CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will distinguish the various types of dementia other than Alzheimer disease

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Don't forget non-Alzheimer dementias

ABSTRACT

Dementia is commonly encountered in the elderly, with prevalence increasing with age. Although Alzheimer disease is the most recognized form of dementia, other types have distinct clinical features and are often overlooked. Proper identification aids patients, caregivers, and physicians in planning and management.

KEY POINTS

Vascular dementia presents as a sudden, stepwise progression of cognitive deficits.

Lewy body dementia often involves prominent visual hallucinations.

Progressive supranuclear palsy starts with gait and balance problems caused by downward-gaze palsy.

Many neurodegenerative conditions involve parkinsonism, but unlike Parkinson disease, they do not tend to respond well to levodopa, and dementia develops early.

Corticobasal degeneration involves markedly asymmetric parkinsonism.

Frontotemporal dementia involves dramatic behavior changes, including inappropriate impulsivity and complete apathy.

Patients with rapidly progressive dementia should be evaluated for a treatable condition such as antibody-mediated encephalitis.

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Dementia is not always due to Alzheimer disease. An accurate diagnosis is important, as the various causative conditions can differ in their course and treatment.

Dementia refers to cognitive impairment severe enough to interfere with the ability to independently perform activities of daily living. It can occur at any age but is most common after age 60. Some studies estimate that 13.9% of people age 71 and older have some form of dementia.[1] The prevalence increases with age, ranging from 5% at age 70 to 79 to 37% at age 90 and older.[1]

Alzheimer disease accounts for about 60% to 80% of cases,[2] or an estimated 4.7 million people age 65 and older in the United States, a number anticipated to climb to 13.8 million by 2050.[3]

Other types of dementia are less often considered and are challenging to recognize, although many have distinct characteristics. This article summarizes the features and management of the more common non-Alzheimer dementias:

- Vascular dementia
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Corticobasal degeneration
- Multiple system atrophy
- Parkinson disease dementia
- Frontotemporal dementia
- Primary progressive aphasia
- Normal-pressure hydrocephalus
- Rapidly progressive dementia (ie, Creutzfeld-Jakob disease, autoimmune disease).

VASCULAR DEMENTIA

After Alzheimer disease, vascular dementia is the most common dementia, accounting for about 20% to 30% of cases. Clinical criteria have not been widely accepted, although several have been published, including those in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) and the National

TABLE 1

Characteristics of neurodegenerative dementias

Disease	Age (y) at diagnosis	Progression	Earlier cognitive symptoms
Alzheimer dementia	Late (> 65) Early (< 65)	Gradual	Early impairment of memory and attention
Vascular dementia	≥ 60	Sudden, stepwise	Executive dysfunction, deficits depend on location of stroke or lesion
Dementia with Lewy bodies	70s [6]	Gradual with fluctuation in cognition	Early Impairment of visual spatial skills and attention Delayed recall is relatively preserved in the beginning
Progressive supranuclear palsy	60s [8]	Gradual	Frontal behavioral disturbance, deficit in verbal fluency or abstract thoughts
Corticobasal degeneration	Around 60	Gradual	Deficit in frontal-parietal cognitive domains, including attention, concentration, executive function, verbal fluency
Multiple system atrophy	≥ 60	Gradual	Late dementia, with deficits in learning, recognition, memory, and verbal fluency
Parkinson disease dementia	70s[6]	Gradual	Impairment in attention, memory, executive and visuospatial functions
Frontotemporal dementia	Mostly < 65	Gradual	Difficulty with language and executive function or behavioral change
Primary progressive aphasia	Around 60	Gradual	Expressive language impairment
Normal-pressure hydrocephalus	50s–60s	Gradual	Impairment of attention, working memory, verbal fluency and executive function; recognition memory is preserved

REM = rapid eye movement

Common cognitive enhancers have demonstrated benefit for vascular dementia

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Risk factors for vascular dementia include cerebrovascular disease (hypertension, diabetes, hyperlipidemia) and coexisting conditions related to atherosclerosis (coronary artery disease, peripheral artery disease).

The Hachinski Ischemic Score is a good bedside tool to help differentiate Alzheimer dementia from vascular dementia.[5]

Sudden onset and stepwise decline

Vascular dementia often presents as a sudden and stepwise progression of cognitive deficits that stabilize and that are caused by vascular insults (TABLE 1).[6–10] Some patients have contin-

Visual hallucinations	Parkinsonism	REM sleep behavior disorder	Autonomic insufficiency	Dominant presenting symptoms
Rare	Late stages	Rare	Rare	Memory loss, cognitive impairment
Rare	Depends upon location of stroke	None	None	Sudden onset of cognitive deficits and impairment
Typical	Within first year	Common	Occasional	Parkinsonism or cognitive impairment
Rare	Symmetric,[9] (1/3 initially asymmetric)	Infrequent[7,8]	Common	Motor symptoms, balance problems, falls
Rare	Asymmetric[9]	Rare[10]	Rare	Motor symptoms
Rare	Symmetric	Common	Common	Autonomic failure, motor symptoms
Occasional at late stage	Asymmetric at onset	Common[7]	Common	Motor symptoms
Rare	Sometimes	Occasional	Infrequent	Behavioral changes
Rare	In late stages	None	None	Expressive language impairment
Rare	May present as parkinsonism	None	None	Gait impairment with urinary frequency and/or cognitive impairment

REM = rapid eye movement

In Lewy body dementia, cognitive impairment is progressive and fluctuating

uous decline after a vascular event, indicating that Alzheimer dementia may also be present. Dementia is then defined as a mixed type.

Behavioral problems such as physical aggression, hallucinations, paranoia, and mood fluctuations are common.[11]

Deficits depend on vascular areas affected

Cognitive deficits are heterogeneous and are often related to the location of the vascular insult. Involvement of subcortical areas may result in executive dysfunction, slowed processing speed, and behavioral changes.[12]

Executive dysfunction may be identified using the Trail Making Test (Part B) or the Executive Interview (EXIT25). Office-based tools such as the Folstein Mini-Mental State Examination, the Montreal Cognitive As-

TABLE 2

Diagnosis of dementia with Lewy bodies

Core features
Fluctuating cognition
Visual hallucinations
Parkinsonism

Suggestive features
Rapid-eye-movement sleep behavior disorder (physically acting out dreams)
Severe neuroleptic sensitivity
Low dopamine-transport activity in basal ganglia demonstrated by single-photon emission computed tomography or positron emission tomography

Diagnosis is probable if either two core features or one core feature and one suggestive feature are present

sessment, or the St. Louis University Mental Status Examination may also uncover these deficits.

Focal neurologic deficits may be found on clinical examination.

Structural neuroimaging may identify small strokes in areas of the brain affecting cognitive function or occlusion of a larger vessel associated with more profound neurologic deficits. Neuroimaging findings may not correlate with any significant decline noted by the patient, suggesting "silent" strokes.

Avoid anticholinergic medications and dopamine agonists for dementia with Lewy bodies

Treat symptoms and manage risk factors

Although the US Food and Drug Administration (FDA) has not approved any pharmacotherapy for vascular dementia, commonly prescribed cognitive enhancers have demonstrated some benefit.[13]

Behavioral problems such as aggression can be disturbing to the patient and the caregiver. Nonpharmacologic methods (eg, redirection, rescheduling care activities to avoid conflict, avoiding issues that lead to agitation) should be tried first to address these problems.

Drug therapy may be used off-label for neuropsychiatric symptoms such as hallucinations, delusions, and combativeness, but clinical trials of these agents for this purpose have shown mixed results,[14] and their use is often associated with significant risk.[15] Antipsychotic drugs are associated with a risk of death and pneumonia when prescribed for dementia. Many also carry a risk of QT prolongation, which is particularly concerning for patients with coronary artery disease or rhythm disturbances.

The key to reducing further decline is to optimize management of vascular risk factors to reduce stroke risk.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies, the next most common neurodegenerative dementia in the elderly, is characterized by progressive loss of cognitive function, prominent visual hallucinations, and parkinsonism (TABLE 1).[6] Disease progression usually occurs over years but can be more rapid than in Alzheimer disease.

Alpha-synucleinopathy results in dysfunction of synaptic vesicles in presynaptic terminals. Lewy bodies may be diffusely spread in cortical and subcortical areas (appearing as spherical masses).

Visual hallucinations are typical

The McKeith criteria[16] are the gold standard for diagnosing probable Lewy body dementia, based on clinical and imaging features (TABLE 2).

Visual hallucinations are usually well formed and detailed. They may initially be pleasant (eg, seeing children and little people) but may evolve to be accompanied by persecutory delusions.

Parkinsonism develops with or after dementia with Lewy bodies

Dementia with Lewy bodies and Parkinson disease dementia share many clinical and pathologic features; Parkinson dementia also is associated with cortical Lewy bodies.

Parkinsonian features include bradykinesia, masked facies, and rigidity. Resting tremor is less common.

The third report of the Dementia With Lewy Bodies Consortium recommends that the condition be diagnosed if dementia occurs before or concurrently with parkinsonism, and dementia with Parkinson disease should be diagnosed if dementia occurs in the context of well-established Parkinson disease.[16] The development of dementia within 12 months of extrapyramidal signs suggests dementia with Lewy bodies.

Cognitive deficits fluctuate

Cognitive impairment in Lewy body dementia is characterized by progressive dementia with

fluctuations in cognitive performance. Family members or caregivers may report that the patient can carry on a conversation one day and the next day be confused and inattentive. Compared with those with Alzheimer dementia, patients with Lewy body dementia have better delayed recall but more problems with executive functioning (planning) and visuospatial skills (following an unfamiliar route, copying a figure).

Specialized imaging provides clues

Dementia with Lewy bodies is associated with diffuse brain atrophy, with no established characteristic pattern on structural neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI).[17] The contrast agent ioflupane iodine-123 injection (DaTscan) used with single-photon emission CT (SPECT) detects dopamine transporters, which are reduced in parkinsonian syndromes. The scan can also help differentiate between Alzheimer dementia and Lewy body dementia by detecting the loss of functional dopaminergic terminals in the striatum in Lewy body dementia. Alpha-synuclein imaging may become another useful diagnostic tool in the future.

Alzheimer medications may help in dementia with Lewy bodies

Medications with anticholinergic effects and dopamine agonists should be discontinued because of possible effects on cognitive function and parkinsonism. In one clinical trial,[18] rivastigmine (Exelon) was found to help cognitive functioning as well as reduce psychotic symptoms in dementia with Lewy bodies, although a recent Cochrane review could not support the evidence for use of all cholinesterase inhibitors in Lewy body dementia.[19] In another trial,[20] memantine (Namenda) was found to improve global clinical status and behavioral symptoms of Lewy body dementia.

Treating hallucinations of dementia with Lewy bodies

Patients with dementia with Lewy bodies are extremely sensitive to the extrapyramidal side effects of neuroleptic drugs. Some evidence indicates that the atypical antipsychotic drug quetiapine (Seroquel) helps with prominent and disturbing psychotic features and is less likely to worsen parkinsonism than other antipsychotics.[21] The best evidence is for clozapine (Clozaril) as a treatment for hallucinations in Parkinson dementia, but the possible side effect of agranulocytosis limits its clinical use. Other atypical antipsychotics such as risperidone (Risperdal) and olanzapine (Zyprexa) are not recommended.[22]

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy is a sporadic atypical parkinsonian disorder with onset between age 50 and 70. Familial cases are infrequent.

Progressive supranuclear palsy presents as early postural instability, vertical supranuclear gaze palsy, and axial muscle rigidity in the first few years. Disease progression is gradual: one study of 50 patients found that the median time from onset to the first key motor impairment (unintelligible speech, no independent walking, inability to stand unassisted, wheelchair-bound, or recommendation for feeding tube placement) was 4 years.[23]

Histologically, progressive supranuclear palsy is characterized by accumulation of tau protein aggregates in the basal ganglia, brainstem, and cerebral cortex. The degenerative process involves dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA)-ergic neurons.[24]

REM sleep behavior disorder precedes motor symptoms in Lewy body, Parkinson, or multiple system atrophy dementia

Gait and balance problems predominate early in progressive supranuclear palsy

The most commonly used diagnostic criteria are from the National Institute of Neurological Disorders and Stroke. The diagnosis of probable progressive supranuclear palsy requires vertical gaze palsy and falls or the tendency to fall within the first year of disease onset and exclusion of other causes.

The earliest symptom is usually gait and balance impairment.[25] Falls (usually backward) and postural instability occur during the first year in 58% of patients.[26] Instead of turning en bloc as in Parkinson disease, patients with progressive supranuclear palsy tend to pivot quickly. Patients may also have a coarse groaning voice and moaning. Insomnia has been reported, but rapid-eye-movement sleep

behavior disorders are infrequent (unlike in Parkinson disease, multiple system atrophy, and Lewy body dementia).[27]

Apathy and extreme mood swings

Cognitive impairment is seen in 50% of patients in the early stage of progressive supranuclear palsy. It mostly involves the frontal lobe, including frontal behavioral disturbances (eg, apathy in 91% of patients[26] or pseudobulbar affect and extreme emotional lability) and deficits in abstract thoughts or verbal fluency (to test this, patients are asked to say as many words as possible from a category in a given time). Ideomotor apraxia (inability to correctly imitate hand gestures and voluntarily pantomime tool use, such as pretending to brush hair) is rare, despite corticobasal degeneration.[28]

Vertical gaze palsy

The hallmark of progressive supranuclear palsy is vertical gaze palsy. Initially, this involves slowing of vertical saccades, followed by diminished vertical gaze and more characteristic downward gaze palsy. These findings may develop over 3 to 4 years. Vertical gaze palsy leads to spilling food and tripping while walking.

The gaze abnormality combined with rare blinking and facial dystonia form the classic facial expression of astonishment called "leonine facies." The face is stiff and deeply furrowed, with a look of surprise.

Axial (especially neck) rigidity is more prominent than limb rigidity. Retrocollis (the head is drawn back) occurs in less than 25% of patients. Parkinsonian features such as bradykinesia affect nearly half of patients by the time of diagnosis.

Instead of the classic symptoms of progressive supranuclear palsy, about one-third of patients present with progressive supranuclear palsy-parkinsonism, which involves asymmetric parkinsonism that initially responds to levodopa.[29]

Marked motor asymmetry helps differentiate corticobasal degeneration from most other neurodegenerative diseases

MRI shows 'hummingbird sign'

Brain MRI shows atrophy of the brainstem, particularly the midbrain. Thinning of the superior part of the midbrain and dilation of the third ventricle ("hummingbird sign" on sagittal sections or "morning glory flower" on axial sections) support a diagnosis of progressive supranuclear palsy and differentiate it from Parkinson disease and other atypical parkinsonian disorders.[30,31]

Levodopa ineffective for supranuclear palsy

There is no treatment to slow progressive supranuclear palsy. Even in high doses, levodopa rarely alleviates parkinsonian features in a clinically meaningful way.[26] Successful experimental biologic therapies have been studied in animal models.[32] Davunetide is thought to help with neuronal integrity and cell survival through the stabilization of microtubules in preclinical studies, but it has not been used in clinical practice.[33]

CORTICOBASAL DEGENERATION

Corticobasal degeneration is a progressive, asymmetric movement disorder often manifesting initially with cognitive or behavioral impairment. It is associated with abnormality of the cytoskeleton protein tau. Onset is usually after age 60.

Asymmetric movement disorder with cognitive dysfunction

This diagnosis is clinical. Diagnostic criteria proposed in 2003 include the following core features[34]:

- Insidious onset and progressive course
- No identifiable cause
- Cortical dysfunction with at least one of the following: apraxia, alien limb phenomenon (one limb moves involuntarily with complex movements, eg, grabbing the other hand), cortical sensory loss, visual hemineglect, nonfluent aphasia
- Extrapyramidal dysfunction: focal rigidity unresponsive to levodopa, asymmetric dystonia.

An international consortium has developed more specific clinical research criteria for probable and possible corticobasal degeneration.[35] In a series of 147 patients, the following clinical features were found: parkinsonism (100%), higher cortical dysfunction (93%), dyspraxia (82%), gait disorder (80%), unilateral limb dystonia (71%), tremor (55%), and dementia (25%).[36]

Behavioral problems commonly include depression; apathy, irritability, and agitation are also reported.[37]

Cognitive testing may reveal deficits in frontal-parietal cognitive domains including attention and concentration, executive function, verbal fluency, and visuospatial skills.[38] Learning disabilities may be improved with verbal cueing (in contrast to Alzheimer disease). Patients may also have impaired graphesthesia (the ability to recognize writing on the skin only by the sensation of touch).[39,40]

Motor examination may reveal marked asymmetry. Hand, limb, speech, and gait apraxias are common. Gait is typically slow, with short steps and shuffling, and a wide-based or freezing gait. Arm swing may be absent on one side.

Asymmetric cortical atrophy

Early on, MRI may be normal. As the disease progresses, asymmetric cortical atrophy may be seen, especially in the posterior frontal and parietal lobes.

Levodopa ineffective in corticobasal degeneration

Corticobasal degeneration responds poorly to levodopa. Botulinum toxin has been used to help with dystonia and limb pain.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy is another atypical parkinsonian disorder, most often diagnosed in men over age 60. It is characterized by sporadic parkinsonism, cerebellar signs (involving balance and coordination), pyramidal tract dysfunction, and autonomic insufficiency in varying combinations. Two major subtypes are recognized, depending on whether the predominating presenting features are cerebellar signs or parkinsonism. In contrast to dementia with Lewy bodies, psychiatric symptoms are not a major feature, except possibly depression.[41]

Diagnosis requires a sporadic progressive disorder that has features of autonomic failure and poor response of parkinsonism or cerebellar ataxia to levodopa.[42]

Multiple system atrophy is usually not associated with dementia in the early stages, but patients develop deficits in learning, recognition, memory, and verbal fluency as the disease progresses.[43] Rapid-eye-movement sleep behavior disorder has been reported in more than half of patients.[44]

A neurologic examination provides clues

Parkinsonian features are usually symmetric, in contrast to idiopathic Parkinson disease. These signs may include akinesia with rigidity, postural instability, hypokinetic speech, and tremor.

Cerebellar signs include nystagmus and dysarthria (speech disturbance), and gait and limb ataxia.

Pyramidal features include extensor plantar responses and hyperreflexia.

Autonomic dysfunction includes orthostatic hypotension, bladder and rectal atony, loss of sweating, urinary or fecal incontinence, and erectile dysfunction.

Electromyography may demonstrate decreased anal sphincter tone.

MRI shows atrophy of putamen and pons

Brain MRI may show atrophy of the putamen (hypointensity of the putamen with a hyperintense rim). Pons atrophy may also be present, revealing a "hot cross bun" sign in axial images. These combined findings have specificity above 90% but limited sensitivity. These signs are useful to distinguish multiple system atrophy from Parkinson dementia, but their absence does not exclude the diagnosis of multiple system atrophy.[45,46]

Multiple system atrophy typically responds poorly to levodopa

Levodopa may improve movement and rigidity, but many respond poorly to treatment or lose response after a few years. Fludrocortisone (Florinef) or vasoconstrictors such as midodrine (Orvaten, Proamatine) may help with orthostatic hypotension.[47,48]

PARKINSON DISEASE DEMENTIA

Dementia eventually develops in most patients with Parkinson disease. Older age and the akinetic rigid form of the disease are associated with higher risk. Diagnosis of idiopathic Parkinson disease before the development of dementia is essential for the diagnosis.

The Movement Disorder Society Task Force has developed new diagnostic criteria.[49] Deficits must be present in at least two of the

Previous diagnosis of Parkinson disease is essential for the diagnosis of Parkinson dementia

four core cognitive domains (attention, memory, executive, and visuospatial functions) and must be severe enough to affect daily functioning.

Behavioral symptoms such as affective changes, hallucinations, and apathy are common.

MRI shows characteristic brain atrophy in Parkinson disease dementia

MRI shows reduced gray matter volume in the frontal lobe in patients with Parkinson disease without dementia compared with controls. In Parkinson disease dementia, reduced volume extends to temporal, occipital, and subcortical areas. No significant volumetric differences have been observed in Parkinson dementia compared with dementia with Lewy bodies.[50] A greater decrease of glucose metabolism has been found in the inferior parietal and occipital lobes in Parkinson disease dementia than in Parkinson disease without dementia.[51]

Rivastigmine effective for dementia

A Cochrane review supports the use of acetylcholinesterase inhibitors in patients with Parkinson disease dementia, with a positive impact on global assessment, cognitive function, behavioral disturbance, and activities of daily living rating scales.[19] At this time, rivastigmine is the only FDA-approved cholinesterase inhibitor for treating Parkinson disease dementia. In clinical trials, memantine did not improve global clinical status or behavioral symptoms of dementia of Parkinson disease.[51]

Rivastigmine is the only drug approved for treating Parkinson dementia

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia frequently starts before age 65 and accounts for 20% to 50% of dementias in this age group.[52] Recognition of the condition in older patients is also growing.[53] Frontotemporal dementia encompasses a spectrum of dementias, including behavioral variant frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia.[54]

Gradual onset of uncharacteristic behaviors

Accepted diagnostic criteria include core features of gradual onset, early decline in social and interpersonal conduct, early impairment of self-regulation, emotional blunting, and loss of insight. Many patients are diagnosed with psychiatric conditions. Changes reported by family and caregivers typically deviate substantially from the person's usual behavior, such as impulsive and inappropriate behaviors or complete withdrawal and apathy.

Language sometimes affected in frontotemporal dementia

Language impairment may be present in some variants. Behavioral and language changes often accompany other forms of dementia (Alzheimer disease, vascular dementia, primary progressive aphasia), making diagnosis more challenging. Office-based testing often does not reveal any deficits, although the Frontal Behavioral Inventory may help.[55] A referral to a clinical neuropsychologist may help identify and quantify cognitive impairments.

MRI shows frontotemporal lobes affected

Structural neuroimaging may not reveal abnormalities initially, but with progression, atrophy may be seen in the frontal and temporal lobes. Functional neuroimaging (positron emission tomography, brain SPECT, functional MRI) show hypometabolism in the same areas.

Treat symptoms

There are no specific FDA-approved therapies for frontotemporal dementia. Acetylcholinesterase inhibitors can help progressive nonfluent aphasia in some cases. Selective serotonin reuptake inhibitors may alleviate depressive symptoms, and low doses of atypical antipsychotic medications may help with impulsivity, disinhibition, and aggressive or disruptive behaviors.[56]

PRIMARY PROGRESSIVE APHASIA

Language impairment predominates

Primary progressive aphasia is a rare form of dementia in which symptoms typically develop around age 60. Pathology is varied. In a study of 60 patients with initial clinical symptoms of primary progressive aphasia, postmortem histology of brain tissue revealed various findings, including those consistent with Alzheimer pathology and motor neuron disease-type inclusions.[57]

Patients typically present with expressive language problems as the primary deficit for

the first 2 years of the disease, with preservation in other cognitive areas such as memory, visuospatial skills, and executive function.[58] Office-based testing may overstate the severity of the dementia, given the dependence of performance on intact language.

It is important to distinguish primary progressive aphasia from other dementias that also affect language. In the frontal variant of frontotemporal dementia, the primary language problem is anomia (inability to name objects) or diminished speech output, which may be accompanied by behavioral problems. Semantic dementia affects word recognition as well as comprehension. In Alzheimer disease, language may be affected along with memory and other areas of cognitive function.

Imaging shows focal degeneration in the left hemisphere

Structural neuroimaging does not initially reveal any deficits, but later it may reveal atrophy in the frontal, perisylvian complex, and temporal areas of the left hemisphere, reflecting the focal nature of the degeneration.[59] Functional neuroimaging (positron emission tomography, SPECT) may reveal hypometabolism or diminished blood flow in these areas prior to changes in structural neuroimaging.[60]

Other communication methods may help

There are no FDA-approved therapies for primary progressive aphasia. Off-label use of some agents (eg, selective serotonin reuptake inhibitors and small doses of antipsychotic medications) has been found useful in small trials.[56] Patients may benefit from learning other forms of communication, such as using sign language, laminated cards with printed words or pictures, or artificial voice synthesizers, to express their needs.

NORMAL-PRESSURE HYDROCEPHALUS

Classic triad: Gait, cognition, incontinence

With the onset of symptoms in the sixth or seventh decade, normal-pressure hydrocephalus affects less than 1% of people age 65 and older. It represents up to 5% of dementias, although estimates are influenced by the varied criteria for diagnosis.[61] It is characterized by the classic triad of gait impairment, cognitive impairment, and urinary frequency or incontinence.[62]

Symptoms progress over a period of years, with gait impairment often predominating. As this triad is common in the geriatric population, identifying other explanations is important. Gait impairment caused by spinal stenosis, peripheral neuropathy, or parkinsonism should be explored. Cognitive impairment could be due to depression, Alzheimer disease, or other forms of dementia. Urinary symptoms may be related to detrusor instability or an enlarged prostate.

Gait impairment initially manifests as slowing of gait, but progresses to difficulty with gait initiation. Gait tends to be wide-based (stance more than 1 foot wide).

Cognitive impairment is typically subcortical, manifested as slowed processing speed and impaired executive function. Recall and working memory may be impaired.

Enlarged ventricles seen on imaging in normal-pressure hydrocephalus

Structural neuroimaging reveals enlarged ventricles (Evan's ratio > 0.358). This can be difficult to distinguish from ventriculomegaly due to cerebral atrophy; assessing the callosal angle on MRI may distinguish the two.[63,64] Diagnosis of normal-pressure hydrocephalus can be confirmed using a cerebrospinal fluid infusion test to assess resistance of fluid to resorption.[65]

Frontotemporal dementia accounts for up to 50% of dementias in people younger than 65

Treat with cerebrospinal fluid drainage

Specific tests should be performed to determine candidacy for surgery. These include a high-volume lumbar puncture (40 to 50 mL) or a trial of external lumbar drainage (10 mL per hour for 48 to 72 hours).[65] Definitive treatment is surgical placement of a shunt to allow cerebrospinal fluid to drain into the atria or peritoneal cavity.

Surgery may improve gait, but cognitive symptoms often remain,[66] and clinical decline may occur after the shunt is placed. Once gait dysfunction is resolved, other explanations for cognitive impairment or residual gait impairment should be considered. An underlying reason for progression of normal-pressure hydrocephalus symptoms after surgical intervention should be identified.[67]

TABLE 3

Diagnosis of Creutzfeldt-Jakob disease

Two of the following must be present:

Myoclonus (muscle twitching)

Pyramidal or extrapyramidal findings

Visual or cerebellar deficits

Akinetic mutism (patient appears alert but is unresponsive)

In addition, one of the following tests must be positive:

Electroencephalography positive for periodic sharp-wave complexes

Cerebrospinal fluid with a positive 14-3-3 protein assay

Magnetic resonance imaging with high signal abnormalities in the caudate nucleus and putamen in diffusion-weighted imaging or fluid-attenuated inversion recovery

RAPIDLY PROGRESSIVE DEMENTIAS

Rapidly progressive dementias are among the most challenging of dementing illnesses. They are characterized by a subacute course and an accelerated rate of decline, developing in less than 2 years. Evaluation should typically be more comprehensive than for other types of dementia. The main goal is to diagnose potentially treatable conditions, such as Hashimoto encephalopathy or paraneoplastic limbic encephalitis, and to distinguish these conditions from diseases with a very poor prognosis, such as Creutzfeldt-Jakob disease.

It is important to distinguish primary progressive aphasia from other dementias that affect language

Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a fatal prion-related neurodegenerative illness. Sporadic disease is most common, but variant, familial, and iatrogenic types have been reported. The most common initial symptoms in sporadic disease are cognitive (39%), cerebellar (21%), behavioral (20%), constitutional (20%), sensory (11%), motor (9%), and visual (7%).[68]

Chronic neurodegenerative diseases can be misdiagnosed as Creutzfeldt-Jakob disease because of an atypical time course and multisystem neurologic findings.

The US Centers for Disease Control and Prevention has adopted criteria for diagnosing probable Creutzfeldt-Jakob disease (TABLE 3). Routine investigations should also not suggest an alternative diagnosis.[69]

Autoimmune diseases

Autoimmune conditions may present as a rapidly progressive dementia, including Hashimoto encephalopathy and antibody-mediated limbic encephalitis, either associated with cancer (paraneoplastic) or without cancer (nonparaneoplastic).

Paraneoplastic limbic encephalitis is a group of inflammatory conditions involving antibodies produced within the cerebrospinal fluid and serum resulting in neurologic symptoms. These antibodies react against proteins expressed mostly by a tumor somewhere else in the body.[70]

Hashimoto encephalitis is a subacute to chronic encephalopathy that may present as dementia with abnormally high levels of thyroid antibodies. The symptoms can vary from confusion to psychosis. There are two main presentations: one involves a relapsing-remitting course with stroke-like episodes (27% of patients) and the second consists of insidious onset of seizures (66% of patients).

Diagnosis involves testing for elevated antithyroid peroxidase and thyroglobulin antibodies. MRI findings are nonspecific. Hashimoto encephalitis responds to treatment with corticosteroids, plasmapheresis, or immunosuppressive therapy.[71]

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