limbic system, and cortex. The DLB clinical syndrome is characterized by visual hallucinations, parkinsonism, fluctuating alertness, falls, and often rapid eye movement (REM) sleep behavior disorder (RBD). Dementia can precede or follow the appearance of parkinsonism. Hence, one pathway occurs in patients with long-standing PD without cognitive impairment, who slowly develop a dementia that is associated with visual hallucinations and fluctuating alertness. When this occurs after an established diagnosis of PD, many use the term *Parkinson's disease dementia* (PDD). In others, the dementia and neuropsychiatric syndrome precede or co-emerge with the parkinsonism, and this constellation is referred to as DLB. Both PDD and DLB may be accompanied or preceded by symptoms referable to brainstem pathology below the substantia nigra including constipation, orthostatic lightheadedness, or RBD, and many researchers conceptualize these disorders as points on a spectrum of α-synuclein pathology.

Patients with PDD and DLB are highly sensitive to metabolic perturbations, and in some patients, the first manifestation of illness is a delirium, often precipitated by an infection, new medicine, or other systemic disturbance. A hallucinatory delirium induced by L-dopa, prescribed for parkinsonian symptoms attributed to PD, may likewise provide the initial clue to a PDD or DLB diagnosis. Conversely, patients with mild cognitive deficits and hallucinations may receive typical or atypical antipsychotic medications, which induce profound parkinsonism at low doses due to a subclinical DLB-related nigral dopaminergic neuron loss. Even without an underlying precipitant, fluctuations can be marked in DLB, with episodic confusion or even stupor admixed with lucid intervals. Despite the fluctuating pattern, however, the core clinical features persist, unlike delirium, which resolves following correction of the inciting factor. Cognitively, DLB features relative preservation of memory but more severe visuospatial and executive deficits than seen in patients with early AD.

The key neuropathologic feature in DLB is the presence of Lewy bodies and Lewy neurites throughout specific brainstem nuclei, substantia nigra, amygdala, cingulate gyrus, and, ultimately, the neocortex. Lewy bodies are intraneuronal cytoplasmic inclusions that stain with periodic acid–Schiff (PAS) and ubiquitin but are now identified with antibodies to the presynaptic protein, α-synuclein. Lewy bodies are composed of straight neurofilaments 7–20 nm long with surrounding amorphous material and contain epitopes recognized by antibodies against phosphorylated and nonphosphorylated neurofilament proteins, ubiquitin, and α-synuclein. Lewy bodies are typically found in the substantia nigra of patients with idiopathic PD, where they can be readily seen with hematoxylin-and-eosin staining. A profound cholinergic deficit, owing to basal forebrain and pedunculopontine nucleus involvement, is present in many patients with DLB and may be a factor responsible for the fluctuations, inattention, and visual hallucinations.

Due to the frequent comorbidity with AD and the cholinergic deficit in DLB, cholinesterase inhibitors often provide significant benefit, reducing hallucinosis, stabilizing delusional symptoms, and even helping with RBD in some patients. Exercise programs maximize motor function and protect against fall-related injury. Antidepressants are often necessary. Atypical antipsychotics may be required for psychosis but can worsen extrapyramidal syndromes, even at low doses, and increase risk of death. Patients with DLB are extremely sensitive to dopaminergic medications, which must be carefully titrated; tolerability may be improved by concomitant use of a cholinesterase inhibitor.

## OTHER CAUSES OF DEMENTIA

*Prion diseases* such as *Creutzfeldt-Jakob disease* (CJD) are rare neurodegenerative conditions (prevalence ~1 per million) that produce dementia. CJD is a rapidly progressive disorder associated with dementia, focal cortical signs, rigidity, and myoclonus, causing death <1 year after first symptoms appear. The rapidity of progression seen with CJD is uncommon in AD so that the distinction between the two disorders is usually straightforward. CBD and DLB, more rapid degenerative dementias with prominent movement abnormalities, are more likely to be mistaken for CJD. The differential diagnosis for CJD includes other rapidly progressive dementing conditions such as viral or bacterial encephalitides, Hashimoto's encephalopathy, central nervous system (CNS) vasculitis, lymphoma, or paraneoplastic/autoimmune syndromes. The markedly abnormal periodic complexes on EEG and cortical ribboning and basal ganglia hyperintensities on fluid-attenuate inversion recovery MRI are diagnostic features of CJD, although rarely, prolonged focal or generalized seizures can produce a similar imaging appearance. **Prion diseases are discussed in detail in Chap. 453e.**

*Huntington's disease* (HD) **(Chap. 449)** is an autosomal dominant degenerative brain disorder. HD clinical hallmarks include chorea, behavioral disturbance, and executive impairment. Symptoms typically begin in the fourth or fifth decade, but there is a wide range, from childhood to >70 years. Memory is frequently not impaired until late in the disease, but attention, judgment, self-awareness, and executive functions are often deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are common. Delusions and obsessive-compulsive behavior may occur. Disease duration is variable but typically lasts approximately 15 years.

*Normal-pressure hydrocephalus* (NPH) is a relatively uncommon but treatable syndrome. The clinical, physiologic, and neuroimaging characteristics of NPH must be carefully distinguished from those of other dementias associated with gait impairment. Historically, many patients treated for NPH have suffered from other dementias, particularly AD, vascular dementia, DLB, and PSP. For NPH, the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate, with an emphasis on executive impairment), and urinary urgency or incontinence. Neuroimaging reveals enlarged lateral ventricles (hydrocephalus) with little or no cortical atrophy, although the sylvian fissures may appear propped open (so-called "boxcarring"), which can be mistaken for perisylvian atrophy. This syndrome is a communicating hydrocephalus with a patent aqueduct of Sylvius **(see Fig. 35-3)**, in contrast to aqueductal stenosis, in which the aqueduct is small. Lumbar puncture opening pressure falls in the high-normal range, and the CSF protein, glucose, and cell counts are normal. NPH may be caused by obstruction to normal CSF flow over the cerebral convexities and delayed resorption into the venous system. The indolent nature of the process results in enlarged lateral ventricles with relatively little increase in CSF pressure. Presumed edema, stretching, and distortion of subfrontal white matter tracts may lead to clinical symptoms, but the precise underlying pathophysiology remains unclear. Some patients provide a history of conditions that produce meningeal scarring (blocking CSF resorption) such as previous meningitis, subarachnoid hemorrhage, or head trauma. Others with long-standing but asymptomatic congenital hydrocephalus may have adult-onset deterioration in gait or memory that is confused with NPH. In contrast to AD, the patient with NPH complains of an early and prominent gait disturbance without cortical atrophy on CT or MRI.

Numerous attempts to improve NPH diagnosis with various special studies and predict the success of ventricular shunting have been undertaken. These tests include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various efforts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. A transient improvement in gait or cognition may follow lumbar puncture (or serial punctures) with removal of 30–50 mL of CSF, but this finding has also not proved to be consistently predictive of postshunt improvement. Perhaps the most reliable strategy is a period of close inpatient evaluation before, during, and after lumbar CSF drainage. Occasionally, when a patient with AD presents with gait impairment (at times due to comorbid subfrontal vascular injury) and absent or only mild cortical atrophy on CT or MRI, distinguishing NPH from AD can be challenging. Hippocampal atrophy on MRI favors AD, whereas a characteristic "magnetic" gait with external hip rotation, low foot clearance, and short strides, along with prominent truncal sway or instability, favors NPH. The diagnosis of NPH should be avoided when hydrocephalus is not detected on imaging studies, even if the symptoms otherwise fit. Thirty to fifty percent of patients identified by careful diagnosis as having NPH will improve with ventricular shunting. Gait may improve more than cognition, but many reported failures