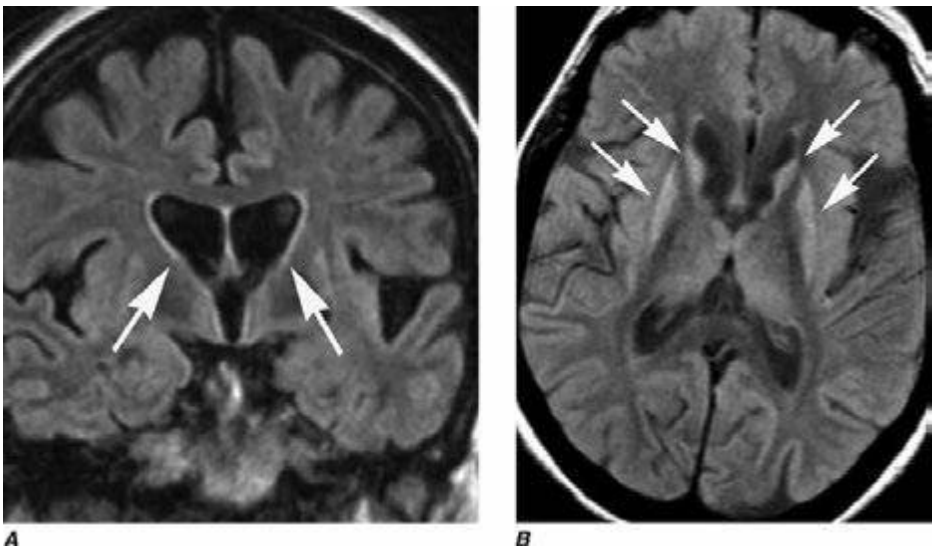

FIGURE 449-8 **Huntington's disease. *A.*** Coronal fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging shows enlargement of the lateral ventricles reflecting typical atrophy (*arrows*). ***B.*** Axial FLAIR image demonstrates abnormal high signal in the caudate and putamen (*arrows*).

the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest. Intermediate forms of the disease with 36–39 repeats are described in some patients, typically with less severe clinical involvement. Acceleration of the process 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. The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the central nervous system (CNS) but whose function is not known. Models of HD with striatal pathology can be induced by excitotoxic agents such as kainic acid and 3-nitropoprionic acid, which promote calcium entry into the cell and cytotoxicity. Mitochondrial dysfunction has been demonstrated in the striatum and skeletal muscle of symptomatic and presymptomatic individuals. Fragments of the mutant huntingtin protein can 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.

TREATMENT HUNTINGTON'S DISEASE

Although the gene for HD was identified more than two decades ago, there is still no disease-modifying therapy for this disorder. Current treatment involves a multidisciplinary approach, with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine-blocking agents may control the choreatic movements. Tetrabenazine (a presynaptic dopamine depleting agent) has been approved for the treatment of chorea in the United States, but can cause secondary parkinsonism. Neuroleptics are generally not recommended because of their potential to induce other more troubling movement disorders and because HD chorea tends to be self-limited and is usually not disabling. Depression and anxiety can be greater 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 anti-psychotics such as clozapine (50–600 mg/d), quetiapine (50–600 mg/d), and risperidone (2–8 mg/d). There is no adequate treatment for the cognitive or motor decline. A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in HD. Drugs that enhance mitochondrial function and increase the clearance of defective mitochondria are being tested as possible disease-modifying therapies. Antiglutamate agents, dopamine stabilizers, caspase inhibitors, neurotrophic factors, and transplantation of fetal striatal cells are areas of active research, but none has as yet been demonstrated to have a beneficial effect in HD. The potential to use transcriptional blockade of the mutant huntingtin gene with small interfering RNAs (siRNAs) is an exciting area currently being explored.

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 adulthood. HDL-1 is due to expansion of an octapeptide repeat in *PRNP*, the gene encoding the prion protein (Chap. 453e). 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. 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 regulating transcription; this condition is identical to spinocerebellar ataxia (SCA) 17 (Chap. 451e), and most patients present primarily with ataxia rather than chorea. Mutations of the *C9Orf* gene associated with amyotrophic lateral sclerosis have also been reported in some individuals with an HDL phenotype.

OTHER CHOREAS

Chorea can be seen in a number of additional disorders. 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 and is thought to be autoimmune in nature. It is characterized by the acute onset of choreiform movements and behavioral disturbances. With the reduction 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, but is self-limited, and treatment is generally 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 NMDA receptor antibody–positive encephalitis following herpes simplex virus encephalitis.

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 self-mutilating 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 transcription factor 1 and a late-onset benign senile chorea (BHC2) have also been described. It is important to ensure that patients with these types of choreas do not have HD.