01 - Chapter 8 Neurocognitive Disorders

Chapter 8 Neurocognitive Disorders

96 NEUROCOGNITIVE DISORDERS Definition Delirium WARDS TIP ■ Delirium is a medical emergency. Terms commonly used for delirium include toxic or metabolic encephalopathy, acute organic brain syndrome, acute confusional state, acute toxic psychosis, and ICU psychosis. ■ Potentially reversible. ■ Can advance to coma, seizures, or death. EPIDEMIOLOGY WARDS TIP Consider delirium as acute brain failure—a medical emergency like other acute organ failures. RISK FACTORS WARDS QUESTIONS ■ Advanced age. Q: What is the “ICU triad?” A: Pain, Agitation, and

Delirium. ■ Prior history of delirium. ■ Severe or terminal illness. ■ Multiple medical comorbidities. ■ Hearing or vision impairment. PRECIPITATING FACTORS WARDS TIP Delirium is commonly experienced by patients in the ICU and postoperative recovery. ■ Alcohol use or withdrawal. ■ Infection. ■ Pain. ■ Dehydration. ■ Malnutrition. ■ Impaired mobility. ■ Sleep deprivation. ■ Organ failure. ■ Mechanical ventilation. The neurocognitive disorders (NCDs) comprise a group of conditions defined by decline from a previous level of cognitive functioning. The six cognitive domains that may be affected include complex attention, executive function, learning and memory, language, perceptual-motor skills, and social cognition (interaction). By definition, cause(s) for the deficits may be ascertained from findings on history, physical exam, and diagnostic testing. The DSM-5 divides the NCDs into three main categories: delirium, mild NCDs, and major NCDs (dementias). ■ May be the only early manifestation of serious illness. ■ Associated with high mortality. Up to 40% of individuals die within 1 year of diagnosis. ■ Up to one-half of hospitalized elderly patients develop delirium. ■ As many as 90% of patients with a preexisting NCD (dementia) will experience a superimposed delirium when admitted to the hospital. ■ Delirium often goes unrecognized (65–88% of the time). ■ Delirium is associated with an increased risk for later development of major NCD. ■ Preexisting cognitive impairment or depression. ■ Polypharmacy, including the use of psychotropic medications (especially benzodiazepines and anticholinergic drugs).

TABLE 8-1. Clinical Scenarios of Delirium on Exam Scenario Likely Diagnosis Diagnostic Testing Delirium + fever + cough + rales Pneumonia Chest x-ray Delirium + dysuria + suprapubic tenderness Urinary tract infection Urinalysis and urine culture Delirium + constricted pupils (miosis) + bradypnea Opioid intoxication Urine toxicology screen Delirium + fever + nuchal rigidity + photophobia Meningitis Lumbar puncture Delirium + tachycardia + tremor + thyromegaly Thyrotoxicosis TSH, free T4, T3 Delirium + insulin use Hypoglycemia Blood glucose ETIOLOGY ■ Almost any medical condition can cause delirium (see examples in Table 8-1). ■ The DSM-5 recognizes five broad categories: •• Substance intoxication delirium. •• Substance withdrawal delirium. •• Medication-induced delirium. •• Delirium due to another medical condition. •• Delirium due to multiple etiologies. CLINICAL MANIFESTATIONS ■ Primarily a disorder of attention and awareness (i.e., orientation). ■ Cognitive deficits develop acutely over hours to days. ■ Symptoms fluctuate throughout the course of a day, typically worsening at night. ■ Other features include deficits in recent memory, language abnormalities, or perceptual disturbances (usually visual, such as illusions or hallucinations). ■ Circadian rhythm disruption and emotional symptoms are common. ■ There are three types of delirium based on psychomotor activity. •• Purely hypoactive (“quiet”) type

- Decreased psychomotor activity, ranging from drowsiness to lethargy to stupor.
- More likely to go undetected.
- More common in the elderly. •• Purely hyperactive type (“ICU psychosis”)
- Manifests with agitation, mood lability, and uncooperativeness.
- More easily identified due to its disruptiveness.
- More common in drug withdrawal or toxicity. •• Mixed type
- Psychomotor activity may remain stable at baseline or fluctuate rapidly between hyperactivity and hypoactivity. ■ Hospitalized patients usually recover within 1 week, although some degree of cognitive deficits can persist for months or even indefinitely. NEUROCOGNITIVE DISORDERS WARDS TIP Common causes of medication-induced

delirium: • Anticholinergics • Benzodiazepines • Nonbenzodiazepine hypnotics (“Z-drugs”) • Opioids (especially meperidine) • Corticosteroids • Tricyclic antidepressants • H2 blockers WARDS QUESTION Q: What are the two most common precipitants of delirium in children? A: Febrile illnesses and medications. WARDS TIP Suspect delirium if a patient presents with altered mental status, disorientation, confusion, agitation, or sudden onset of psychotic symptoms.

98 NEUROCOGNITIVE DISORDERS TABLE 8-2. DSM-5 Criteria for Delirium WARDS TIP ■ Disturbance in attention and awareness. ■ Disturbance in an additional cognitive domain. A quick, first-glance bedside exam for suspected substance/medication intoxication is VALEUMS. ■ Not occurring during a coma. • Vital signs • Alertness Level • Eyes (pupil size and position) • Urine (bladder distention or incontinence) • Mucous membranes (moisture) • Skin (temperature and moisture) DIAGNOSIS KEY FACT Delirium generally manifests as diffuse background slowing on electroencephalography (EEG). An exception is delirium tremens, which is associated with fast EEG activity. EEG lacks sensitivity and specificity for making the diagnosis but is useful for ruling out nonconvulsive seizures. WARDS TIP Consider obtaining a head CT for a patient with delirium under the following circumstances: • No underlying cause evident on initial evaluation. • In the context of head trauma. • New focal neurologic deficits detected on exam. • Patient is unable or unwilling to cooperate with a neurologic examination. • No improvement despite treatment of already identified causes. TREATMENT ■ Treat the underlying cause(s). ■ Develops acutely over hours to days, represents a change from baseline, and tends to fluctuate. ■ Not better accounted for by another neurocognitive disorder. ■ Evidence from history, physical, or labs that the disturbance is a direct consequence of another medical condition, substance intoxication/withdrawal, exposure to toxin, or due to multiple etiologies. ■ Table 8-2 summarizes the DSM-5 diagnostic criteria. ■ A useful clinical tool for evaluation of a patient with suspected delirium is the Confusion Assessment Method (CAM). •• This method takes 5 minutes to perform and has a high sensitivity and specificity. •• Delirium is diagnosed in a patient with inattention of acute onset and/ or fluctuating course along with either disorganized thinking or altered consciousness.

- Inattention manifests as distractibility or difficulty maintaining focus during the evaluation.
- Disorganized thinking is demonstrated via derailment or loose associations.
- Level of consciousness ranges from vigilant (hyperalert) to alert (normal) to lethargic (drowsy, but easily aroused) to stuporous (difficult to arouse) to comatose (unarousable to verbal stimulation). ■ Once delirium has been diagnosed, the cause(s) should be sought. •• Finger-stick blood glucose, pulse-oximetry, arterial blood gases, and electrocardiography can quickly provide useful data at bedside. •• Labs typically obtained in a delirium workup include a basic metabolic panel, serum magnesium, complete blood count with differential, urinalysis, and urine culture. •• Urine and blood drug screen, blood alcohol level, therapeutic drug levels (e.g., antiepileptics, digoxin, lithium), hepatic panel, thyroid hormone levels, inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate), vitamin B12 level, or chest x-ray may also be warranted depending on the clinical presentation. •• Head imaging (head CT or brain MRI), EEG, and lumbar puncture should be performed if focal neurological deficits are present or a cause of delirium cannot be identified with the initial workup. ■ Address potential exacerbating factors: Mobility limitations, sensory deficits, sleep cycle disruption, constipation, urinary

retention, dehydration, electrolyte abnormalities, uncontrolled pain, and medications.

■ Encourage a family member to stay at the bedside to help with supervision and orientation. ■ Utilize a one-to-one sitter if needed. ■ Reorient the patient on a regular basis regarding time, place, and situation. Open window shades during the day and place whiteboards, calendars, and clocks in plain sight. ■ D2 antagonists (i.e., antipsychotics) are indicated for treatment of agitation that endangers the patient or others. •• Haloperidol is the preferred agent and can be administered orally, intramuscularly, or intravenously. •• D2 antagonists exacerbate extrapyramidal symptoms; use with caution in patients with Parkinsonism. ■ Avoid benzodiazepines (except in alcohol or benzodiazepine withdrawal) as they may worsen the delirium by causing paradoxical disinhibition or over-sedation. ■ Avoid the use of restraints. They can worsen agitation and cause injury. When restraints are necessary, reassess often and remove as soon as possible. Use the least restrictive means appropriate for the situation. An 83-year-old female is admitted to the hospital after presenting with a fever and altered mental status. Her home nurse aide reports that the patient was in her usual state of health until 24 hours prior to admission when she became confused and seemed to be talking to herself. In a few hours, her mental status improved then deteriorated again. After the patient dialed 911 to report that she was being held hostage by terrorists, her nurse aid called an ambulance on her behalf. On examination, the patient is somnolent and has difficulty responding to questions appropriately. She is disoriented to place and time. When the daughter calls to check in, she shares that her mother has had progressive memory deficits over the past several years. The patient can no longer drive and requires assistance with finances and meal preparation. What is the most likely acute diagnosis? The patient most likely has delirium. She presents with a sudden change in cognition as manifested by confusion, disorientation, and hallucinations. She has had an acute change from her baseline behavior. Her symptoms wax and wane throughout the day, representing the typical fluctuation found in delirium. She presents with a fever, likely secondary to an infection. If confirmed, her diagnosis would be delirium due to the specific infectious etiology. Collateral information points to a prior diagnosis of major neurocognitive disorder (dementia). She has a history of memory impairment that began gradually and has progressively worsened. There is also history of impairment in executive functioning, and she can no longer care for herself. The existence of a major neurocognitive disorder is a risk factor for the development of a superimposed delirium. NEUROCOGNITIVE DISORDERS WARDS QUESTION Q: In what scenarios is it appropriate to use benzodiazepines to treat delirium? A: Alcohol and benzodiazepine withdrawal.

100 NEUROCOGNITIVE DISORDERS DIAGNOSIS KEY FACT Thyroid dysfunction can cause reversible cognitive impairment. Hypothyroidism is typically accompanied by fatigue and cold intolerance. Hyperthyroidism in the elderly may manifest as an “apathetic thyrotoxicosis,” characterized by depression and lethargy. Thyroid function tests are often included in the initial workup of any new onset psychiatric illness. Objective findings on cognitive testing (preferably standardized neuropsychological testing) Mild and Major Neurocognitive Disorders ■ The non-delirium NCDs are characterized by a chronic cognitive decline that impacts functioning in daily activities (Table 8-3). ■ Individuals with mild NCDs (mild cognitive impairment [MCI] or cognitive impairment, no dementia [CIND]) experience difficulty with some of the more complex activities of daily living but are able to maintain their independence. ■ Patients with major NCDs require assistance with independent activities of daily living (IADLs), such as paying bills, managing medications, or shopping for groceries. Over time, the basic activities of daily living (e.g., feeding, toileting,

bathing) are affected, eventually leading to total dependence. ■ The mild and major NCDs are also subcategorized by etiology (Table 8-4). •• The dementias comprise a large group of progressive and irreversible major NCDs that primarily affect the elderly. •• Several other major NCDs present similarly to the dementias, but their progression may be arrested or even reversed with treatment (e.g., vitamin B12 deficiency, thyroid dysfunction, normal pressure hydrocephalus). ■ The Mini Mental State Exam (MMSE) is a screening test used due to its speed and ease of administration. •• Assesses orientation, attention/concentration, language, constructional ability, and immediate and delayed recall. •• Sensitive for major NCDs (e.g., dementias), particularly moderate-to-severe forms.

- Perfect score: 30.
- Dysfunction: <25. •• Not as sensitive for mild NCDs and early major NCDs. •• Lacks specificity. •• Norm tables are available to adjust for age and education. TABLE 8-3. DSM-5 Criteria for Mild and Major NCDs Criterion Mild NCDs Major NCDs Functional decline in at least one cognitive domain relative to baseline as evidenced by Concern (expressed by the patient or caretaker) Mild decline Significant decline Modest impairment Substantial impairment Effect on functioning in daily life. Ability to perform IADLs preserved Impaired performance of IADLs/ADLs Deficits do not occur exclusively in the context of a delirium Deficits are not better explained by another mental disorder. ADLs, basic activities of daily living; IADLs, independent activities of daily living.

TABLE 8-4. Clinical Scenarios of Neurocognitive Disorders on Exam Scenario Likely Diagnosis

> 65-year-old patient with memory impairment + executive dysfunction + poor insight progressing later to psychiatric/ behavioral disturbances + insomnia + apraxia. 65-year-old patient with executive dysfunction + cognitive slowing + stepwise progression ± focal neurologic abnormalities ± history of known stroke. 60-year-old patient with gait apraxia + urinary urgency → incontinence + executive dysfunction + apathy. Normal pressure hydrocephalus 50-year-old patient with parkinsonism preceding cognitive decline by several years. Parkinson disease 50-year-old patient with concomitant development of cognitive impairment (visuospatial dysfunction) + parkinsonism, as well as REM sleep behaviors + fluctuating alertness level + visual hallucinations. Patient of any age with cognitive slowing + short-term memory impairment + fatigue + cold intolerance. Hypothyroidism Patient of any age with cognitive slowing + depression + vegan diet + paresthesias/numbness + ataxia. Vitamin B12 deficiency ■ Another commonly used screening tool is the Mini-Cog. •• Consists of three-item recall and clock-drawing tasks. •• Positive screening for cognitive impairment:

- No items recalled after 3 minutes.
- Only one to two items recalled with abnormal clock drawing. •• Negative screening:
- All three items repeated correctly after 3 minutes.

- One to two items recalled with normal clock drawing. ■ Other commonly used screening tools include: •• Blessed Orientation-Memory-Concentration (BOMC). •• Montreal Cognitive Assessment (MoCA). •• Frontal Assessment Battery (FAB). ■ An abnormal screening test indicates the need for further testing, preferably formal neuropsychological testing. ALZHEIMER DISEASE (AD) Alzheimer disease is the most common underlying etiology of major NCDs (dementias). Clinical Manifestations ■ Gradually progressive decline in cognitive functions. ■ The primary cognitive domains affected are memory, learning, and language. ■ Personality changes, mood swings, and paranoia are very common. ■ Motor and sensory symptoms appear in advanced disease. ■ Death often occurs within 10 years of diagnosis. NEUROCOGNITIVE DISORDERS Alzheimer disease Vascular NCD NCD with Lewy bodies WARDS QUESTION Q: What are the “four As” of Alzheimer disease? A: Amnesia, agnosia, apraxia, and aphasia. KEY FACT Postmortem pathological examination of the brain is the only way to definitively diagnose Alzheimer disease.

102 NEUROCOGNITIVE DISORDERS Diagnosis KEY FACT Senile plaques and neurofibrillary tangles are found in Alzheimer disease, as well as Down syndrome and even in normal aging. Etiology KEY FACT Adults with Down syndrome are at increased risk of developing Alzheimer disease in midlife. Epidemiology Treatment WARDS TIP Antipsychotics carry a black box warning about increased risk of death in patients with dementia. ■ A multidisciplinary approach is necessary. ■ A diagnosis of possible NCD due to AD is made based on the presence of characteristic clinical findings: •• Insidious onset. •• Gradual progression. •• Impairment in one (mild NCD) or more (major NCD) cognitive domains. ■ NCD due to AD is probable if there is evidence of causation by one of several single-gene variants. ■ Accumulation of extraneuronal beta-amyloid plaques and intraneuronal tau protein tangles is associated with progressive brain atrophy. ■ Approximately 1% of AD results from an autosomal dominant single-gene mutation (amyloid precursor protein, presenilin 1, or presenilin 2), which is associated with an early onset of symptoms. ■ The epsilon-4 variant of the apolipoprotein gene is a risk factor for developing early-onset AD. ■ AD pathology is estimated to play a role in 60–90% of major NCDs. ■ Approximately 50% of patients with AD pathology have an NCD due to multiple etiologies. ■ Two-thirds of patients diagnosed with AD are female. ■ Diagnosis is made after the age of 65 in the vast majority of individuals. ■ No cure or truly effective treatment yet available. ■ Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) may slow clinical deterioration by 6–12 months in up to 50% of patients with mild-to-moderate AD. ■ The NMDA receptor antagonist, memantine, may provide a modest benefit to patients with moderate-to-severe disease. ■ Antipsychotic medications are often used to treat agitation and aggression. •• Because they are associated with increased mortality in patients with dementia, low doses should be prescribed for short periods of time. •• Ideally, informed consent should be obtained from patients and/or their designated decision makers. •• Monitor closely for side effects. ■ Supportive care via behavioral, social, and environmental interventions. ■ Any treatment plan must include caregiver support. VASCULAR DISEASE (VASCULAR COGNITIVE IMPAIRMENT) ■ Second most common single cause of major NCD. ■ Evidence of vascular disease is found in half of all major NCDs, most commonly comorbid with AD pathology (NCD due to multiple etiologies).

■ Cognitive decline occurs as a result of at least one of the following mechanisms: •• Large vessel strokes, usually cortical. •• Small vessel strokes (lacunar infarcts) to subcortical structures. ••

Microvascular disease affecting the periventricular white matter. ■ Effects vary based on the size, location, and number of infarcts. Risk Factors ■ Hypertension. ■ Diabetes. ■ Smoking. ■ Obesity. ■ Hyperlipidemia. ■ Atrial fibrillation. ■ Coronary artery disease. ■ Advanced age. Clinical Manifestations ■ Presentation and progression of cognitive impairment are variable. •• Classically demonstrates a stepwise deterioration corresponding with the occurrence of micro-infarcts (i.e., multi-infarct dementia). •• May present with acute onset followed by partial improvement. •• May have an insidious onset with gradual decline similar to AD. ■ Complex attention and executive function are the cognitive domains typically affected in small vessel disease. ■ Confirmation of the diagnosis requires neuroimaging with clinical correlation. Treatment ■ No cure or truly effective treatment yet available. ■ Manage and mitigate risk factors with the goal of preventing future strokes. ■ Symptomatic treatment is similar to AD. A 68-year-old female is brought to the clinic by her husband. He reports that his wife has recently seemed confused and overly emotional. The patient is able to complete her daily activities, but reports increased difficulty with planning and decision-making. Her medical history is significant for hypertension and transient ischemic attacks (TIAs). A physical exam reveals a carotid bruit. What is the likely diagnosis? Mild vascular NCD. LEWY BODY DISEASE (LBD) As reflected in its name, the major pathologic features of LBD are Lewy bodies (pathologic aggregations of alpha-synuclein) and Lewy neurites in the brain, primarily in the basal ganglia. NEUROCOGNITIVE DISORDERS KEY FACT A lesion to the frontal lobe can manifest with a spectrum of symptoms including personality changes, disinhibition, inappropriate behavior, aggression, apathy, amotivation, and paranoia.

104 NEUROCOGNITIVE DISORDERS Clinical Manifestations ■ Progressive cognitive decline. ■ Core features: ■ Suggestive features: ■ Indicative biomarkers: Diagnosis Treatment ■ Levodopa-carbidopa for Parkinsonism. ■ Commonly coexists with AD and/or cerebrovascular disease as NCD due to multiple etiologies. •• Waxing and waning of cognition, especially in the areas of attention and alertness. •• Visual hallucinations—Usually vivid, colorful, well-formed images of (commonly small) people, animals, or objects. •• Rapid eye movement (REM) sleep behavior disorder (not included in the DSM-5 core features but often associated)—Violent movements during sleep in response to dreams (often fighting). •• Development of extrapyramidal signs (Parkinsonism) at least 1 year after cognitive decline becomes evident. •• Pronounced antipsychotic sensitivity (i.e., extrapyramidal symptoms). •• Postural instability and recurrent falls. •• Loss of consciousness or transient unresponsiveness. •• Autonomic dysfunction. •• Olfactory agnosia or diminished sense of smell. •• Nonvisual hallucinations and delusions. •• Excessive sleepiness. •• Depression, apathy, and anxiety. •• REM sleep without atonia (RWSA) demonstrated via polysomnography. •• Decreased 123iodine-MIBG uptake on myocardial scintigraphy. •• Evidence of reduced dopamine receptor uptake in the basal ganglia via SPECT or PET. ■ Definitive diagnosis can only be made with autopsy. ■ Possible NCD with Lewy bodies: Only one core feature without evidence from indicative biomarkers OR one or more indicative biomarker(s), but no core clinical features. ■ Probable NCD with Lewy bodies: Two or more core features OR one core feature and one or more indicative biomarker(s). ■ Cholinesterase inhibitors for cognitive and behavioral symptoms. ■ Quetiapine or clozapine for psychotic symptoms. •• Use the lowest effective dose for the shortest period of time possible. •• Monitor closely for adverse effects, such as extrapyramidal signs, sedation, increased confusion, autonomic dysfunction, and signs of neuroleptic malignant syndrome (NMS). •• Not as effective as in idiopathic Parkinson disease. •• May exacerbate psychosis or REM sleep behavior disorder. ■ Melatonin and/or clonazepam for REM sleep behavior disorder.

FRONTOTEMPORAL DEGENERATION (FTD) ■ FTD includes a diverse group of clinical and pathological disorders that typically present between the ages of 45 and 65. ■ Approximately 40% are familial, and 10% are autosomal dominant. Clinical Manifestations ■ Cognitive deficits in attention, abstraction, planning, and problem solving. ■ Behavioral variant: •• Disinhibited verbal, physical, or sexual behavior. •• Overeating or oral exploration of inanimate objects. •• Lack of emotional warmth, empathy, or sympathy. •• Apathy or inertia. •• Perseveration, repetitive speech, rituals, or obsessions. •• Decline in social cognition and/or executive abilities. ■ Language variant (primary progressive aphasia): •• Difficulties with speech and comprehension. ■ Relative sparing of learning/memory and perceptual-motor function. ■ Many individuals have features of both the behavioral and language variants. ■ Increased sensitivity to adverse effects of antipsychotics. Pathology Marked atrophy of the frontal and temporal lobes. Diagnosis ■ Definitive diagnosis cannot be made until autopsy. ■ FTD is probable if frontotemporal atrophy is evident on structural imaging or hypoactivity is visualized on functional imaging with clinical correlates. Treatment ■ Symptom-focused. ■ Serotonergic medications (e.g., SSRIs, trazodone) may help reduce disinhibition, anxiety, impulsivity, repetitive behaviors, and eating disorders. HIV INFECTION ■ HIV is the most common infectious agent known to cause cognitive impairment. ■ In patients with HIV, 33% have asymptomatic neurocognitive impairment that appears on exam, 12% have mild NCD, and 2% have major NCD. ■ Severe forms of NCD due to HIV infection have become much less common with the widespread use of antiretroviral drugs. Risk Factors ■ History of severe immunosuppression. ■ High viral loads in the CSF. ■ Advanced HIV infection. NEUROCOGNITIVE DISORDERS

106 NEUROCOGNITIVE DISORDERS Clinical Manifestations Treatment HUNTINGTON DISEASE (HD) ■ Autosomal dominant mode of inheritance. Clinical Manifestations ■ Average age at diagnosis is 40 years. ■ Increased rate of suicide (7%). Diagnosis PARKINSON DISEASE (PD) ■ Variable presentation depending on the part(s) of the brain affected. ■ Decline may be observed in executive functioning, attention, working memory, and psychomotor activity. ■ Psychiatric and neuromotor symptoms may also be present. Diagnosis Mild or major NCD attributable to confirmed HIV infection. ■ Antiretroviral therapy (ART) improves cognition in some patients. ■ Psychostimulants target fatigue, apathy, and psychomotor retardation. ■ A genetic disorder resulting from trinucleotide (CAG) repeats in the gene encoding the huntingtin (HTT) protein on chromosome 4. ■ Characterized by a triad of motor, cognitive, and psychiatric symptoms. ■ Cognitive decline and behavioral changes can precede onset of motor signs by up to 15 years. ■ Executive function is the primary cognitive domain affected. ■ Psychiatric manifestations include depression, apathy, irritability, obsessions, impulsivity, paranoia, delusions, and hallucinations. ■ Patients are often aware of deteriorating mentation. ■ Movement disorders include chorea (jerky, dance-like movements) and bradykinesia. ■ Extrapyramidal movement disorder in an individual with either a family history of HD or genetic testing that confirms an increased number of CAG trinucleotide repeats in the HTT gene. ■ Mild or major NCD may be diagnosed prior to onset of motor signs if an individual is determined to be at risk based on family history or genetic testing. Treatment Symptom-directed therapy with tetrabenazine or atypical (second-generation) antipsychotics. ■ An idiopathic, progressive neurodegenerative disease characterized by depletion of dopamine in the substantia nigra pars compacta (located in the basal ganglia). ■ Up to 75% of patients with PD meet the criteria for major NCD, typically in advanced disease.

Clinical Manifestations ■ Motor signs include muscular (lead-pipe or cogwheel) rigidity, resting tremor, bradykinesia, and postural instability. ■ Cognitive manifestations consist of executive dysfunction and visuospatial impairments. ■ Depression, anxiety, personality changes, and apathy are common. ■ Psychotic symptoms, including visual hallucinations and paranoid delusions, may result from the disease itself or from adverse effects of the medications used to treat the motor symptoms. ■ Prodromal symptoms and signs (e.g., micrographia, hyposmia, hypogeusia, constipation, personality changes, mood disorders, and REM-sleep behavior disorder) may occur up to two decades before motor abnormalities appear. Diagnosis ■ Diagnosis of PD requires the presence of bradykinesia and either tremor or rigidity. ■ Associated with asymmetry of motor symptoms. ■ Mild or major NCD is attributed to PD if cognitive decline appears after the onset of motor symptoms and no other underlying etiology is identified. ■ Typically responds favorably to dopaminergic therapy. Treatment ■ Motor symptoms are most commonly treated with carbidopa-levodopa and/or dopamine agonists. ■ High-frequency deep brain stimulation may lessen severe motor symptoms, but is associated with increased risk of depression. ■ Cholinesterase inhibitors are used to target cognitive symptoms and may also ameliorate some of the neuropsychiatric symptoms (hallucinations). ■ Psychotic symptoms may respond to a reduction in the dose of dopamine agonists. ■ Low-dose quetiapine and clozapine are the preferred medications for treatment of psychosis. Avoid other antipsychotics since they can worsen the motor symptoms of PD. ■ Pimavanserin is a serotonergic medication approved by the FDA to treat PD psychosis. PRION DISEASE (TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES) ■ A form of subacute spongiform encephalopathy caused by proteinaceous infectious particles (prions). ■ The most common type is sporadic Creutzfeldt–Jakob disease (sCJD). ■ Variant CJD (vCJD, aka bovine spongiform encephalopathy or mad cow disease) is a rare food-borne prion disease. ■ Up to 15% are familial (autosomal dominant), involving prion protein (PRNP) gene mutations. ■ Less than 1% of cases are iatrogenic. Clinical Manifestations ■ Insidious onset with rapidly progressive cognitive decline (over months to years). NEUROCOGNITIVE DISORDERS KEY FACT Symptoms of Parkinson disease can be exacerbated by antipsychotic medications. KEY FACT Rapidly progressive cognitive decline with myoclonus is suggestive of Creutzfeldt–Jakob disease.

 ■ Presentation and progression vary by type. ■ Typical clinical features of CJD. Evaluation ■ EEG: Periodic sharp wave complexes. Diagnosis Treatment ■ No effective treatment yet available. WARDS QUESTION Q: What are the “three Ws” of NPH? A: Wobbly (abnormal gait), Wet (urinary urgency → incontinence), Wacky (cognitive impairment). Clinical Manifestations ■ Classically presents with a clinical triad: •• Gait disturbance (“Wobbly”).

- May begin as urinary urgency. •• Myoclonus (often triggered by startle response) is found in most individuals. •• Visual (e.g., hallucinations, cortical blindness) or cerebellar disturbance (e.g., nystagmus, ataxia). •• Pyramidal (e.g. positive Babinski sign, spasticity, hyperactive reflexes) or extrapyramidal dysfunction (e.g., bradykinesia, rigidity, dystonia). •• Akinetic mutism in end-stage disease. ■ Brain MRI: Hyperintensities in the caudate head, putamen, or at least two cortical regions on DWI or FLAIR. ■ CSF analysis: Positive RT QuIC assay and/or presence of 14-3-3 protein. ■ A diagnosis of probable sCJD requires either of the following scenarios: •• A neuropsychiatric disorder with a positive CSF RT-QuIC assay. •• Rapid progression of cognitive decline with two or more of the typical clinical features listed above AND typical findings on MRI, EEG, or CSF analysis. ■ Definitive diagnosis requires analysis of brain tissue obtained via biopsy or autopsy. ■

Death usually occurs within 1 year of diagnosis. NORMAL PRESSURE HYDROCEPHALUS (NPH) ■ NPH is a potentially reversible cause of cognitive dysfunction. ■ The etiology is either idiopathic or secondary to obstruction of CSF reabsorption sites due to infection (meningitis) or hemorrhage (subarachnoid or intraventricular).

- Most likely to be the first manifestation.
- Slow with short steps.
- Broad-based with outwardly rotated feet.
- Feet appear to be stuck to the floor (magnetic gait).
- Postural instability leads to recurrent falls. •• Urinary incontinence (“Wet”).
- Gait disturbance may interfere with reaching the toilet before urinary incontinence.
- In later stages, apathy may contribute.

•• Cognitive impairment (“Wacky”).

- Insidious onset.
- Executive dysfunction.
- Psychomotor retardation.
- Decreased attention.
- Apathy. •• Enlargement of ventricles out of proportion to cortical atrophy on imaging.
- Localized elevation of cerebrospinal fluid (CSF) pressure but normal opening pressures on lumbar puncture. •• Clinical improvement following CSF removal via lumbar puncture. Treatment ■ Placement of a shunt (usually ventriculoperitoneal) may improve symptoms. ■ Cognitive impairment is least likely to improve. NEUROCOGNITIVE DISORDERS

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