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Young-Onset Dementia

Dulanji K Kuruppu, BS Neuroscience, BS Biology, BA Psychology and
Indiana University School of Medicine, 5457 Fieldhurst Lane, Plainfield, IN 46168, Telephone: 317-450-8801

Brandy R Matthews, MD [Assistant Professor, Residency Program Director]
Department of Neurology, Indiana University School of Medicine, 355 W. 16th Street, Suite 4700, Indianapolis, IN 46202, Telephone: 317-944-4000, Fax: 317-963-7559

Dulanji K Kuruppu: dkuruppu@iupui.edu

Abstract

Young-onset dementia (YOD) is an neurological syndrome that affects behavior and cognition of patients younger than 65 years of age. Although frequently misdiagnosed, a systematic approach, reliant upon attainment of detailed medical history, collateral history from an informant, neuropsychological testing, laboratory studies, and neuroimaging, may facilitate earlier and more accurate diagnosis with subsequent intervention. The differential diagnosis of YOD is extensive and includes early-onset forms of adult neurodegenerative conditions including Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy body dementias, Huntington's disease, and prion disease. Late-onset forms of childhood neurodegenerative conditions may also present as YOD and include mitochondrial disorders, lysosomal storage disorders, and leukodystrophies. Potentially reversible etiologies including inflammatory disorders, infectious diseases, toxic/metabolic abnormalities, transient epileptic amnesia, obstructive sleep apnea, and normal pressure hydrocephalus also represent important differential diagnostic considerations in YOD. This review will present etiologies, diagnostic strategies, and options for management of YOD with comprehensive summary tables for clinical reference.

Keywords

young-onset dementia; early-onset dementia; neurodegenerative disease; dementia/reversible

Introduction

Young-onset dementia (YOD) is a devastating condition that typically afflicts patients between the ages 45-64 years. Common symptoms include behavioral changes, psychiatric manifestations, and cognitive decline. This eventually leads to a deterioration of day-to-day function, which affects not only the patient but also causes significant caregiver burden. Approximately 67-98 per 100,000 people aged 45-64 years carry a diagnosis of YOD.[1-3] Although less likely to be considered in differential diagnoses than the more common late-

Corresponding Author: Brandy Matthews, MD, Department of Neurology, Indiana University School of Medicine, Goodman Hall, Suite 4700, 355 W. 16th Street, Indianapolis, IN 46202, brmatthe@iupui.edu.

onset dementias (LOD), a growing awareness and, consequently, increasing number of cases of YOD has heightened its profile in recent years.

YOD often presents in its early stages as behavioral changes, depression, and psychosis, and patients may not develop cognitive deficits until later in the disease process.[4] This invariably leads to a longer time-to-diagnosis.[5] Despite the advancement of methods of diagnosis, YOD is frequently misdiagnosed.[4] In order to avoid misdiagnosis, it is critically important to attain a thorough medical history, collateral behavior history from an informant, and detailed family history in advance of ordering additional studies. In some cases of YOD, treatment can completely reverse symptoms while in others, early diagnosis and intervention can improve quality of life and inform decisions regarding family planning.

The differential diagnosis within YOD is extensive. Specifying diagnostic categories such as, early-onset forms of adult neurodegenerative conditions, late-onset forms of childhood neurodegenerative conditions, and reversible conditions, may facilitate a more timely and accurate diagnosis. Early-onset forms of adult neurodegenerative conditions, such as Alzhiemer's disease (AD), are the most common cause of YOD. Late-onset forms of childhood neurodegenerative conditions, such as mitochondrial disorders, lysosomal storage disorders, and leukodystrophies, are also important considerations and represent the most common causes of YOD in patients younger than 35 years.[6] Perhaps the most important category of YOD is the reversible causes of YOD, which include inflammatory, infectious, toxic, and metabolic etiologies. The multiple neuropathologies differ in terms of additional symptoms, blood test results, characteristic findings on neuroimaging, cerebrospinal fluid (CSF) analyses, neurophysiology studies, and tissue biopsy. Several of the YODs have hereditary forms, and genetic testing is an increasingly popular method for confirming diagnoses and evaluating risk in family members.

Due to the broad nature of the topic, much of the information in this review is tabulated, in an effort to facilitate a rational approach to differential considerations, diagnostic strategies, and management.

Diagnosis

Diagnostic Delay and Misdiagnosis

There is a considerable delay in the diagnosis of YOD compared to LOD.[5] On average, it is not until 2 to 3 years after the onset of symptoms that YOD is diagnosed.[7] In part, this delay is explained by patients and family members not considering the possibility of dementia at a young age, which delays seeking medical advice. Even when subject to evaluation, YOD is often misdiagnosed for a variety of reasons. Clinicians, who are more familiar with LOD, are less likely to consider a diagnosis of dementia in young patients. Also, YOD has a broader differential diagnosis compared to LOD.[4] Although AD is the most common cause of YOD, it accounts for only 34% of YOD compared to about 80% of LOD.[3] Another reason for misdiagnoses in YOD are the often prominent psychiatric manifestations and affected nonmemory cognitive domains.[4] Changes in personality, behavior, and cognition are often deemed referable to mood disorders such as depression or anxiety. Admittedly, the distinction between neurologic and psychiatric illness in this age group is often difficult, and

there is considerable overlap given shared neuroanatomy and neurochemistry. Signs and symptoms that suggest a psychiatric rather than neurodegenerative diagnosis include abrupt onset, identifiable emotional precipitant, and lack of progression over time. Periodic clinical reassessment also helps clarify this distinction.[8] Early and accurate diagnosis of YOD is critically important as it may impact prognosis and management.

Clinical Assessment

The first step towards accurate diagnosis is performing a thorough clinical assessment. This involves obtaining a clinical history including symptoms in all cognitive domains (not exclusively memory), behavioral features and psychiatric history, degree of functional impairment, temporal profile of mode of onset and progression of symptoms, past medical history, social history including educational and occupational attainment, and family history of neuropsychiatic illness. Other important points may include specific dementia risk factors including head injury with loss of consciousness or alcohol/drug exposure.[4,8] It is critically important to obtain a collateral history from a reliable informant, as patients may have little insight into their deficits or forget important historical details. Once this information is gathered, the clinician should perform a thorough neurological exam with special attention to pyramidal, extrapyramidal, and cerebellar signs. Bedside cognitive assessment with screening instruments such as the Mini Mental State Examination[9] or the Montreal Cognitive Assessment[10] and formal neuropsychological testing are valuable to clarify the affected cognitive domains. The combination of historical details, cognitive and behavioral features, and findings on the neurological examination guide the generation of diagnostic hypotheses related to the presumed underlying neuroanatomy. This “dementia-plus” algorithm has been advocated by other in the field and provides a useful framework for the clinical assessment of YOD.[11]

Laboratory investigations

Laboratory investigations are important in the diagnosis of YOD; however a rational, step-wise approach is advised. It is advisable to perform simple tests before those that are complex and invasive.[11] Blood tests may be useful in diagnosing toxic/metabolic encephalopathies, infectious etiologies such as HIV or syphilis, and autoimmune illnesses. All patients with YOD should have neuroimaging (preferably MRI) and possibly CSF analysis according to professional organization guidelines.[12] Patterns of brain atrophy and signal change on a variety of MRI sequences are useful in narrowing the differential diagnosis. In patients who demonstrate minimal changes on MRI, FDG-PET imaging may be a useful adjunct to detect regions of hypometabolism. CSF analysis may facilitate the identification of infectious or inflammatory etiologies of YOD. Neurophysiology studies such as electroencephalography (EEG), electromyography (EMG), and nerve conduction studies (NCS) can reveal associated seizure activity, myopathy, and neuropathy, respectively. Tissue biopsy may be helpful to diagnose mitochondrial disorders via muscle biopsy and lysosomal storage disorders or leukodystrophies via enzyme assay of skin fibroblasts or leukocytes. Cerebral biopsy, although not often performed, has proven to be a relatively safe and efficacious method of diagnosing dementia, and should be considered if there is even a low index of suspicion for a potentially treatable disease.[13] Genetic testing, although cost-prohibitive if not ordered selectively, is available to confirm many YOD

diagnoses for patients, as well as to predict susceptibility in family members. If families choose to undergo genetic testing, it should be preceded by formal genetic counseling.

Early-Onset Forms of Adult Neurodegenerative Disorders

Early-onset forms of adult neurodegenerative disease are the most common cause of YOD in patients under age 65. Of these, the most common is AD followed by vascular dementia (VaD) and frontotemporal dementia (FTD).[4] Other causes include alpha synuclein pathologies, Huntington's disease, Creutzfeldt Jakob disease, chronic traumatic encephalopathy, and Fahr's disease (Table 1). Many of these diseases are associated with genetic mutations rendering an accurate and detailed family history important. Detailed descriptions of AD, FTD, dementia with Lewy Bodies, and prion diseases are included elsewhere in this issue.

While cognitive decline is a common manifestation of all of the early-onset forms of adult neurodegenerative disease, they may be differentiated on the basis of associated symptoms and neuroimaging findings. Genetic testing and post-mortem neuropathological studies may confirm diagnoses. Although pharmacotherapy is available to target specific symptoms, disease-modifying therapies are not currently available, with the notable exception of vascular disease, which may be impacted by cerebrovascular risk factor management.

AD classically presents with memory decline and may progress to include psychiatric and motor symptoms, both of which may be more common in early-age of onset forms.[14] Diagnosis is based on clinical and family history, characteristic neuroimaging, CSF analysis, and selective genetic testing in early-onset forms.[15-17] Post-mortem cerebral biopsy reveals beta amyloid plaques and intraneuronal neurofibrillary tangles, which represent targets for future disease-modifying therapies.[18] Cognitive and behavioral symptoms of AD are treated symptomatically with cholinesterase inhibitors and memantine.[19,20]

The most common presentation of VaD, referable to systemic vascular pathology and known cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, and tobacco smoking, manifesting as static cognitive deficits arising in the context of identifiable large-vessel stroke, are beyond the scope of this review. Other causes of vascular dementia in younger patients include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral amyloid angiopathy (CAA). In addition to cerebrovascular disease, there are symptoms specific to each disorder: migraine with aura and mood disturbance in CADASIL[21], and headache with focal neurological deficits in CAA.[22] Diagnosis is often made via MRI, with anterior temporal lobe involvement in CADASIL[23] and characteristic hemosiderin deposition in CAA.[24] Definitive diagnosis of CADASIL and CAA may be accomplished with EM of skin biopsy,[25] neuropathology,[24] and gene testing.[26,27] VaD, in general, may be treated with antiplatelet therapy and lowering blood pressure and cholesterol, but the role and benefit of these interventions in CADASIL and CAA has not been clearly established.[28,29] For example, use of aspirin in CAA may lead to increased risk of intracerebral hemorrhage.[30]

Frontotemporal dementia (FTD) presents with early-onset behavior change or aphasia and may have associated motor features.[31] Among those younger than 60 years old, FTD is the

most common neurodegenerative cause of dementia.[32] Diagnosis is based on clinical history, characteristic neuroimaging, and in some cases, genetic testing.[33,34,35] Unlike AD, frontotemporal dementia has not been shown to improve symptomatically with cholinesterase inhibitors and memantine.[36]

Alpha synuclein pathology is considered to be the cause of both Lewy body dementia (LBD) and multiple system atrophy (MSA). LBD is characterized by dementia with fluctuating alertness, visual hallucinations, and parkinsonism. Diagnosis is made with clinical history and examination; routine neuroimaging is not as helpful for this diagnosis except to rule out other causes. Polysomnography may be useful to confirm the presence of REM sleep behavior disorder (RBD), a commonly associated feature of alpha-synucleinopathies.[37] Symptomatic treatment involves cholinesterase inhibitors, atypical neuroleptics, and occasionally levodopa.[38] MSA is associated with parkinsonism, autonomic failure, ataxia, pyramidal signs, and RBD.[39] Diagnosis may be based on poor response to levodopa, which helps distinguish MSA from Parkinson's disease,[40] characteristic neuroimaging including the brainstem “hot cross bun” sign,[41] and genetic testing in some cases.[42,43]

Huntington's disease (HD) results from an autosomal dominant mutation on chromosome 4 with CAG trinucleotide repeats in the huntingtin (*HTT*) gene.[44] In early adulthood, patients present with chorea, changes in personality, and depression.[45] Gene testing quantifying the number of repeats on *HTT* can confirm diagnosis. HD is susceptible to genetic anticipation in which successive generations have increased symptom severity due to increasing instability of CAG repeats during gamete formation.[44] MRI shows atrophy of the caudate and putamen.[46] Postmortem neuropathology reflects this finding with degeneration of neurons in the caudate and putamen as well as intraneuronal inclusions containing huntingtin.[47] Symptoms can be treated with typical and atypical neuroleptics, benzodiazepines, tetrabenazine, and supportive measures, but the illness is uniformly fatal.[48] HD serves as a model for genetic testing rationale and genetic counseling methods for early-onset forms of adult neurodegenerative diseases, as it was one of the first YODs in which genetic mutations were identified as a significant contributor to pathogenesis.

Creutzfeldt-Jakob disease is a rapidly progressive neurodegenerative disease caused by abnormal conformation of prion proteins, which is characterized by dementia, ataxia, and myoclonus.[49] Diagnosis of this disorder is based on characteristic neuroimaging with cortical ribboning and basal ganglia and thalamic changes on diffusion-weighted and FLAIR sequences,[50] EEG pattern with periodic sharp waves, CSF analysis with 14-3-3 protein elevation,[51] and in some cases genetic testing.[52] Neuropathology can confirm diagnosis, but is complicated due to issues with transmissablity.[51]

Chronic traumatic encephalopathy (CTE) has been recently emphasized due to the growing number of high-profile athletes who are suffering this disorder as a result of prior repetitive head trauma. CTE leads to impairment in executive function, depression, apathy, lack of impulse control, and parkinsonism.[53] Beyond the clinical history, there are no definitive diagnostic methods aside from post-mortem neuropathology, which shows aggregates of hyperphosphorylated tau and TDP-43, atrophy of cerebral and medial temporal lobes, ventriculomegaly, and large cavum septum pellucidum.[54] Treatment is symptomatic.

Fahr's disease is another less common and ill-defined neurodegenerative disorder that presents with changes in movement, speech, and behavior.[55] Head CT scan is the preferred diagnostic imaging tool and reveals bilateral calcium deposits in the basal ganglia.[56] Routine lab studies are normal, but CSF may show increased homocarnosine.[57] Genetic testing may be useful if there is a convincing family history.[58] Neuropathological examination reveals calcium deposits in the basal ganglia and within the walls of arteries and veins.[59]

Late-Onset Forms of Childoohd Neurodegenerative Disorders

Late-onset forms of childhood neurodegenerative disorders are the most common cause of YOD in patients under age 35[6], and warrant careful consideration in all patients presenting with YOD between the ages of 30-50 years. Patients may have normal early development but may have subclinical onset in early childhood.[6] Mitochondrial disorders, lysosomal storage disorders, and leukodystrophies all represent childhood neurodegenerative illnesses with well-described adult-onset forms (Table 2). Accurate and detailed family history is of critical importance in clinical assessment of these patients due to the hereditary features of their illnesses.

Mitochondrial disorders, which include mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and Kearns-Sayre syndrome, are rare disorders characterized by poor growth, muscle weakness, problems with vision and hearing, and multi-organ involvement including the nervous system.[60-62] The symptoms are quite variable because the distribution of defective mitochondrial DNA varies from one organ to another. Diagnosis is made on the basis of increased lactate in blood and CSF,[63] increased protein in CSF, characteristic neuroimaging with fluctuating abnormalities defying typical vascular distributions,[64-67] electroencephalography (EEG), electromyography (EMG) with nerve conduction studies (NCS),[68] electrocardiography (EKG), muscle biopsy,[69] respiratory chain studies, and genetic testing.[70-72] Of these studies, muscle biopsy and genetic testing are often the key to confirming diagnosis.

Lysosomal storage disorders include Tay Sachs disease, Gaucher's disease type 2 and 3, Niemann-Pick disease type C, Fabry's disease, and Kuf's disease. All are rare disorders that commonly cause developmental delay, deafness, blindness, hepatosplenomegaly, cardiac and pulmonary problems, and neurological dysfunction.[73-78] Tay Sachs disease and Gaucher's disease, in particular, are more common among the Ashkenazi Jewish population. Enzyme assays[75-80] and genetic testing[81-85] are utilized to arrive at a definitive diagnosis, but this can be supplemented in some instances with bone marrow exam,[75] neuroimaging,[86] and neuropathological confirmation from nerve or brain biopsy.[78,80,87,88]

Leukodystrophies that cause YOD include adrenoleukodystrophy, metachromatic leukodystrophy, Alexander disease, leukoencephalopathy with vanishing white matter, Pelizaeus-Merzbacher disease, adult polyglucosan body disease, and cerebrotendinous xanthomatosis. All are characterized by white matter pathology which may lead to cognitive dysfunction and behavioral problems, movement and speech disorders, problems with vision and hearing, and feeding difficulties.[89-94] MRI T2-weighted and FLAIR sequences reveal

hyperintensity in affected white matter areas of the brain, and are a key to pursuing a more specific leukoencephalopathy diagnosis.[91,95-100] Blood work,[90,101] enzyme assays,[90,102,103] MR spectrospcopy,[98,104,105] electrophysiology,[93,106] CSF analysis,[107] genetic testing,[108-114] and neuropathology with brain or nerve biopsy[89,115-117] may also aid in diagnosis.

Unfortunately, as with young-onset forms of adult neurodegenerative diseases, there are currently no therapies that can completely reverse these disease processes once neuronal death has occurred. Symptomatic therapy for mitochondrial disease may be possible with supplementation using coenzyme Q10, L-carnitine, L-arginine, and a recommendation for aerobic exercise.[118-120] Enzyme replacement therapy and bone marrow transplant may be an option for patients with identifiable lysosomal storage disorders.[75,121] Dietary changes and stem cell transplants may benefit patients with defined leukodystrophies.[90,101,122,123] It is likely in the best interest of such patients to facilitate referral to a center specializing in the treatment of these disorders in an effort to explore the use of orphan drugs and emerging biotechnology.

Reversible Forms of Young-Onset Dementia

It is most important for clinicians caring for patients with YOD to have a heightened awareness of potentially reversible forms of YOD. Reversible etiologies include inflammatory disease, infectious disease, toxic/metabolic disorders, and other, not easily categorized causes (Table 3). These diseases may present at any age and progress over variable lengths of time in advance of accurate diagnosis and treatment. A variety of symptoms may accompany the cognitive and functional decline, depending on the neuroanatomic substrate of the pathology.

The inflammatory causes of YOD include multiple sclerosis, neurosarcoidosis, and paraneoplastic and autoimmune limbic encephalitis. Multiple sclerosis is classically characterized by multi-focal neurological deficits dispersed in time, which may include cognitive deficits associated with sensory and motor dysfunction, changes in vision, and ataxia.[124] Neurosarcoidosis may be characterized by neuropathy, neuroendocrine dysfunction, focal neurological deficits, myelopathy, hydrocephalus, and meningitis.[125] Paraneoplastic and autoimmune limbic encephalitis is associated with auto-antibodies or the inflammatory response to tumors outside the nervous system and may cause changes in cognition, mood, behavior, and seizures.[126] Diagnosis is based on clinical history and examination in addition to blood work,[125,126] neuroimaging,[124-127] CSF,[125] EEG,[126] and in some cases neuropathology from brain or nerve biopsy.[125,128] Treatment is typically immunosuppression, with the empiric use of steroids or other more disease-specific therapies.[125,129-133]

The infectious etiologies of YOD include HIV dementia, neurosyphilis, Whipple disease, and progressive multifocal leukoencephalopathy (PML). In addition to cognitive decline, these disorders have the following additional symptoms: mood disorder and systemic illness in HIV dementia;[134] meningitis and tabes dorsalis in neurosyphilis;[135] arthralgia, GI symptoms, oculomasticatory myorhythmia, and ataxia in Whipple disease;[136] and changes in vision, hemiparesis, and ataxia in PML.[137] Diagnosis is facilitated by targeted blood

work,[137-139] CSF,[138,140] characteristic neuroimaging,[137,139] PCR,[141] and tissue biopsy.[136] Treatment includes disease-specific antivirals and antibiotics, as well as anti-inflammatory agents.[139,142-145]

Toxic and metabolic causes of YOD are numerous. Toxic causes include alcohol, other drugs of abuse, and heavy metal poisoning. In addition to changes in cognition, symptoms of abuse of alcohol and other drugs include psychiatric symptoms, ataxia, tremor, blurred vision, dysarthria, respiratory difficulties, and coma.[146] Non-cognitive symptoms of heavy metal poisoning include psychiatric symptoms, distal sensory and motor neuropathy, GI symptoms, and weakness.[147] The toxic encephalopathies are most often diagnosed using blood or urine levels of the toxin and described neuroimaging features.[146,147] Treatment involves cessation/avoidance of the toxin with intravenous fluid resuscitation and toxin specific antidotes, such as IV thiamine before glucose for alcohol overuse, flumazenil for sedative overdose, and chelation for heavy metal poisoning.[146-148]

Metabolic encephalopathy may be caused by excess ammonia in hepatic encephalopathy, uremia, hyponatremia, or hypernatremia. Symptoms include confusion and agitation with associated motor features.[149] The diagnosis typically relies on routine laboratory studies, and treatment is targeted toward the underlying disorder that has created the metabolic derangement.[150-153]

Endocrinopathies that may cause YOD are glucose dysregulation, thyroid or parathyroid dysfunction, Addison's disease, and Cushing's disease. Symptoms include confusion with weakness or fatigue, and other symptoms specific to each endocrinopathy.[154-160] Diagnosis relies on laboratory blood testing,[154,157,161,162] neuroimaging,[161,163] EEG,[164] or end-organ stimulation/suppression tests.[165,166] Treatment is targeted to the underlying cause.[154,157,160-162,167,168] Nutritional deficiencies in B12, thiamine, and niacin can also lead to YOD. Vitamin B12 deficiency may cause cognitive dysfunction with associated megaloblastic anemia, jaundice, fatigue, atrophic glossitis, or subacute combined degeneration of the spinal cord.[169] Thiamine deficiency may result in confusion with prominent anterograde memory deficits, ataxia, and ophthalmoplegia.[146] Dementia associated with niacin deficiency is associated with dermatitis and diarrhea.[170] Diagnosis most often relies on the combination of laboratory assessment of vitamin levels and neuroimaging.[146,169,170] Treatment is supplementation and nutritional support.[146,169,171]

There are several other potentially reversible causes of YOD. Wilson's disease is due to mutation of ATP7B gene which inhibits copper metabolism,[172] leading to cognitive dysfunction with prominent psychiatric features, associated movement disorders, liver disease, and Kayser-Fleischer rings on ophthalmological exam.[173] Diagnostic laboratory features are low serum copper and ceruloplasmin with high urinary copper.[174] Treatment involves chelation with penicillamine, trientine, or zinc.[174] Transient epileptic amnesia (TEA) presents with recurrent episodes of anterograde memory loss.[175] EEG shows temporal lobe spikes, and neuroimaging often reveals atrophy of the hippocampus. The cognitive symptoms may be reduced with the initiation of anticonvulsants, although accumulated hippocampal pathology in TEA is not reversible.[175]

Obstructive sleep apnea (OSA) may present as cognitive dysfunction as a result of hypoxemia or sleep deprivation.[176] It is also an independent risk factor for stroke and, as such, may contribute to vascular dementia.[177] Diagnosis is confirmed with polysomnography, and treatment involves behavior modification with weight loss and sleep position counseling, positive airway pressure, oral devices, or surgery.[178] Normal pressure hydrocephalus (NPH) can also present as dementia in variable combination with gait disturbance and urinary incontinence. After the diagnosis is relatively confirmed via neuroimaging and ancillary testing, it can be treated neurosurgically, with variable success, using a ventricular shunt.[179]

As the description implies, reversible forms of YOD do potentially respond to disease-modifying therapies. In summary, the inflammatory diseases are treated with immunosuppression, the infectious diseases with antivirals or antibiotics, toxins with cessation of exposure and antidote, metabolic derangements and endocrinopathies with correction of electrolyte and hormone levels, and nutritional deficiencies with supplementation. It is important to recognize that some of the disorders described as potentially reversible, including multiple sclerosis,[129-132] progressive multifocal leukoencephalopathy,[144,145] HIV dementia,[139] and thiamine deficiency[146] may cause irreversible damage to the nervous system in advance of the diagnosis and intervention. Reversible causes of YOD should be investigated early and thoroughly in all cases of YOD, given the implications for patients and caregivers.

Treatment

Pharmacological Treatment

The approved pharmacological treatments for young-onset forms of adult neurodegenerative diseases are similar to those for LOD.[8] Acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine may offer symptomatic benefit in AD but do not modify the disease progression.[19] The use of these medications in other forms of YOD is still under investigation, although studies in FTD and CADASIL have been disappointing.[180,181] Memantine, a NMDA receptor antagonist, has also shown some symptomatic benefit in AD when used alone or in combination with acetylcholinesterase inhibitors;[20] however, trials in FTD patients have been not demonstrated clear benefit.[182,183] Treatment strategies for adult-onset forms of childhood neurodegenerative disorders and potentially reversible forms of YOD are included in Tables 2 and 3.

Depression frequently accompanies all varieties of YOD and should be targeted with antidepressants. Selective serotonin reuptake inhibitors are suggested, as they do not tend to worsen cognition. Sedatives or atypical neuroleptics may be required if a patient exhibits refractory psychotic symptoms, poses a threat to himself or others, or if other behavioral treatments have failed. However, these drugs may result in extrapyramidal syndromes and may be associated with increased mortality risk, such that they should be used at the lowest effective dosage for the shortest time possible.[184] Regardless of the pharmacoptherapy, it is important to prescribe medications according to current guidelines and ensure routine follow-up.

Non-Pharmacological Treatment

Non-pharmacological treatment may be equally as important as pharmacological treatment in YOD. It is very important to assess safety in YOD as patients often lack insight and demonstrate impaired judgment. Environmental modification, including distraction with exercise or activities and restricting access to food and harmful instruments, plays an important role. Patients who wish to drive should be evaluated by an occupational therapist. Occupational and speech therapists may assist with other daily activities and alternative modes of communication. Support groups may help patients and caregivers share stories with others in similar situations. Legal counsel may be helpful; it is advisable for patients to create living wills and select a power of attorney early in the course of YOD. Home nursing or residential nursing care are often important resources for patients and families in later stages of YOD.

An important aspect of non-pharmacological treatment is acknowledgement of caregiver burden. YOD is particularly devastating because it strikes patients during their most productive years. Leaving the work force may accelerate a loss of autonomy and the premature loss of income and employment benefits, including health insurance and retirement, may be particularly detrimental to families dealing with YOD.[185] Psychological and emotional struggles such as social isolation are common as progressive disability and changes in behavior inhibit the patient and caregiver from interacting with others.[7] Caregivers of YOD patients report a higher level of stress, burden, and depression compared to caregivers of LOD. This is likely the result of a high proportion of behavioral disturbances in YOD patients, lack of formal and informal support for YOD caregivers, and inadequate preparation for the role of caregiving at a young age.[186] Treatment of YOD must also target caregivers to ensure that they have access to community/home support and respite options.

Conclusion

YOD refers to dementia affecting individuals younger than 65 years of age and is characterized by protean manifestations that reflect extensive and diverse neuropathological substrates. While the broad differential diagnosis of YOD can be divided into the categories of early-onset forms of adult neurodegenerative disorders, late-onset forms of childhood neurodegenerative disorders, and potentially reversible forms of YOD, employing a diagnostic algorithm that screens for typical causes of cognitive and behavioral dysfunction followed by a rational approach to ancillary testing that is based on selected historical and examination features is advised. A systematic approach to diagnosing YOD allows for early diagnosis and intervention with the ultimate goal of symptom reversal or, at minimum, improvement in quality of life for patients and caregivers. The development of future disease-modifying interventions will continue to rely upon the ability of clinicians to accurately diagnose YOD in its earliest stages, ideally even while cognitively asymptomatic.

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Table 1

Early-onset forms of adult neurodegenerative disorders

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Alzheimer dementia[14-20]	Sporadic AD mutation of *APP*, *PSEN1*, or *PSEN2*	40-50 years	8-10 years	Behavioral features (agitation, withdrawal, hallucinations), motor symptoms, myoclonus	CT or MRI (cerebral cortical atrophy); FDG-PET (cerebral hypometabolism posterior> anterior); CSF (low Aβ 42 and high tau); genetic testing	Cholinesterase inhibitor (donepezil, rivastigmine, galantamine), NMDA receptor antagonist (memantine)
Vascular dementia						
CADASIL[21,23,25,26,28]	AD mutation of *NOTCH3* on Chr19	30-60 years	Variable	Psychiatric features (mood disturbance, apathy), migraine with aura, cerebrovascular disease, seizures	MRI (begin asT2 hyperintensities in temporal lobe/ external capsule and subcortical infarcts, progress to diffuse white matter changes); EEG (epileptiform discharges over affected areas); skin biopsy (granular osmophilic material in media of arterioles on EM); genetic testing	Antiplatelet therapy, control hypertension and hypecholesterolemia
Cerebral amyloid angiopathy[22,24,27,29,30]	Sporadic AD mutations in the *APP*, *CST3*, or *ITM2B* genes	45-70 years	Variable	Lobar intracerebral hemorrhage, headache, focal neurological deficits	MRI (gradient echo sequence with multiple microbleeds in cortex; routine sequences may reveal lacunar infarctions or confluent white matter changes); genetic testing	Lipid lowering agents
Behcet's disease[187,188]	Autoimmune (triggered by infection) associated with HLA-B51	20-40 years	Variable	Oral/urogenital/ cutaneous lesions, ocular disease, vascular disease, arthritis, seizures, psychiatric symptoms and	MRI (lesions of corticospinal tract, brainstem, periventricular white matter, spinal cord, basal ganglia); CSF (elevated opening pressure, increased	Glucocorticoids, immunosuppressant medications

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Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
				personality change personality change	protein or pleocytosis)	
Frontotemporal dementia[31,33-36]	Sporadic AD mutation of *MAPT* or *GRN* on Chr17 or hexanucleotide repeat *C9ORF72*	35-87 years	3-12 years	Behavior and personality change, aphasia, dysarthria, dysphagia, associated parkinsonism or motor neuron disease	CT or MRI (regionally specific frontal and temporal atrophy); FDG-PET (anterior> posterior hypometabolism); genetic testing	SSRI
Alpha synuclein pathology						
Lewy body dementia[37,38,42]	Sporadic Rare mutations in *SNCA, SNCB*	50-83 years	10-15 years	Fluctuating alertness, visual hallucinations, parkinsonism, REM sleep behavior disorder	MRI (normal for age or mild atrophy of cortex and putamen); polysomnography for loss of muscle atonia in REM sleep	Cholinesterase inhibitor, SSRI, +/- low dose atypical neuroleptic, +/-levodopa
Multiple system atrophy[37,39-41,43]	Sporadic Rare associations with *SNCA* gene	54-60 years	6-10 years	Parkinsonism with anterocollis, autonomic failure, ataxia, pyramidal signs, REM sleep behavior disorder, nocturnal stridor	MRI (brainstem “hot cross bun” sign or hypointensity of extreme capsule); polysomnography for loss of muscle atonia in REM sleep; autonomic testing; genetic testing	**Poor response** to levodopa, florinef, or midodrine for orthostatic hypotension
Huntington's disease[44-48]	AD mutation of CAG repeats in *HTT* gene on Chr4	35-44 years	15-18 years	Chorea, prominent behavioral features and personality change	MRI (atrophy of caudate and putamen); genetic testing	Typical or atypical neuroleptics, tetrabenazine
Creutzfeldt Jakob disease[49-52]	Sporadic (sCJD) Acquired (vCJD) Iatrogenic (iCJD) Genetic (gCJD) AD mutation of *PRNP* on Chr20	30-50 years	2 months to 2 years	Ataxia, myoclonus, personality change	MRI (DWI and FLAIR sequences with cortical ribboning, hyperintense basal ganglia and thalamus); CSF (incr 14-3-3 protein); EEG (triphasic or sharp wave bursts every 0.5 to 2 sec); genetic testing	

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Fahr's disease[55-59]	Familial but no gene identified	30-50 years	Variable	Change in personality and behavior or psychosis, motor speech disorder, ataxia, movement disorder, seizures	CT (Ca deposits in bilateral basal ganglia or cerebellum); MRI (calcified areas of basal ganglia and cerebellum hypointense on T2 and hyperintense on T1 sequences); blood tests (**normal** Ca, P, Mg, alkaline phosphatase, calcitonin, PTH)	
Chronic traumatic encephalopathy[53,54]	Repetitive injury to brain (e.g. professional athletes, blast injury)	Variable	Variable	Depression, apathy, poor impulse control, multi-domain cognitive decline, variable parkinsonism	MRI (generalized and medial temporal lobe atrophy or ventriculomegaly)	

Abbreviations: CSF = cerebrospinal fluid
CT = computed tomography
MRI = magnetic resonance imaging
FDG-PET = fluorodeoxyglucose positron emission tomography
SPECT = single-photon emission computed tomography
DWI = diffusion weighted imaging
EM = electron micrography
EEG = electroencephalography
SSRI = selective serotonin reuptake inhibitor
REM = rapid eye movement
AD = autosomal dominant tomography
Chr = chromosome
HLA = human leukocyte antigen
PTH = parathyroid hormone

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Table 2

Late-onset forms of childhood neurodegenerative disorders

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Mitochondrial disorders						
MELAS[61,66,68,69,70,118,119]	Mutation in mitochondrial DNA gene *MT-TL1* and *MT-ND5*	2-10 years	10-35 years	Normal early development, short stature, generalized tonic-clonic seizures, headache, anorexia, vomiting, exercise intolerance, proximal limb weakness, stroke-like episodes, lactic acidosis, sensorineural hearing loss	MRI (T2 hyperintensity in posterior cerebrum, DWI signal changes in stroke-like regions); Blood tests (elevated lactate); CSF (elevated lactate, elevated protein but <100 mg/dL); EEG (generalized epileptiform discharges); CT (basal ganglia calcification); EMG and NCS; muscle biopsy (ragged red fibers that stain for cytochrome c oxidase or ragged blue fibers that stain for succinate dehydrogenase); respiratory chain studies (defect in complex I or IV); genetic testing	Coenzyme Q10, L-carnitine
MERRF[61,64,65,69,71,118]	Mutation in mitochondrial DNA gene *MT-TK*	Childhood	-	Normal early development, myoclonus, generalized epilepsy, ataxia, weakness, hearing loss, short stature, optic atrophy, Wolff-Parkinson-White syndrome	MRI (basal ganglia calcification, bilateral putaminal necrosis, atrophy of brain stem and cerebellum); Blood tests (elevated lactate and pyruvate); CSF (elevatedlactate and pyruvate, elevated protein but <100 mg/dL); EEG (generalized spike and wave discharges with background slowing or focal epileptiform discharges); EMG and NCS; EKG; muscle biopsy (ragged red fibers that do not stain for cytochrome c oxidase but stain for succinate dehydrogenase); respiratory chain studies; genetic testing	Coenzyme Q10, L-carnitine

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Kearns-Sayre syndrome[62,63,67,69,72,118]	Deletion of mitochondrial DNA	Before 20 years	-	Pigmentary retinopathy, progressive external ophthalmoplegia, cardiac conduction block, ataxia, deafness, diabetes mellitus and other endocrinopathies	MRI (hyperintensity of basal ganglia, brainstem, cerebral/cerebellar white matter);Blood tests (elevated lactate and pyruvate); CSF (elevated lactate and pyruvate, elevated protein >100 mg/dL); EMG and NCS; fasting serum glucose to screen for diabetes; EKG; muscle biopsy (ragged red fibers that do not stain for cytochrome c oxidase but stain for succinate dehydrogenase); respiratory chain studies; genetic testing	Coenzyme Q10, L-carnitine
Lysosomal Storage disorders						
Tay Sachs disease[73,74,79,81,87]	AR mutation of *HEXA* gene on Chr15 -> decreased hexosaminidase A activity	3-6 months; adult onset forms reported	3-4 years; adult onset is longer duration	Weakness, dystonia, ataxia, motor neuron disease, psychiatric symptoms	Enzyme assay of serum or leukocytes (decreased or absent hexosaminidase A activity with normal or increased hexosaminidase B activity); genetic testing	
Gaucher's disease type 2 and 3[75,82]	AR mutation of *GBA* gene on Chr1 -> decreased gluco-cerebrosidase activity	Before 2 years	Type 2 is 1-2 years, type 3 is 30-40 years	Hepatosplenomegaly, pancytopenia, lung disease Type 2: bulbar signs, pyramidal signs. Type 3: oculomotor apraxia, seizures, myoclonus, bone disease	Enzyme assay of peripheral blood leukocytes (decreased glucocerebrosidase activity); bone marrow exam (Gaucher cells that stain with periodic acid-Schiff); genetic testing	Enzyme replacement therapy, bone marrow transplant
Niemann-Pick disease type C[76,83,86,88]	AR mutation of *NPC1* on Chr18 or *NPC2* on Chr14 -> decrease in protein transport across cell membrane	Mid-to-late childhood	20-30 years	Psychiatric symptoms, ataxia, vertical supranuclear gaze palsy, dystonia, seizures, dysarthria, dysphagia	MRI (atrophy of white matter tracts and bilateral hippocampus, thalamus, superior cerebellum, insula); fibroblast culture with decreased cholesterol esterification and filipin staining; genetic testing	
Fabry's disease[77,80,84,121]	XLR mutation of *GLA* gene on ChrX ->	4-8 years	33-37 years	Acroparesthesia, angiokeratoma, hypohidrosis, corneal	Enzyme assay of plasma, leukocytes, or cultured cells (decreased alpha	Enzyme replacement therapy, **reversible**

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
	decreased alpha galactosidase activity decreased alpha galactosidase activity decreased alpha galactosidase activity			and lenticular opacities, proteinuria, renal disease, cardio- and cerebrovascular disease	galactosidase activity); genetic testing	
Kufs disease (adult-onset form)[78,85]	AD mutation of *CTSD* on Chr11, *PPT* on Chr1, *CLN3* on Chr16, *CLN5* on Chr13, *CLN4* on Chr20; AR mutation of *CTSD* on Chr11, *PPT* on Chr1, *CLN5* on Chr13	15-50 years	10 years	Ataxia, pyramidal and extrapyramidal motor features Type A: myoclonic epilepsy Type B: behavior change	EEG (atypical spike and slow wave in type A or generalized slowing in type B); peripheral lymphocytes or skin biopsy (EM with curvilinear profiles, fingerprint profiles, granular osmophilic deposits); enzyme assay of leukocytes or fibroblasts (decreased PPT1, TPP-1, or cathepsin D activity); genetic testing	
Leukodystrophies						
Adrenoleuko- dystrophy[89,95,101,108,122]	XLR mutation of *ABCD1* gene on ChrX -> decreased transport of VLCFA into peroxisomes for beta oxidation	4-8 years (20-30 years inadreno-myelo-neuro-pathy)	Variable	Behavioral changes with motor dysfunction, impaired vision and hearing, adrenal insufficiency; Adrenomyeloneuropathy: paraparesis, sphincter disturbance, sexual dysfunction; Carrier females have milder disease and later onset	MRI (T2 hyperintensity in parieto-occipital region with enhancing lesion margins); increased concentration of VLCFA in plasma or skin fibroblasts; genetic testing	Decr VLCFA in diet, steroid replacement therapy, bone marrow transplant
Meta-chromatic leuko-dystrophy (adult-onset form)[89,96,102,104,109,123]	AR mutation of *ARSA* gene on Chr22 -> decreased arylsulfatase A activity	16+ years	20+ years	Behavioral features with personality change, peripheral neuropathy, seizures, incontinence, motor symptoms including weakness and incoordination progress to spasticity	MRI (T2 diffuse symmetric periventricular hyperintensities with anterior to posterior gradient and cerebral atrophy); enzyme assay of leukocytes (decreased ARSA activity); urine sulfatides; MRS (decreased N-acetylaspartate); genetic testing	Bone marrow transplant
Alexander disease (juvenile- and adult-onset form)[94,100,107,110,117]	AD mutation of *GFAP* gene on Chr17 which encodes glial	4-10 years in juvenile-onset, young adulthood in adult-onset	Few years to decades	Bulbar/pseudobulbar signs, ataxia, seizures, megalencephaly, breathing difficulty	MRI (T2 frontal predominant extensive white matter abnormalities with hypointensity in	

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
	fibrillary acidic protein fibrillary acidic protein				periventricular regions; hyperintensity of basal ganglia and thalamus; brain stem abnormalities, and contrast enhancement); EEG (nonspecific, slow waves over frontal area); CSF (increased αβ-crystallin and heat shock protein 27, increased glial fibrillary acidic protein); genetic testing	
Leukoen-cephalopathy with vanishing white matter (adult-onset form)[91,111,116]	AR mutation of *EIF2B* on Chr12 which initiates DNA translation; triggered by infection or trauma	Adulthood	-	Delayed motor and intellectual development, behavioral features, transient optic neuritis or hemiparesis, headache	MRI (T1 diffuse hypointensity of white matter; T2 diffuse hyperintensity of white matter); genetic testing	
Pelizaeus-Merzbacher disease[92,98,105,106,112]	XLR mutation of *PLP1* on ChrX which is component of CNS myelin	Before 5 years	30-70 years	Nystagmus, hypotonia, spastic quadriparesis, ataxia, dystonia, athetosis; Carrier females have milder symptoms	MRI (T2 and FLAIR hyperintensity in cerebral hemispheres, cerebellum, and brainstem with thin corpus callosum); genetic testing	
Adult polyglucosan body disease[93,99,103,113]	AR mutation of *GBE1* on Chr3 -> decreased glycogen branching enzyme activity	40+ years	Variable	Neurogenic bladder, gait abnormality, mixed upper and lower motor neuron disease, distal sensory loss	MRI of brain and spinal cord (paraventricular, subcortical, deep white matter changes that extend to cervical-medullary junction; generalized atrophy); EMG and NCS (axonal lumbosacral polyradiculoneuropathy); assay of skin fibroblasts or muscle (decreased glycogen brancher enzyme activity); sural nerve biopsy (intra-axonal polyglucosan bodies); genetic testing	
Cerebro-tendineous xantho- matosis[90,97,114,115]	AR mutation of *CYP27A1* on Chr2 -> decreased sterol 27-	20 years	-	Diarrhea in infancy, cataracts, xanthomas (Achilles), psychiatric features, pyramidal and cerebellar signs,	Blood tests (high plasma cholestanol, normal/low plasma cholesterol, decreased chenodeoxycholic acid,	Cheno-deoxycholic acid, HMG-CoA reductase inhibitor

Disorder	Pathogenesis	Age of Onset	Disease Duration	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
	hydroxylase activity hydroxylase activity			dystonia, atypical parkinsonism, peripheral neuropathy, seizures	increased bile alcohols and glyconjugates); MRI (T2 bilateral hyperintensity of dentate nuclei and cerebral/ cerebellar white matter); CSF (increased cholestanol and apolipoprotein B); enzyme assay of fibroblasts, liver, leukocytes (decreased sterol 27-hydroxylase activity); genetic testing	

Abbreviations: CSF = cerebrospinal fluid
CT = computed tomography
MRI = magnetic resonance imaging
DWI = diffusion weighted imaging
EMG = electromyography
NCS = nerve conduction study
EEG = electroencephalography
EKG = electrocardiography
EM = electron micrography
MRS = magnetic resonance spectroscopy
FLAIR = fluid attenuated inversion recovery
AR = autosomal recessive
XLR = X-linked recessive
AD = autosomal dominant
Chr = chromosome
CNS = central nervous system
MELAS = mitochondrial encephalomyopathy lactic acidosis, and stroke-like episodes
MERRF = myoclonic epilepsy with ragged red fibers
VLCFA = very long chain fatty acids

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Table 3

Reversible forms of young-onset dementia

Disorder	Pathogenesis	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Inflammatory				
Multiple sclerosis[124,128-132]	Sporadic	Age of onset is 20-40 years; more common in females; may be relapsing/ remitting, primary progressive, progressive relapsing, or secondary progressive and present with sensory disturbance of limbs, partial or complete vision loss, motor dysfunction of limbs, diplopia, and ataxia	MRI (enhancing and non-enhancing lesions in brain and/or spinal cord white matter with characteristic perpendicularly oriented “Dawson's fingers” in the periventricular region); CSF (elevated oligoclonal bands and IgG index)	Corticosteroids for acute attack; other immunomodulatory agents for long-term therapy
Neurosarcoidosis[125]	Sporadic	Cranial mononeuropathy (esp CN V, II, VIII), neuroendocrine dysfunction, myelopathy, hydrocephalus, aseptic meningitis, peripheral neuropathy, myopathy, multi-focal neurological deficts	MRI (meningeal or parenchymal enhancement, parenchymal nodules); CSF (elevated opening pressure, normal or low glucose, mononuclear pleocytosis, incr IgG, oligoclonal bands, elevated ACE level); chest CT for lung or lymph node involvement; biopsy for noncaseating granuloma	Corticosteroids for acute symptoms, other immunomodulatory agents for long-term therapy
Paraneoplastic and Autoimmune Limbic encephalitis[126,127,133]	Associated with multiple antibodies +/− occult or known malignancy	Acute/subacute changes in mood and behavior change, complex-partial seizures	MRI (T2 sequence with hyperintensity or contrast enhancement in medial temporal lobes); CSF (elevated protein); EEG (focal or generalized slowing or epileptiform activity in temporal region); paraneoplastic and autoimmune antibody testing on serum +/− CSF	Immunosuppression with high dose corticosteroids acutely, treat underlying tumor, chronic therapy may require long-term immunomodulatory agents
Infectious				
HIV dementia[134,139]	HIV infection with consequent immune activation of microglia	Psychomotor slowing, mood lability	MRI (cerebral atrophy especially in basal ganglia and frontal white matter); blood tests (low CD4 count, high HIV viral load); CSF (rule out other opportunistic causes)	HAART therapy treats HIV infection to reduce dementia risk

Disorder	Pathogenesis	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Neurosyphilis[135,138,142]	Treponema pallidum	Personality change; meningitis, decr visual acuity, hearing loss, general paresis, tabes dorsalis	MRI (meningeal enhancement), blood tests (VDRL, FTA-ABS); CSF (VDRL, FTA-ABS, incr protein, lymphocyte pleocytosis)	Penicillin G, ceftriaxone if penicillin-allergic, doxycycline if resistant
Whipple disease[136,141,143]	Tropheryma whipplei	Migratory arthralgia, weight loss, GI symptoms, oculomasticatory myorhythmia, ataxia, endocarditis	MRI (variable depending on symptoms); CSF PCR of saliva or stool; upper endoscopy with small bowel biopsy (periodic acid-Schiff-positive macrophages in lamina propria)	Ceftriaxone or penicillin for initial therapy; TMP-SMX as maintenance therapy
Progressive multifocal leuko-encephalopathy[137,140,144,145]	Reactivation of JC virus in immunosuppressed patients	Hemianopia, hemiparesis or monoparesis, ataxia	MRI (multifocal non-enhancing lesions limited to white matter that do not conform to vascular territories without mass effect); CSF (PCR detection of JC virus); EEG (nonspecific diffuse slowing)	HAART and high-dose glocucorticoid therapy if coinfected with HIV; stop immunosuppression; cytarabine for pt with hematologic malignancy; **not reversible**
Toxins				
Alcohol and other drugs of abuse (sedatives, inhalants, etc.)[146,148]	Ingestion with neurotoxic effects Alcohol-related dementias include thiamine deficiency, hepatic encephalopathy, and Marchiafava-Bignami disease	All drugs of abuse: ataxia, tremor, blurred vision, dysarthria, psychiatric symptoms, seizures, coma Sedative overdose: respiratory depression Inhalant overdose: respiratory distress, headache, arrhythmia	All drugs of abuse: urine and serum drug screen Thiamine deficiency: MRI (signal change or atrophy of anterior thalamus or mamillary bodies) Hepatic encephalopathy: MRI (T1 hyperintensity in globus pallidus) Marchiafava-Bignami disease: MRI (signal change in the corpus callosum) Chronic alcohol use: MRI (atrophy in cerebellar vermis> hemispheres)	Cessation of offending agent Alcohol overdose: IVthiamine before glucose Sedative overdose: flumazenil
Heavy metal poisoning[147]	Occupation/environmental exposures	Mercury poisoning: psychiatric symptoms, distal sensory and motor neuropathy, GI symptoms, weakness, developmental delay, inflammation of gums, constricted visual fields, deafness, ataxia Arsenic poisoning: arrhythmia and ARDS Lead poisoning: anemia	Mercury poisoning: mercury level in blood >100 mcg/L and urine >100 mcg/L Arsenic poisoning: arsenic level in urine >50 mcg/L Lead poisoning: lead level in blood >25 mcg/dL; NCS	Avoid exposure; chelation

Disorder	Pathogenesis	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Metabolic encephalopathy[149-153]	Hepatic encephalopathy: excess ammonia Renal failure or dialysis disequilibrium syndrome: uremia Hyponatremia Hypernatremia	All: weakness, agitation, fluctuating cognition and behavior, seizures, coma	All: blood tests (comprehensive metabolic panel, ammonia); MRI of brain primarily to exclude other Diagnoses Hepatic encephalopathy: MRI (T1 hyperintensity in globus pallidus)	All: treat underlying cause Hepatic encephalopathy: lactulose and rifaximin Uremia: dialysis Hyponatremia: correct slowly with IVF to avoid central pontine myelinolysis
Wilson's disease[172-174]	AR mutation in *ATP7B* on Chr13 inhibits copper metabolism	Psychiatric symptoms, liver disease, movement disorder or rigid dystonia, ataxia, Kayser-Fleischer rings on slit-lamp exam	Blood tests (low copper and ceruloplasmin); urine (increased copper excretion); liver biopsy (incr hepatic copper concentration); genetic testing	Penicillamine, trientine, zinc
Endocrinopathy				
Glucose dysregulation (hypoglycemia, hyperglycemia)[154]	Hypoglycemia: insulin, alcohol, malnourishment, liver disease Hyperglycemia: diabetes esp type I with inadequate insulin or acute infection	Hypoglycemia: change in behavior with anxiety, visual changes, seizures, palpitations, diaphoresis, variable focal neurological deficits, perioral paresthesia around mouth Hyperglycemia: polyuria, polydipsia, GI symptoms, weakness, fatigue, shortness of breath, fruity breath	Hypoglycemia: blood tests (glucose <60 mg/dL, assess for associated metabolic derangements) Hyperglycemia: blood tests (glucose >200 mg/dL, assess for associated metabolic derangements)	Hypoglycemia: carbohydrates (15-20g oral glucose), glucagon injection, IV dextrose Hyperglycemia: IVF, insulin
Thyroid dysfunction (hypothyroidism, hyperthyroidism)[155,156,161,164,167]	Hypothyroidism: autoimmune thyroiditis, infiltrative disease, TSH orTRH deficiency Hyperthyroidism: Graves disease, multinodular goiter	Hypothyroidism: weakness, fatigue, cold intolerance, constipation, dry skin, weight gain, hoarseness, bradycardia, depression Hyperthyroidism: heat intolerance, anxiety/ irritability, tremor, diaphoresis, diarrhea, weight loss, tachycardia, Graves ophthalmopathy	Blood tests for both (TSH, free T4, thyroid autoantibodies); MRI (to rule out other possibilities); thyroid ultrasound Hypothyroidism: EEG (slow background activity) Hyperthyroidism: EEG (epileptiform activity)	Hypothyroidism: levothyroxine Hyperthyroidism: radioactive iodine, antithyroid medications, beta blocker, or thyroidectomy
Parathyroid dysfunction (hypoparathyroidism, hyperparathyroidism)[157,158,162,163]	Hypoparathyroidism: radiation of head/ neck, radioactive iodine, low calcium intake Hyperparathyroidism: parathyroid adenoma or hyperplasia, parathyroid carcinoma, ectopic PTH from non-parathyroid neoplasm, multiple genetic mutations	Hypoparathyroidism: weakness, fatigue, irritability/anxiety/ depression, tetany, seizures, muscle cramps, papilledema, extrapyramidal symptoms Hyperparathyroidism: weakness, fatigue, bone	Blood tests for both (Ca, PTH, Phosphorus, Mg, creatinine, vitamin D, alkaline phosphatase); urinary calcium Hypoparathyroidism: CT (basal ganglia calcification)	Hypoparathyroidism: calcium and vitamin D Hyperparathyroidism: avoid calcium in diet, saline hydration, calcitonin, bisphosphonates, glucocorticoids, dialysis

Disorder	Pathogenesis	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
		pain, myalgia, depression, nephrolithiasis, osteoporosis pain, myalgia, depression, nephrolithiasis, osteoporosis pain, myalgia, depression, nephrolithiasis, osteoporosis	bone mineral density, renal imaging	
Addison's disease[159,165,168]	Primary adrenal insufficiency, autoimmune/infectious adrenalitis, metastatic cancer or lymphoma, adrenal hemorrhage or infarction, abrupt withdrawal from corticosteroids	GI symptoms, weakness, fatigue, lethargy, fever, systemic “shock” and coma, hyperpigmentation if primary adrenal insufficiency	Blood tests: 8 AM serum cortisol and plasma ACTH; ACTH stimulation test; basal ACTH, renin, aldosterone levels	IVF resuscitation, glucocorticoids (hydrocortisone, dexamethasone, prednisone, fludrocortisone), DHEA if glucocorticoids fail
Cushing's syndrome[159,160,166]	Cushing's disease (pituitary hypersecretion of ACTH), ectopic secretion of ACTH by nonpituitary tumors, ectopic secretion of CRH, adrenal adenoma or hyperplasia, exogenous glucocorticoids	Central obesity, moon facies, supraclavicular fat pads, skin atrophy, purple striae, proximal muscle weakness, hirsutism, oligomenorrhea, impotence, obesity, hypertension, glucose intolerance	Late night salivary cortisol, urinary cortisol, low dose dexamethasone suppression test (2 of these must be abnormal); CT or MRI of adrenal glands or pituitary gland	Resection of ACTH- or cortisol-secreting tumor; pituitary irradiation; bilateral adrenalectomy; somatostatin analog for metastatic or ectopic ACTH-secreting tumor
Nutritional deficiency				
B12[169,171]	pernicious anemia, gastrectomy/ gastritis, strict vegans	megaloblastic anemia, jaundice, fatigue, atrophic glossitis, subacute combined degeneration (sensory and motor findings referable to spinal cord tracts), peripheral polyneuropathy	blood test (low B12 and folate, high homocysteine and methylmalonic acid, Ab to intrinsic factor); peripheral blood smear (macrocytic RBC, hypersegmented neutrophils); Schilling test; EMG and NCS; MRI spine (T2 hyperintensity of dorsal columns)	intramuscular B12 (1 mg every day for 1 week, then 1 mg every week for 4 weeks, then 1 mg every month until deficiency is reversed)
Thiamine (associated with Wernicke-Korsakoff syndrome)[146]	Malnourishment associated with chronic alcoholism, hyperemesis	Prominent anterograde memory deficits with confabulation, ataxia, ophthalmoplegia	Blood test (thiamine, RBC folate); MRI (signal abnormality or atrophy of medial thalamus, mamillary bodies, periaqueductal gray matter)	IV thiamine before glucose
Niacin (pellagra)[170]	Malnutrition associated with alcoholism or anorexia, carcinoid syndrome, prolonged use of isoniazid, Hartnup disease (defective amino acid transporter)	Dermatitis, diarrhea	Bloodwork (low niacin, tryptophan, NAD, NADP)	Niacin supplementation (25-300 mg by mouth daily)
Transient epileptic amnesia[175]	Unknown	More common in elderly; recurrent transient episodes of isolated anterograde memory loss, interictal memory difficulties	EEG (temporal lobe spikes); CT or MRI (atrophy of hippocampus)	Anticonvulsant therapy affects progression but does not completely reverse cognitive deficits

Disorder	Pathogenesis	Clinical Features in addition to Cognitive Dysfunction	Specific Diagnostic Studies with Suggested Order of Testing	Interventions in addition to Supportive Care
Obstructive sleep apnea[176,178]	Intermittent hypoxemia or sleep deprivation; Risk factors include obesity, large neck circumference, anatomically narrow airway	Snoring, snort arousals, morning headache, daytime somnolence, irregular respiratory patterns during sleep	Polysomnography with apneic pauses	Behavior modification (weight loss, change sleep position), positive airway pressure, oral devices, uvular and palatal surgery
Normal pressure hydrocephalus[179]	Impaired CSF flow; more common after head trauma, CNS infection, CNS hemorrhage	Gait disturbance (“magnetic”), urinary incontinence	MRI (ventriculomegaly, periventricular white matter hyperintensity, no evidence of CSF flow obstruction); high volume LP or CSF drain to identify patients that may respond to shunt placement	Ventriculoperitoneal shunt; cognitive deficits rarely reverse with this procedure although intervention may prevent further decline

Abbreviations: CSF = cerebrospinal fluid
LP = lumbar puncture
MRI = magnetic resonance imaging
EMG = electromyography
NCS = nerve conduction study
EEG = electroencephalography
PET = positron emission tomography
CT = computed tomography
EKG = electrocardiography
ACE = angiotensin converting enzyme
HIV = human immunodeficiency virus
HAART = highly active antiretroviral therapy
VDRL = venereal disease research laboratory
FTA-ABS = fluorescent treponemal antibody-absorption
PCR = polymerase chain reaction
ARDS = adult respiratory distress syndrome
IVF = intravenous fluids
TSH = thyroid-stimulating hormone
TRH = thyrotropin-releasing hormone
T4 = thyroxine
T3 = triiodothyronine
PTH = parathyroid hormone
ACTH = adrenocorticotropic hormone
DHEA = dehydroepiandrosterone
CRH = corticotropin-releasing hormone
Ab = antibody
NAD = nicotinamide adenine dinucleotide
NADP = nicotinamide adenine dinucleotide phosphate