5–15 years). It often develops in association with prior exposure to group A streptococcal infection (Chap. 153) and is thought to be autoimmune in nature. It is characterized by the acute onset of choreiform movements and behavioral disturbances. With the reduc tion in the incidence of rheumatic fever, the incidence of Sydenham's chorea has fallen, but it can still be seen in developing countries. The chorea generally responds to dopamine-blocking agents, valproic acid, and carbamazepine, and is usually self-limited. Treatment is gener ally restricted to those with severe chorea. Chorea may recur in later life, particularly in association with pregnancy (chorea gravidarum) or treatment with sex hormones. Several reports have documented cases of chorea associated with N-methyl-d-aspartate (NMDA) recep tor antibody–positive encephalitis, following herpes simplex virus encephalitis, and in paraneoplastic syndromes associated with antiCRMP-5 or anti-Hu antibodies (Chap. 99). Systemic lupus erythe matosus (Chap. 368) is the most common systemic disorder that is associated with chorea. The chorea may last for only a few days but can be long-lasting and persist for years. Chorea can also be seen with hyperthyroidism, autoimmune disorders including Sjögren's syn drome, infectious disorders including HIV, metabolic alterations, and polycythemia rubra vera. Chorea has been described following openheart surgery in the pediatric population. It may also occur in associa tion with many medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, and lithium). In particular, chorea is commonly seen as a side effect of chronic levodopa treatment in patients with PD (Chap. 446).

■ ■BALLISM/HEMIBALLISMUS Ballism is a violent form of choreiform movement composed of wild, flinging, large-amplitude movements most frequently affecting proxi mal limb muscles on one side of the body (hemiballism). The move ments may only affect one limb (monoballism) or, more exceptionally, both upper or lower limbs (paraballism). The movements may be so severe as to cause exhaustion, dehydration, local injury, and, in extreme cases, death. Fortunately, dopamine-blocking drugs can be very help ful, and importantly, hemiballismus is usually self-limiting and tends to resolve spontaneously after weeks or months. The most common cause is a partial lesion (infarct or hemorrhage) in the STN, but in 30–40% of cases, the lesion is found in the putamen, thalamus, or parietal cortex. In extreme cases, pallidotomy or DBS of the GPi can be effective and abolish the involuntary movements. Interestingly, surgically induced lesions and DBS of the STN in PD patients are usually not associated with hemiballismus. TICS A tic is a brief, rapid, recurrent, stereotyped and seemingly purpose less motor contraction. Motor tics can be simple, with movement only affecting an individual muscle group (e.g., blinking, twitching of the nose, jerking of the neck), or complex, with coordinated involvement of multiple muscle groups (e.g., jumping, sniffing, head banging, and echopraxia [mimicking movements]). Phonic (or vocal) tics can also be simple (e.g., grunting) or complex (e.g., echolalia [repeating other people's words], palilalia [repeating one's own words], and coprolalia [expression of obscene words]). Patients may also experience sensory tics, composed of unpleasant focal sensations in the face, head, or neck. These

can be mild and of little clinical consequence or severe and dis abling. Tics may present in adulthood and can be seen in association with a variety of disorders, including PD, HD, trauma, dystonia, drugs (e.g., levodopa, neuroleptics), and toxins. TOURETTE'S SYNDROME Tourette's syndrome (TS) is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette. It predominantly affects males, and the prevalence is estimated to be 0.03–1.6%, but it is likely that many mild cases do not come to medical attention. TS is characterized by multiple motor tics, often accompanied by vocaliza tions (phonic tics). Patients characteristically can voluntarily suppress tics for short periods of time but then experience an irresistible urge to express them. Tics vary in intensity and may be absent for days or weeks only to recur, occasionally in a different pattern. Tics tend to present between ages 2 and 15 years (mean 7 years) and often lessen or even disappear in adulthood, particularly in males. Associated behavioral disturbances include anxiety, depression, attention-deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder. Patients may experience personality disorders, self-destructive behav iors, difficulties in school, and impaired interpersonal relationships. Etiology and Pathophysiology TS has a high heritability and is thus thought to be a genetic disorder, but no specific monogenic cause has yet been identified. Current evidence supports a complex inheritance pattern with an important contribution of de novo, likely gene-disrupting variants. Genome-wide linkage studies have suggested Slit, Trk-like 1, and histidine decarboxylase (HDC) genes as conferring genetic risk for TS. The risk of a family with one affected child having a second one with TS is ~25%. The pathophysiology of TS is not known, but alterations in dopamine neurotransmission, opioids, and secondmessenger systems have been proposed. TREATMENT Tics and Tourette's Syndrome There is no cure for tics or TS. Patients with mild disease often only require education and counseling (for themselves and family mem bers). In a high proportion of patients, the severity of tics wanes in adult life, becoming less of a medical problem, thus arguing for conservative management if possible during the first decades of life.

Drug treatment to help control tics is indicated when the tics are disabling and interfere with quality of life and social interactions. Therapy is individualized, and few treatment regimens have been properly evaluated in double-blind trials. Some physicians use the α-agonist clonidine, starting at low doses and gradually increas ing the dose and frequency until satisfactory control is achieved. Guanfacine (0.5–2 mg/d) is an α-agonist that is preferred by some because it only requires once-daily dosing. Other physicians prefer to use neuroleptics, but treatment can be complicated by tardive dyskinesia and weight gain. Atypical neuroleptics are usually used initially (risperidone, olanzapine, ziprasidone) because they are thought to be associated with a reduced risk of tardive dyskinesia. If they are not effective, low doses of classical neuroleptics such as hal operidol, fluphenazine, pimozide, or tiapride can be tried because the risk of tardive dyskinesia in young people is relatively low. Tet rabenazine and deuterated tetrabenazine may be recommended but are associated with depression. The dopamine D1 antagonist ecopi pam was reported to provide benefits without serious side effects in a controlled trial of short duration in TS. Antiepileptic drugs such as topiramate may provide benefit for some patients. Botulinum toxin injections can be effective in controlling focal tics that involve small muscle groups. There is also interest in the potential value of a wrist device that delivers electrical pulses and has been reported to reduce the frequency and severity of tics in an open-label study. The potential value of closed-loop DBS targeting the anterior portion of the internal capsule, the GPi, or the thalamus is currently being explored for severely affected patients. A large-scale public database and registry for DBS in TS has been established. Behavioral fea tures, and particularly anxiety and compulsions, can be a

disabling feature of TS and should be treated as appropriate. Behavioral and speech therapies are also occasionally employed but have not been formally tested. ADHD medications such as methylphenidate are sometimes used to increase attention and concentration but may also exacerbate tics.

CHAPTER 447 Tremor, Chorea, and Other Movement Disorders MYOCLONUS Myoclonus is a brief, rapid (<100 ms), shock-like, jerky movement consisting of single or repetitive muscle discharges that can occur with or without a pattern and with a variable frequency. Myoclonic jerks can be focal, multifocal, segmental, or generalized and can occur sponta neously, in association with voluntary movement (action myoclonus), or in response to an external stimulus (reflex myoclonus). Myoclonic jerks can be severe and interfere with normal movement or benign and of no clinical consequence, as is commonly observed in normal people who can experience myoclonic jerks when waking up or falling asleep (hypnagogic jerks). Negative myoclonus consists of a brief loss of muscle activity (e.g., asterixis in hepatic failure). Palatal myoclonus (or palatal tremor) involves contractions of the soft palate and may be associated with an audible click that can be disturbing to the patient and family members. This is usually idiopathic and benign but can be related to a lesion in the cerebellum or brainstem. Myoclonus may also occur consequent to injury to a peripheral or cranial nerve (e.g., hemifacial spasm). Myoclonic jerks differ from tics in that they are typically not repetitive, are not suppressible, and can severely interfere with normal voluntary movement. They can be associated with abnormal neuronal discharges in cortical, subcortical, brainstem, or spinal cord regions, particularly in cases related to hypoxemia (especially following cardiac arrest), encephalopathy, and neurodegeneration. Reversible myoclonus can be seen with metabolic disturbances (renal failure, electrolyte imbalance, hypocalcemia), toxins, and many medications. Hereditary myoclonus syndromes can be grouped into three classes based on clini cal features: prominent myoclonus, prominent myoclonus combined with another prominent movement disorder, and disorders that usually present with other phenotypes but can also manifest as a prominent myoclonus syndrome. An additional movement disorder is seen in nearly all myoclonus syndromes, most commonly ataxia or dystonia. Furthermore, cognitive decline and epilepsy are present in the majority

of patients. The frequent association with epilepsy suggests that a brief epileptic-like discharge could underlie myoclonus in some situations.

Myoclonic epilepsy is a disorder comprised of myoclonus and epi lepsy. It can be associated with other focal neurologic deficits, has a variable but progressive course, and may ultimately be fatal. The most common form of action myoclonus of cortical origin with general ized epilepsy is myoclonic epilepsy or Unverricht-Lundborg disease (EPM-1). Ataxia may also be a feature. This is an autosomal recessive disease caused by pathogenic variants in the CSBT gene. Other causes are Lafora body epilepsy or progressive myoclonic epilepsy (PME2) caused by mutations in the EPM2A or NHLRC1 genes. Neuronal ceroid lipofuscinosis (Batten’s disease) is another consideration. In patients with less severe or absent epilepsy, mitochondrial disorders and neurodegenerative disorders affecting the cerebellum (i.e., SCAs) should be considered. Essential myoclonus is a relatively benign familial condition characterized by multifocal, very brief, lightninglike movements that are frequently alcohol sensitive. Mutations in the epsilon-sarcoglycan gene have been associated with myoclonus seen in association with dystonia (myoclonus-dystonia). PART 13 Neurologic Disorders The precise cause of myoclonus is not known but, in some cases, is thought

to be due to overexcitability or impaired inhibition of cortical or peripheral nerve stimuli related to a particular movement. Imaging studies are seeking to define the altered connectivity in neuronal cir cuits that underlies myoclonus. TREATMENT Myoclonus Treatment primarily consists of managing the underlying condition or removing an offending agent. Pharmacologic therapy involves one or a combination of GABAergic agents such as valproic acid (800–3000 mg/d), piracetam (8–20 g/d), clonazepam (2–15 mg/d), levetiracetam (1000–3000 mg/d), or primidone (500–1000 mg/d). Treatment may be associated with striking clinical improvement in chronic cases in which a cortical origin for the myoclonic dis charges has been identified (e.g., postanoxic myoclonus, progressive myoclonic epilepsy). In some cases, combinations of drugs may prove helpful. The serotonin precursor 5-hydroxytryptophan (plus carbidopa) may be useful in cases of postanoxic myoclonus. DBS can be highly effective in myoclonus-dystonia. Botulinum toxin has been used successfully in some patients with focal myoclonus, palatal myoclonus, and hemifacial spasm. Some patients with hemi facial spasm have also been reported to benefit from neurosurgical decompression of the involved facial nerve. DRUG-INDUCED MOVEMENT DISORDERS This important group of movement disorders is primarily associated with drugs that block dopamine receptors (neuroleptics) or central dopaminergic transmission. These drugs are widely used in psychiatry, but it is important to appreciate that drugs used in the treatment of nausea or vomiting (e.g., prochlorperazine [Compazine]) or gastro esophageal disorders (e.g., metoclopramide [Reglan]) are neurolep tic agents and can cause these disorders. Hyperkinetic movement disorders secondary to neuroleptic drugs can be divided into those that present acutely, subacutely, or after prolonged exposure (tardive syndromes). Dopamine-blocking drugs can also be associated with a reversible parkinsonian syndrome for which anticholinergics are often concomitantly prescribed, but these drugs are not effective antiparkinsonian agents and are associated with cognitive side effects, and there is concern that such treatment might actually increase the risk of developing a tardive syndrome. ■ ■ACUTE Dystonia is the most common acute hyperkinetic drug reaction (see above). It is typically generalized in children and focal in adults (e.g., blepharospasm, torticollis, or OMD). The reaction can develop within minutes of exposure and can be successfully treated in most cases with parenteral administration of anticholinergics (benztropine),

diphenhydramine, benzodiazepines (lorazepam, clonazepam, or diaz epam), or dopamine agonists. The abrupt onset of severe spasms may occasionally be confused with a seizure; however, there is no loss of consciousness, and no automatisms, electroencephalogram abnormali ties, or postictal features typical of epilepsy. The acute onset of chorea, stereotypic behavior, and tics may also be seen, particularly following exposure to CNS stimulants such as methylphenidate, cocaine, or amphetamines. In rare cases, the airway may be affected and must be protected. ■ ■SUBACUTE Akathisia is the most common reaction in this category. Akathisia consists of motor restlessness with a need to move that is alleviated by movement. It is most frequently associated with use of neuroleptic drugs and generally starts within 2 weeks of initiating therapy. It can also be seen with calcium channel blockers, antiemetics, cocaine, and sedatives. The cause is not known but is thought to relate to blocking the dopaminergic system. Therapy consists of lowering the dose or removing the offending agent. When this is not possible, symptoms may be ameliorated with benzodiazepines, anticholinergics, beta blockers, or dopamine agonists. Treatment is generally effective, but in chronic cases, it may become associated with anxiety, depression, and even suicide. ■ ■TARDIVE SYNDROMES These disorders develop months to years after initiation of a neu roleptic agent. Tardive dyskinesias (TD) are most common and typically present with

choreiform movements involving the mouth, lips, and tongue. In severe cases, the trunk, limbs, and respiratory muscles may also be affected. In approximately one-third of patients, TDs remit within 3 months of stopping the drug, and most patients gradually improve over the course of several years. However, abnor mal movements may also develop, persist, or worsen after stopping the offending agent. The movements are often mild and more upset ting to the family than to the patient, but in some cases, they can be severe and disabling, particularly in the context of an underlying psychiatric disorder. Second-generation or atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) are thought to be associated with a lower risk of causing TD in comparison to traditional antipsychotics, although they do not eliminate this risk. Younger patients have a lower risk of developing neuroleptic-induced TD, whereas the elderly, females, and those with underlying organic cerebral dysfunction are at greater risk. Chronic neuroleptic use is associated with increased risk of TD, and the U.S. Food and Drug Administration has specifically warned that use of metoclopramide for >12 weeks increases the risk of TD. Because TD can be permanent and resistant to treatment, antipsychotics should be used judiciously and atypical neuroleptics should be the preferred agent whenever possible, although there are now questions as to the risk of TD with atypical neuroleptics as well. In all patients on these agents, the need for continued use should be regularly evaluated. The cause of TD is not known with certainty, but it is thought to be related to hypersensitivity of dopamine receptors following the use of dopa mine D2–blocking agents. This concept is based on observations that acute discontinuation can lead to accentuation of TD, while higher doses of these agents or the introduction of more potent neuroleptics can alleviate symptoms (at least transiently). Another hypothesis is that structural changes at the receptor level due to toxic effects of the neuroleptic may be causative. It has also been suggested that there may be a genetic predisposition in individuals who develop TD. Treatment primarily consists of tapering and withdrawal of the offending agent. If the patient is receiving a traditional antipsychotic, and withdrawal is not possible, replacement with an atypical antipsy chotic (e.g., clozapine) should be tried. Abrupt cessation of a neurolep tic should be avoided because acute withdrawal can induce worsening. TD can persist after withdrawal of antipsychotics and can be difficult to treat. Tetrabenazine, a vesicular monoamine transporter type 2 (VMAT-2) inhibitor that blocks storage of dopamine, has been used to treat TD but is short-acting and is associated with a dose-related

new onset or worsening of parkinsonian features. Valbenazine, an ester of tetrabenazine, has been approved for the treatment of tardive dyskinesia in a dose of 80 mg/d based on efficacy in double-blind trials, but it is associated with sleepiness and QT prolongation. Deuterated tetrabenazine has also been approved for this indication. Deuteration provides a longer half-life with lower Cmax, reducing risk of parkinso nian side effects. It can be individually titrated and permits the use of higher doses with lower risk of side effects. In open-label studies, benefits have also been reported with valproic acid (750–3000 mg/d), anticholinergics, and botulinum toxin injections. Other approaches include baclofen (40–80 mg/d) and clonazepam (1–8 mg/d). In some refractory cases, pallidal DBS may be an option. Chronic neuroleptic exposure can also be associated with a tardive dystonia, with preferential involvement of axial muscles and charac teristic rocking movements of the trunk and pelvis. Gray coloration of skin can be a clue that the patient is receiving a neuroleptic in patients for whom the cause of the dystonia is not obvious. Tardive dystonia can be more troublesome than tardive dyskinesia and frequently persists despite stopping medication. Valproic acid, anticholinergics, and botulinum toxin may occasionally be beneficial, but patients are frequently refractory to medical therapy. Tardive akathisia, tardive TS, and tardive tremor

syndromes are rare but may also occur after chronic neuroleptic exposure. Neuroleptic medications can also be associated with a neuroleptic malignant syndrome (NMS). NMS is characterized by the acute or subacute onset of muscle rigidity, elevated temperature, altered mental status, hyperthermia, tachycardia, labile blood pressure, and renal fail ure with markedly elevated creatine kinase levels. Symptoms typically evolve within days or weeks after initiating the drug. NMS can also be precipitated by the abrupt withdrawal of dopaminergic medications in PD patients. Treatment involves immediate cessation of the offending antipsychotic drug and the introduction of a dopaminergic agent (e.g., a dopamine agonist or levodopa), dantrolene, or a benzodiazepine. In very severe cases, when oral intake is not possible, a patch (delivering rotigotine subcutaneously) or an infusion pump (delivering apomor phine or levodopa subcutaneously) may be required. Treatment may need to be undertaken in an intensive care setting and include sup portive measures such as control of body temperature (antipyretics and cooling blankets), hydration, electrolyte replacement, and control of renal function and blood pressure. Drugs that have serotonin-like activity (tryptophan, MDMA or “ecstasy,” meperidine) or that block serotonin reuptake can induce a rare, but potentially fatal, serotonin syndrome that is characterized by confusion, hyperthermia, tachycardia, and coma, as well as rigidity, ataxia, and tremor. Myoclonus is often a prominent feature, in contrast to NMS, which it resembles in other respects. Patients can be managed with propranolol, diazepam, diphenhydramine, chlorpromazine, or cyproheptadine, as well as supportive measures. A variety of other drugs can be associated with hyperkinetic move ment disorders. Some examples include phenytoin (chorea, dystonia, tremor, myoclonus), carbamazepine (tics and dystonia), tricyclic antidepressants (dyskinesias, tremor, myoclonus), fluoxetine (myoclo nus, chorea, dystonia), oral contraceptives (dyskinesia), β-adrenergics (tremor), buspirone (akathisia, dyskinesias, myoclonus), digoxin, cimetidine, diazoxide, lithium, methadone, and fentanyl (dyskinesias). And as described in an earlier chapter (Chap. 446), treatment of PD with levodopa can be associated with dyskinetic movements; these are typically choreiform, but dystonia and myoclonus may also occur. PAROXYSMAL DYSKINESIAS Paroxysmal dyskinesias are a group of rare disorders characterized by episodic, brief involuntary movements that can manifest as various types of hyperkinetic movements, including chorea, dystonia, tremor, myoclonus, and ballism. There are three main types: (1) paroxysmal kinesigenic dyskinesia (PKD), where the involuntary movements are triggered by sudden movement; (2) paroxysmal nonkinesigenic dyski nesias (PNKD), where the attacks are not induced by movement; and (3) rare cases of paroxysmal exertion-induced dyskinesia (PED), where attacks are induced by prolonged exercise.

PKDs are characterized by brief, self-limited attacks induced by the onset of movement such as running but also occasionally by unex pected sound or photic stimulation. Attacks may affect one side of the body, last seconds to minutes at a time, and recur several times a day. They usually manifest as a mixed hyperkinetic movement disor der with dystonic posturing of a limb, ballismus, and chorea, which may also become generalized. PKD is most commonly familial with an autosomal dominant pattern of inheritance and mutations in the proline-rich transmembrane protein 2 (PRRT2) gene but may also occur secondary to various brain disorders such as multiple sclerosis or hyperglycemia. PKD is more frequent in males (4:1), and the onset is typically in the first or second decade of life. About 70% report sensory symptoms such as tingling or numbness of the affected limb preceding the attack by a few milliseconds. The evolution is relatively benign, and there is a trend toward resolution of the attacks over time. Treatment with low-dose anticonvulsant therapy such as carbamazepine or phe nytoin is advised when the attacks are frequent and interfere with daily life activities and is effective in ~80% of patients. Some clinical features of PKD (abrupt and

short-lasting attacks preceded by an “aura”), the association with true seizure episodes, and its favorable response to anticonvulsant drugs have led to speculation that it is epileptic in ori gin, but this has not been established.

CHAPTER 447 Tremor, Chorea, and Other Movement Disorders PNKD involves attacks of generalized dyskinesias precipitated by alcohol, caffeine, stress, or fatigue. In comparison to PKD, the epi sodes have a relatively longer duration (minutes to hours) and are less frequent (one to three per day). PNKD is inherited as an autosomal dominant condition with high (~80%) but incomplete penetrance. A missense mutation in the myofibrillogenesis regulator (PNKD) gene has been identified in several families. Recognition of the condition and elimination of the underlying precipitating factors, where possible, are the first priorities. Tetrabenazine, neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treat ment may not be required if the condition is mild and self-limited. Most patients with PNKD do not benefit from anticonvulsant drugs, but these should be tried, and some may respond to clonazepam or other benzodiazepines. PED is characterized by a combination of chorea, athetosis, and dystonia in excessively exercised body regions, with the legs being most frequently affected. They are frequently familial. A single attack lasts from a few minutes to an hour and occurs after prolonged physi cal exercise. In addition to the movement disorder, several patients have other disease manifestations between episodes such as epilepsy, hemolytic anemia, and migraine. The SLC2A1 (solute carrier family 2 member 1) gene, previously linked to GLUT1 (glucose transporter of the blood-brain barrier) deficiency syndrome, can also cause parox ysmal PED. Treatment includes avoiding prolonged physical exercise. Whereas anticonvulsants and most medications are typically not effec tive, a ketogenic diet may be an effective therapeutic option. Other (rare) forms of paroxysmal dyskinesia are caused by pathogenic variants in the ECHS1, GLDC, KCNMA1, SCN8A, and TMEM151A genes. RESTLESS LEGS SYNDROME Restless legs syndrome (RLS) is a neurologic disorder that affects ~10% of the adult population (it is rare in Asians). It was first described in the seventeenth century by the English physician Thomas Willis but has only recently been appreciated to be a bona fide movement disorder. The four core symptoms required for diagnosis are an urge to move the legs usually caused or accompanied by an unpleasant sensation in the legs; symptoms that begin or worsen with rest; partial or complete relief by movement; and worsening during the evening or night. Symptoms are often mild but can cause significant morbidity in some individuals. Symptoms most commonly begin in the legs but can spread to, or even begin in, the upper limbs. The unpleasant sensation is often described as a creepy-crawly feeling, paresthesia, or burning. In ~80% of patients, RLS is associated with periodic leg movements (PLMs) during sleep and occasionally while awake. These involuntary move ments are usually brief, lasting no more than a few seconds, and recur every 5–90 s. The restlessness and PLMs are a major cause of

sleep disturbance, leading to poor-quality sleep and daytime sleepi ness. RLS is also commonly associated with depression, anxiety, and hypertension.

The mean age of onset in familial forms is in the third decade, although pediatric cases are recognized. The severity of symptoms is variable. Secondary RLS may be associated with pregnancy or a range of underlying disorders, including anemia, ferritin deficiency, renal failure, and peripheral neuropathy. There is an association with abnormalities of iron metabolism, possibly because low iron can result in reduced dopamine levels. Diagnosis is made on clinical grounds but can be supported by polysomnography and the demonstration of PLMs. Recent studies suggest

that age, sex, and genetic markers can be used to accurately predict who is likely to develop RLS in 90% of cases. The neurologic examination is normal. Secondary causes of RLS should be excluded, and ferritin levels, glucose, and renal func tion should be measured. The pathogenesis is thought to be associated with an alteration in dopamine function, which may be peripheral or central, but this has not been specifically defined. Primary RLS is often familial and has a strong genetic component; however, no causative gene has yet been identified. Genome association studies have identi fied >150 variants associated with RLS risk, with the strongest candi dates in the PTPRD, BTBD9, and MEIS1 genes. Interestingly no genetic linkage to iron has been identified. PART 13 Neurologic Disorders Most RLS sufferers have mild symptoms that do not require specific treatment. General measures to improve sleep hygiene and quality should be attempted first. If symptoms remain intrusive, low doses of dopamine agonists, e.g., pramipexole (0.25–0.5 mg), ropinirole (1–2 mg), or patch rotigotine (2–3 mg), taken 1–2 h before bedtime are generally effective. Levodopa may also be effective but is more likely to be associated with augmentation (spread and worsening of symptoms and emergence during the day) or rebound (reappearance sometimes with worsening of symptoms at a time related to the drug's short halflife). Augmentation can also be seen with chronic use of drugs such as dopamine agonists, particularly if higher doses are employed. Other drugs that have been reported to be effective in individual cases include anticonvulsants, analgesics, and opiates, but these are not commonly employed. Tonic motor activation (TOMAC) is a nonpharmacologic approach to RLS that has not responded to drug therapy and has recently been approved in the United States. The treatment involves electrical stimulation of the peroneal nerves during the night and is reported to be effective and to improve sleep quality. Management of secondary RLS should be directed to correcting the underlying disor der (e.g., iron replacement for anemia). OTHER DISORDERS THAT MAY PRESENT WITH A COMBINATION OF PARKINSONISM AND HYPERKINETIC MOVEMENTS ■ ■WILSON'S DISEASE (SEE ALSO CHAP. 427) Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism that produces neurologic, psychiatric, and liver manifestations, alone or in combination. It is caused by mutations in the ATP7B gene encoding a P-type ATPase. The disease was first described by the English neurologist Kinnier Wilson at the beginning of the twentieth century, although at around the same time, the Ger man physicians Kayser and Fleischer separately noted the characteris tic association of corneal pigmentation (Kayser-Fleischer rings) along with hepatic and neurologic features. WD has a worldwide prevalence of ~1 in 30,000, with a mutation carrier frequency of 1 in 90. About half of WD patients (especially younger patients) present with liver abnormalities. The remainder present with neurologic disease (with or without underlying liver abnormalities), and a small proportion have hematologic or psychiatric problems at disease onset. Neurologic onset usually manifests in the second decade with tremor, rigidity, and dystonia. The tremor is usually in the upper limbs, bilateral, and asymmetric. Tremor can be on intention or occasionally at rest, and in advanced disease can take on a wing-beating character istic (a flapping movement when the arms are held outstretched with the fingers opposed). Other features can include parkinsonism with

bradykinesia, dystonia (particularly facial grimacing), dysarthria, and dysphagia. More than half of those with neurologic features have a his tory of psychiatric disturbances, including depression, mood swings, and overt psychosis. Kayser-Fleischer (KF) rings are seen in virtually all patients with neurologic features and 80% of those with hepatic pre sentations. KF rings represent the deposition of copper in Descemet's membrane around the cornea. They consist of a characteristic grayish rim or circle at the limbus of the cornea and are best detected by slitlamp examination.

Neuropathologic examination is characterized by neurodegeneration and astrogliosis in the basal ganglia, particularly in the striatum. WD should always be considered in the differential diagnosis of a movement disorder, particularly when arising in the first decades of life. Low levels of blood copper and ceruloplasmin and high levels of urinary copper may be present, but normal levels do not exclude the diagnosis. Brain imaging usually reveals generalized brain atrophy in established cases, and ~50% have signal hypointensity in the caudate head, puta men, globus pallidus, substantia nigra, and red nucleus on T2-weighted MRI scans. However, the correlation of imaging changes with clinical features is not good. Liver biopsy with demonstration of high copper levels and genetic testing remain the gold standard for diagnosis. In the absence of treatment, the course is progressive and leads to severe neurologic dysfunction and early death in most patients, although a small proportion experience a relatively benign course. Treatment is directed at reducing tissue copper levels and maintenance therapy to prevent reaccumulation. There is no clear consensus on optimal treatment, and patients should be managed in a unit with expertise in treating this disease. Penicillamine is frequently used to increase copper excretion but may lead to a worsening of symptoms in the initial stages of therapy. Side effects are common and can to some degree be attenuated by co-administration of pyridoxine. Tetrathiomolybdate blocks the absorption of copper and can be used instead of penicillamine. Trientine tetrahydrochloride and zinc are useful drugs for maintenance therapy. Effective treatment can reverse the neurologic features in most patients, particularly when started early. However, some patients may still progress, especially those with hepatocerebral disease. KF rings tend to decrease after 3–6 months and disappear by 2 years. Adherence to maintenance therapy is a major challenge in long-term care. Patients with advanced hepatic disease may require a liver transplant, and the potential role of organ-specific chelation therapy is under investigation. Gene therapy studies that involve an infusion of a working copy of the ATP7B gene into the liver are being investigated clinically, while preclinical studies are testing the novel chelator methanobactin. ■ ■NEURODEGENERATION WITH BRAIN

IRON ACCUMULATION Neurodegeneration with brain iron accumulation (NBIA) represents a group of inherited disorders characterized by iron accumulation in the basal ganglia. Clinically, they can manifest as a progressive neurologic disorder with a variety of clinical features including parkinsonism, dystonia, neuropsychiatric abnormalities, and retinal degeneration. Cognitive disorders and cerebellar dysfunction may also be seen. Pre sentation is usually in childhood, but adult cases have been described. Multiple genes have been identified. Pantothenate kinase-associated neurodegeneration (PKAN), formerly known as Hallervordan-Spatz disease, is caused by a mutation in the PANK2 gene and is the most common form of NBIA, accounting for ~50% of cases. Onset is usu ally in early childhood and is manifest as a combination of dystonia, parkinsonism, and spasticity. MRI shows a characteristic low signal abnormality in the center of the globus pallidus on T2-weighted scans caused by iron accumulation and known as the “eye of the tiger” sign. Numerous other gene mutations have been described associated with iron accumulation, including PLA2G6, C19orf12, FA2H, ATP13A2, WDR45, FTL, CP, COASY, and DCAF17. One must be cautious, however, not to assume that all cases with iron accumulation in the basal ganglia represent an NBIA because iron accumulation in some basal ganglia regions is normal, and excess iron accumulation may occur in the basal ganglia as a nonspecific secondary consequence of

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