Dementia

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Abstract

Dementia often is defined as a progressive cognitive disturbance leading to a loss of independent function. Most clinicians are familiar with the typical pattern of amnestic Alzheimer's disease, the most common neurodegenerative presentation of dementia. Atypical dementia presentations, including atypical Alzheimer's variants, however, may pose a diagnostic challenge for even experienced clinicians. In this article the authors discuss clinical "pearls" for the diagnosis of various neurodegenerative dementia syndromes. When considering the causes of dementia, the mnemonic VITAMINS can be helpful in considering various etiologies.

Keywords

- dementia
- Alzheimer's disease
- dementia with Lewy bodies
- frontotemporal dementia
- progressive supranuclear palsy
- corticobasal degeneration
- primary progressive aphasia
- Jakob-Creutzfeldt disease

Alzheimer's Disease

Alzheimer's disease (AD) accounts for an estimated 60 to 80% of individuals 65 years or older presenting with dementia.[2] The majority of patients with AD present with a typical anterograde amnestic syndrome, with retention of social graces.[3] The most salient clinical feature of typical AD on formal neurocognitive testing is a pattern of memory loss corresponding to mesial temporal lobe atrophy: patients rapidly forget new information, and recall improves little with cueing. Patients with AD, however, will often have dysfunction in at least one other cognitive domain. Additionally, well-established atypical variants of AD exist with predominantly visuospatial, language or frontal/executive features.

Biomarkers may be helpful in establishing the probability of underlying AD pathology (intraneuronal hyperphosphorylated tau tangles and extraneuronal amyloid β [Aβ] plaques). Fluorodeoxyglucose positron emission tomography (PET) may be used to confirm the hallmark finding of temporoparietal hypometabolism in patients with AD,[3] but this test is being supplanted by markers of Aβ amyloid deposition, such as the amyloid (Avid Radiopharmaceuticals) PET scan (e.g. Amyvid; Avid Radiopharmaceuticals Inc.). Although a negative amyloid PET scan strongly suggests a diagnosis other than AD, the interpretation of a positive scan in an elderly patient is more nuanced. Older patients might have amyloid deposition, but not have AD, or they might have mixed pathologies, such as some amyloid deposition along with dementia with Lewy bodies (DLBs). Commercially available cerebrospinal fluid (CSF) analysis may confirm a decrease in CSF amyloid β and an increase in total and phosphorylated tau protein in cases of AD (CSF must be collected directly into a polypropylene tube, as CSF Aβ sticks strongly to nonpolypropylene plastic and could result in artificially low Aβ).

The first step in treatment of a patient with AD, or any form of dementia, is assessment of home safety and caregiver resources. A clinician should assess if a patient is safe unattended. A caregiver should be asked about lapses in a patient's

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turning off the stove burner. A patient should be asked if they know the appropriate plan in case of a fire or other emergency. Access to hazardous items, such as firearms and toxic materials, must be assessed and appropriately adjusted. Patients and caregivers must also be asked about any recent dysfunctions while driving. Some states mandate reporting drivers with a diagnosis of dementia, regardless of driving history. Clinicians must be aware of state law and perform their due diligence, or else they may be liable. Ultimately, some assessment should be made of a caregiver's support system and access to resources (Alzheimer's Association: 1–800–660–1992, http://www.alz.org; Family Caregiver Alliance: 1–800–445–8106, http://www.caregiver.org).

The current mainstay of treatment for AD remains symptomatic management with cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine. Patients may report a subjective improvement in memory and attention after initiation of these medications, but responses are commonly more subtle, with improved stability of symptoms over time. Patients should receive an electrocardiogram to rule out heart block, and receive information about potential side effects (bradycardia, gastrointestinal [GI] distress, vivid dreams, muscle cramps, etc.) prior to induction of a cholinesterase inhibiter. Donepezil is often the first-line treatment in AD. In our experience, doses exceeding 10 mg provide little added benefit in AD and will increase the potential for side effects. The patch formulation of rivastigmine typically has fewer GI side effects, and may be considered in patients who do not tolerate donepezil. Memantine, an uncompetitive N-methyl-D-aspartate receptor antagonist, sometimes is used as an adjunct to cholinesterase inhibitors. This medication is approved for moderate to severe AD, and may provide some symptomatic benefit in late disease.

To date, there are no supplements or nonpharmacological interventions that have been shown to reverse or slow the process of AD. There are lifestyle changes, however, that should be considered. The Mediterranean diet (which is rich in fish, legumes, fruits, vegetables, and unsaturated fatty acids, and low in meat and dairy products) has been associated with a decreased risk of mild cognitive impairment and conversion to AD.[4] Additionally, exercise may improve function in activities of daily living in patients with dementia, though evidence for improvement of cognition is less compelling.[5] We typically recommend gradually increasing to at least 30 minutes of exercise per day, at least 5 days per week, including light resistance training.

Atypical Alzheimer's Disease

Early-onset AD (EOAD), occurring under age 65, typically has a distinct clinical syndrome, with increased disturbances in visuospatial, attention, and executive tasks rather than an isolated predominant amnestic syndrome. Additionally, patients with EOAD may have more widespread frontal, parietal, occipital, and temporal atrophy on imaging than typical AD cases, which usually have medial temporal and parietal atrophy.[6]

The frontal/dysexecutive variant of AD present with chiefly dysexecutive syndrome and represents a minority of AD patients. A small portion of this frontal/dysexecutive variant of AD can be further subdivided into a so-called behavioral variant of AD. These patients may meet formal clinical criteria for behavioral variant frontotemporal dementia (bvFTD), though their clinical syndrome is generally milder than typical bvFTD and more often occurs with concomitant memory disturbance.[7]

The language variant of AD presents first and foremost as a primary progressive aphasia. This syndrome is further described below in our discussion of logopenic variant primary progressive aphasia (lvPPA).

The visuospatial variant of AD presents with a syndrome known as *posterior cortical atrophy* (PCA). A minority of PCA cases alternatively have underlying Lewy body, corticobasal degeneration, or prion disease pathology. Posterior cortical atrophy is associated with higher-order visuospatial and cognitive syndromes, including profound visual agnosias (with retained object knowledge), Bálint's syndrome (simultagnosia, optic ataxia, and optic apraxia), Gerstmann's syndrome (acalculia, agraphia, finger agnosia, left/right disorientation), and apraxia.[8]

Lewy Body Disease

Lewy body-mediated disorders, including PD and DLB, frequently experience a clinical prodrome (often decades before their obvious decline) including depression, anosmia, severe constipation, and rapid eye movement (REM) sleep behavior disorder (RBD).[9] A presentation with RBD suggests $>$ 75% chance of developing an α-synuclein-mediated disease later in life.

Dementia with Lewy bodies refers to a clinical syndrome arising from intraneuronal deposition of Lewy bodies (containing α-synuclein) diffusely in the cortex and within the substantia nigra. Clinical DLB is restricted to patients with the central feature of dementia preceding or concurrent with (within 1 year) parkinsonism, whereas PD with dementia (PDD) refers to dementia occurring over 1 year after the onset of parkinsonism.[10] Most experts feel that DLB and PDD fall along a spectrum of Lewy body disease. To meet criteria for probable DLB, a patient must have the central feature and have either two or more core features or at least one core feature and one suggestive feature.

- The core features of DLBs include[10]
  - Spontaneous features of parkinsonism (as discussed above)
  - Pronounced fluctuations in attention/alertness
  - Visual hallucinations in DLB are often of animals, insects, children, or small people, frequently accompanied by the realization that the hallucinations are benign or unreal. Extracampine hallucinations (a sense of something or someone is present in their periphery, just out of view) and visual distortions (such as seeing faces in tree bark or in patterned clothing) are also common.

- The suggestive features of DLB include[10]
  - Extreme neuroleptic sensitivity
  - RBD
  - Low dopamine transporter uptake in basal ganglia demonstrated by 123-β-CIT single photon emission computed tomography (SPECT; ioflupane i-123 and iodine [DaTscan]), or FDG-PET imaging that shows a distinctive pattern. In contrast to bilateral temporoparietal reductions in FDG metabolism seen in AD, DLB shows globally reduced cortical metabolism, most notably in the visual association cortex of the occipital lobe.[11,12] The "cingulate island" sign refers to the relative sparing of the posterior cingulate relative to the precuneus and cuneus seen in DLB, but not AD.[13]

Additional supportive clinical features of DLB include autonomic dysfunction (including syncope, hypotension, erectile dysfunction, and urinary incontinence), depression, low uptake on MIBG (metaiodobenzylguanidine) myocardial scintigraphy, imaging findings as discussed above, prominent slow waves on electroencephalography (EEG), and elaborate delusions. Elaborate delusions in DLB might consist of reduplicative paramnesias, in which the patient feels that their home is actually a copy, or Capgras' syndrome, in which they feel a loved one is an imposter.

The typical cognitive profile of DLB on neuropsychological testing involves visuospatial difficulty with a subcortical pattern of dysfunction, involving poor attention, executive dysfunction, and poor memory, specifically with poor immediate recall. They usually, however, have relatively better delayed recall of learned information than patients with AD.[14]

Rivastigmine patch is typically the first line of treatment for cognitive symptoms in patients with Lewy body disease. This medication also has established efficacy in treating the behavioral features of Lewy body disease, including apathy, anxiety, delusional thinking, and visual hallucinations.[15] We recommend optimization with rivastigmine, or another acetyl cholinesterase inhibitor, prior to induction of a levodopa trial in patients with Lewy body-related cognitive decline, to mitigate the hallucinations and psychosis that might occur. Antipsychotics should be avoided as much as possible, though judicious use of quetiapine (which has low D2 affinity) may be considered in patients with disruptive refractory psychosis. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram and escitalopram, should also be considered in patients with Lewy body disease, given their high rate of depression.

Frontotemporal Dementia

Frontotemporal dementia (FTD) refers to clinical syndromes arising from progressive degeneration of the frontal and anterior temporal lobes. It is the most common dementia syndromes under age 65. Frontotemporal dementia is subdivided into three clinical syndromes: *behavioral variant frontotemporal dementia* (bvFTD), and two forms of primary progressive aphasia: *nonfluent/agrammatic variant primary progressive aphasia* (nfvPPA) and *semantic variant primary progressive aphasia* (svPPA; previously called semantic dementia). These aphasia syndromes are further discussed below. Corticobasal syndrome (CBD) and progressive supranuclear palsy (PSP) are clinically defined largely by motor features, but their cognitive and behavioral syndromes are typically within the FTD spectrum.

Patients with bvFTD are distinct in that a behavioral disturbance is the foremost feature of their disease. They typically lack insight or concern regarding their inappropriate behavior. To meet criteria for bvFTD, patients should have at least three of the following features:

1. Early behavioral disinhibition
2. Early loss of empathy
3. Early apathy or inertia
4. Obsessive/compulsive behavior
5. Dietary changes (including binge eating)
6. Executive dysfunction on formal testing, with relative sparing of episodic memory and visuospatial skills[16]

Importantly, executive dysfunction alone is not specific to the disease, although many patients are referred to our center with an erroneous diagnosis of bvFTD solely due to such deficits.[16]

An obvious loss of disgust is often present, including disregard for personal hygiene. Aggression and irritability may occur, but passivity and ambivalence are often the most prominent features of their personality change.

Most of the symptoms of bvFTD correlate with areas of atrophy in bilateral (often right > left) frontotemporal lobes (►**Fig. 1**). The right temporal lobe variant of svPPA (a temporal lobe predominant disorder), however, also overlaps with the

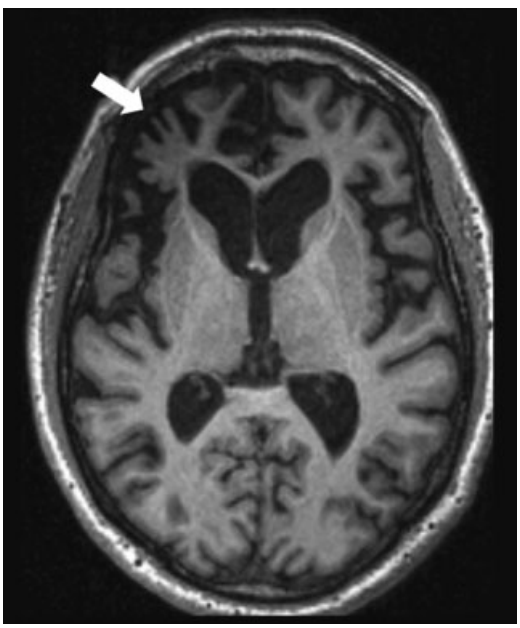

Fig. 1 Axial T1-weighted magnetic resonance imaging (MRI) in a 62-year-old patient with behavioral variant frontotemporal dementia showing profound right > left frontal lobe (*arrows*) atrophy. Orientation is radiological.

clinical syndrome of bvFTD, which is discussed below with other progressive aphasias.

Patients with bvFTD may also develop motor neuron disease (FTD-MND).[17] As many as one in seven bvFTD patients develop MND, which presents like sporadic MND, although leg muscles may be spared in the early stages. *Frontotemporal dementia-MND* has strong associations with TDP-43 type B protein deposition on pathology and the *C9Orf72* mutation or other mutations. *C9Orf72* mutations are large hexanucleotide repeat expansions (GGGGCC) in the intron region of chromosome 9, leading to RNA nuclear accumulation and suppression of gene expression. *C9Orf72* mutations are the most common genetic cause of bvFTD-MND, accounting for about a third of familial cases in the Western world. Motor features may precede bvFTD, presenting first as amyotrophic lateral sclerosis, or follow the onset of bvFTD. The bvFTD clinical phenotype may also overlap with corticobasal syndrome and progressive supranuclear palsy motor syndromes.

Selective serotonin reuptake inhibitors, such as citalopram and escitalopram, have been observed to have some efficacy in controlling the behavioral symptoms of bvFTD, irritability, impulsivity, dietary change, repetitive behavior, obsessive/compulsive behavior, disinhibition, and inappropriate sexual behavior. Acetylcholinesterase inhibitors are generally not helpful in bvFTD and may worsen behavioral symptoms.[18]

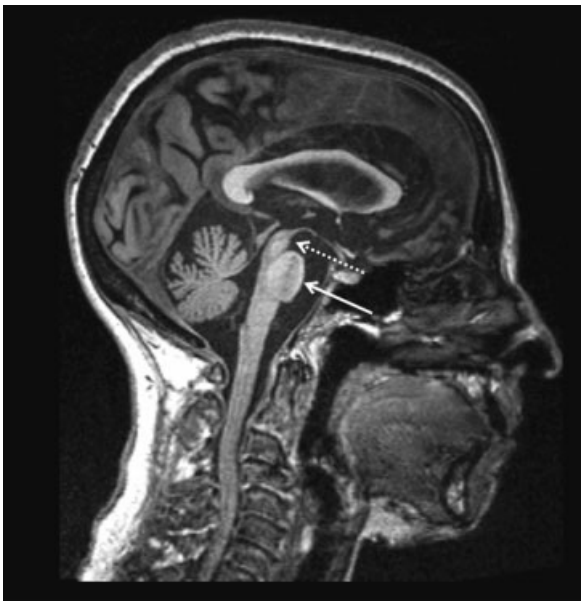

Fig. 2 Sagittal T1-weighted magnetic resonance imaging in 63-year-old a patient with progressive supranuclear palsy, showing "hummingbird sign." Atrophy of the midbrain tegmentum (arrow with dashed line) resembles a hummingbird head in the midsagittal plane, with a relatively preserved pons (arrow with solid line) that resembles the bird's belly.

Progressive Supranuclear Palsy

The core features of the classic progressive supranuclear palsy (PSP; Steele-Richardson syndrome) are early gait instability and supranuclear gaze palsy (mostly affects vertical downward saccades).[19] Early severe falls (usually backward and out of proportion to the degree of parkinsonism) are a major red flag that a patient might have PSP. The atypical parkinsonism of PSP often includes axial predominant and symmetric rigidity, a lack of tremor, and prominent masking of facies. Patients typically have a hypophonic and nasal voice, as well as dysphagia. Other classic exam findings might include a wide open stare, the procerus sign (furrowing of the brow), and perseveration while attempting to clap three times (applause sign), although some of these are relatively nonspecific. The applause sign, for example, is merely indicative of a frontal lobe dysfunction. The parkinsonism of PSP is usually not very L-dopa responsive (although mild benefit can occur with low doses), but a trial can be useful diagnostically. Dementia in PSP involves frontal lobe dysfunction with hallmark apathy, executive dysfunction, and sometimes a nonfluent aphasia. Some studies suggest the hummingbird or penguin sign on sagittal MRI (►**Fig. 2**) is highly suggestive of PSP,[20] but this is controversial and probably at best it might be helpful in differentiating PSP from idiopathic PD, which usually can be done by history and examination.

Aside from the classic PSP phenotype, other variants exist including PSP-parkinsonism (which may have asymmetric moderately L-dopa responsive parkinsonism); PSP-pure akinesia with gait freezing (PSP-PAGF), characterized by severe decreased movement, gait freezing, rigidity, and reduced fine motor tasks; corticobasal syndrome (CBS; see below); and nonfluent variant primary progressive aphasia (see nfvPPA below; also called primary nonfluent aphasia or PNFA).[21]

Behavioral symptoms in PSP may be treated with SSRIs, as with bvFTD. A trial of levodopa is warranted in patients with parkinsonism from PSP. A minority of patients with PSP may be levodopa responsive, particularly patients with the PSP-parkinsonism clinical phenotype.

Corticobasal Syndrome

Patients with probable corticobasal syndrome (CBS) exhibit at least two hallmark (usually asymmetric) motor findings, including limb rigidity, dystonia, or limb myoclonus, along with at least two additional cortical phenomena, including alien limb syndrome, cortical sensory disturbance (with neglect, astereognosis, or agraphesthesia), or apraxia (orobuccal or limb).[22] They typically present with a dysexecutive pattern of cognitive decline.

It is important to make a distinction between CBS and corticobasal degeneration (CBD). CBS is a pathological diagnosis defined by tau (4-repeat variety) immunoreactive inclusions in the glia and neurons of the cortex and striatum, particularly in the form of astrocytic plaques in gray and white matter. Corticobasal degeneration is the most common cause of CBS, but it does not underlie the majority of CBS, and the terms are not synonymous. Corticobasal syndrome may be described in patients with underlying AD, PSP, Jakob-Creutzfeldt disease (JCD), and CBD pathology, as well as various other known underlying pathologies of FTD spectrum disease.[23]

Although CBD was historically thought to have a classic CBS presentation, it has several clinical phenotypes including the executive motor (EM) clinical phenotype (with a dysexecutive dementia a variable amount of CBS motor features), bvFTD, nonfluent primary progressive aphasia (described below), and rare cases of PCA.[23]

Primary Progressive Aphasia

Primary progressive aphasia (PPA) is a term applied to neurodegenerative diseases with a disabling language disturbance as the first and most prominent feature. All three variants of PPA (svPPA, nfvPPA, and lvPPA) may experience difficulty with confrontational naming, but the mechanism of their naming errors is unique to each syndrome. Differences in fluency, repetition, comprehension, and object knowledge (what objects are) are also points of distinction among the following three PPA variants[24]:

1. *Semantic variant PPA* (svPPA) is a clinical syndrome with asymmetric atrophy of the anterior temporal lobes (►**Fig. 3**). Patients with predominantly left temporal atrophy typically experience disruption in the retrieval of semantic information (knowledge of what things are). This primary loss of semantic information leads to their inability to identify items and understand isolated words. Patients usually also experience poor knowledge of irregular spelling, leading to surface dyslexia in which they incorrectly pronounce irregularly spelled words phonetically (e.g., colonel, knight, yacht, etc.). Their speech is typically vague and imprecise, referring to objects as "things" or by superordinate or vague categories, such as calling a cat or a dog "that animal." Repetition, phonology, and fluency usually intact. Despite this loss of word meaning, they can be quite fluent and even chatty. The right temporal predominant variant of svPPA may appear less aphasic at presentation, as patients will chiefly lose semantic knowledge of faces and emotional content; they can differentiate among faces, but do not know who they are, nor do they understand the emotional expressions. Whereas both left and right svPPA patients may experience disinhibition and compulsions, the right temporal variant has the most overlap with the bvFTD phenotype. Patients with right temporal svPPA symptoms may appear cold or gleefully childish and experience hyposexuality, faddish changes in food preference, and philosophical intensification (including hyperreligiosity).
2. *Nonfluent variant PPA* (nfvPPA) is due to left posterior frontal and insular atrophy, and presents with effortful, halting, groping, and distorted/slurred word production. Fluency usually markedly impaired, with loss of grammar and decreased overall speech output. Repetition is also impaired. There is relative retention of language comprehension, but patients with nfvPPA may have difficulty interpreting syntactically or grammatically complicated sentences. As stated earlier, nfvPPA is most commonly due to underlying CBD pathology.
3. *Logopenic variant PPA* (lvPPA) individuals experience frequent word finding pauses, but their confrontational naming and casual speech are most disrupted by either recurrent substitution of one word by another real word (semantic paraphasia) or of a syllable for another intended syllable (phonemic paraphasia). Semantic paraphasias often involve closely related words (e.g., car for van, finger for hand, clock for watch). With phonemic paraphasias, the words often are nonsensical, but well pronounced. Fluency is intact though word-finding pauses may cut their speech into islands of fluency with intact grammar. Single-word and sometimes longer sentence comprehension also are spared. Repetition is impaired, particularly with longer phrases. As discussed above, most lvPPA cases are due to underlying Alzheimer's pathology. The hallmark imaging findings of lvPPA include predominant left posterior perisylvian (particularly superior temporal) and/or lateral parietal atrophy.

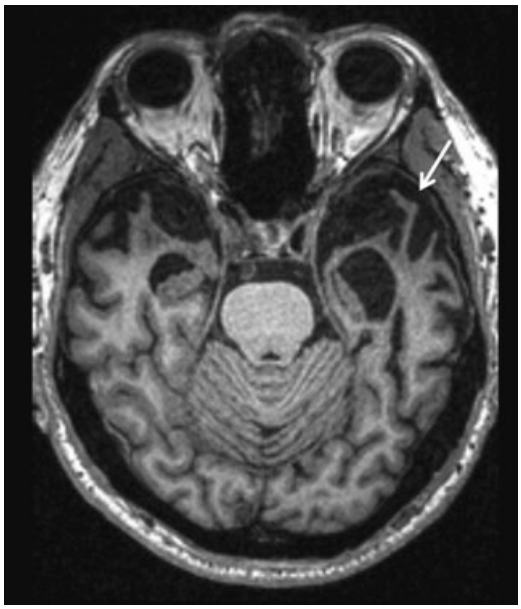

Fig. 3 T1-weighted magnetic resonance imaging in a 63-year-old patient with semantic variant primary progressive aphasia, showing profound left (noted by an arrow) greater than right anterior temporal lobe atrophy. Orientation is radiological.

Rapidly Progressive Dementia

For most neurodegenerative diseases, it takes several years from onset to the development of dementia. Rapidly progressive dementias (RPDs) are often defined as conditions in which from onset of symptoms to dementia takes < 1 to 2 years, typically weeks to months. The prototypical and most common RPD is Jakob-Creutzfeldt disease (JCD). Other common causes of RPD are atypical presentations of nonprion neurodegenerative diseases (e.g., AD, DLBs, FTD, CBD, PSP, etc.), autoimmune diseases (antibody-mediated encephalopathies), infections, neoplasms, and toxic metabolic causes.[25–27] Unfortunately, JCD is universally fatal and sometimes difficult to distinguish from a host of other, potentially treatable disorders. It is therefore crucial to entertain a wide differential diagnosis in

Table 1 VITAMINS mnemonic for the differential of dementia, including RPD, and some examples of various RPDs

Vascular	Multiple infarctions, strategic infarct dementia, arteriovenous malformations and fistulas, hypertensive encephalopathy
Infection	Neurosyphilis, Whipple's disease, Lyme disease, viral encephalitis including HIV and HSV, coccidiomycosis, and other fungal infections
Toxic-metabolic	Wernicke's encephalopathy, osmotic demyelination syndrome, hepatic encephalopathy, acute intermittent porphyria, leukoencephalopathies, and inborn errors of metabolism
Autoimmune	Autoimmune encephalitis (paraneoplastic or not), ADEM, lupus cerebritis, sarcoid
Malignancy	Gliomatosis cerebri, CNS lymphoma, metastases
Iatrogenic	Psychotropic medication, particularly with polypharmacy, anticholinergics
Neurodegenerative	JCD, AD, DLB, bvFTD, PSP, and CBD
Systemic/seizure/structural	Sarcoid, nonconvulsive status epilepticus, normal pressure hydrocephalus, hydrocephalus, spontaneous intracranial hypotension

Abbreviations: AD, Alzheimer's disease; ADEM, acute disseminated encephalomyelitis; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; CBS, corticobasal syndrome; CNS, central nervous system, DLB, dementia with Lewy bodies; HIV, human immunodeficiency virus; HSV, herpes simplex virus; JCD, Jakob-Creutzfeldt disease; RPD, rapidly progressive dementia; PSP, progressive supranuclear palsy.

all RPD cases. A comprehensive differential diagnosis may be aided by the pneumonic, VITAMINS (vascular, infection, toxic-metabolic, autoimmune, malignancy, iatrogenic, neurodegenerative, systemic/seizure/structural; ►**Table 1**).

The most common first symptom in JCD(~40% of cases) involves cognitive disturbance (executive dysfunction, memory issues, language impairment), followed by behavioral/psychiatric changes, cerebellar ataxia, and even constitutional symptoms (~20% each). Visual symptoms (e.g., blurring, hallucinations, or diplopia) present in approximately 10% of patients. Extrapyramidal features, including parkinsonism, chorea, and dystonia, are less common and occur in just under 10% of subjects.[28] Myoclonus, typically stimulus-sensitive, or "startle" occurs in the majority of cases. Periodic sharp waves at a frequency of 1 to 2 Hz on EEG occur in about 2/3 of CJD cases, but often require serial testing and usually are not present until late stage of disease.

Prominent psychiatric features (e.g., anxiety, depression, or psychosis) and seizures may suggest an autoimmune-mediated RPD etiology, including limbic encephalitis (anti-Hu, N-methyl-D-aspartate receptor, voltage-gated potassium channel complex, CV2, etc.).[29] Some of these syndromes may be paraneoplastic and precede the discovery of an antecedent neoplasm. Prominent and early psychiatric features can also occur in CJD as well as other RPDs, however. A small percentage of CJD cases (<5%) have seizures.

Brain magnetic resonance imaging (MRI) is generally the most sensitive study for detecting early JCD and is highly specific. Findings include a cortical ribbon of hyperintensity ("cortical ribboning") seen on fluid-attenuated inversion-recovery (FLAIR) and diffusion-weighted imaging (DWI). Common locations include the cingulate gyrus, portions of the neocortex (typically sparing the precentral gyrus), and FLAIR/DWI hyperintensity in the striatum and/or thalamus (►**Fig. 4**). These findings are supported by matching hypointensity on apparent diffusion coefficient (ADC) sequences, suggesting restricted diffusion.[30,31] Unfortunately, even experienced radiologists often miss the pathognomonic findings of JCD on MRI[32,33]; thus, it is crucial that neurologists review their patient's MRIs personally. In addition to FLAIR, DWI, ADC MRI sequences, other necessary sequences when RPD is suspected should include T1 with and without contrast, T2 and gradient recalled echo (GRE; or some other hemosiderin sequence) to exclude amyloid angiopathy.[34]

Cerebrospinal fluid evaluation is essential in cases of suspected RPD; CSF 14–3-3 alone is neither sensitive (53–97% in the literature) nor specific (40–100%) enough to constitute a valid investigation for JCD, but a positive test can be support the presence of rapid neuronal injury due to

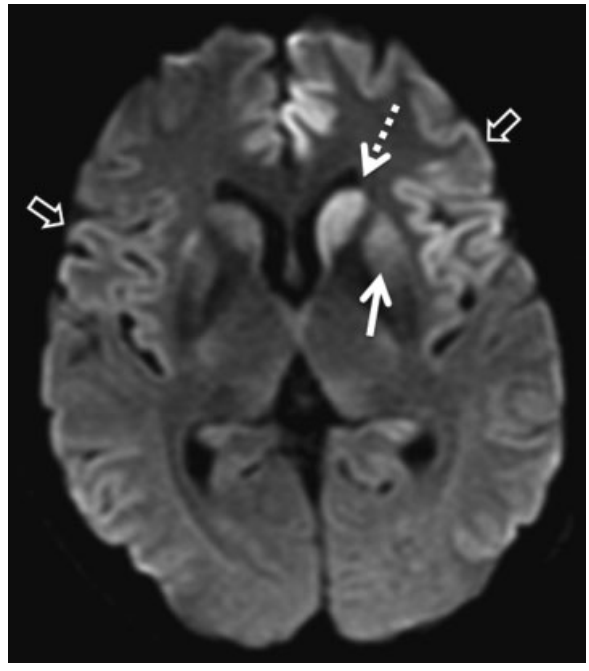

Fig. 4 Diffusion-weighted imaging (DWI) magnetic resonance imaging in a 47-year-old patient with Jakob-Creutzfeldt disease demonstrating restricted diffusion (hyperintensity) of the caudate (*dashed arrow*) and putamen (*solid arrow*), as well as cortical ribboning (*arrow outline*). Orientation is radiological.

CJD or other etiologies. Use of multiple biomarkers of rapid neuronal injury, including 14–3-3, total tau, and neuron-specific enolase (NSE may) increase the sensitivity, but cannot be used to definitively confirm or exclude JCD. A newer, highly specific test for prion disease, reverse-templated quake-induced conversion (RT-QuIC) is available in some countries through their CJD surveillance centers. This test has about 98 specificity for JCD, but unfortunately a much lower sensitivity (77–92%), although modifications to this test are leading to improved sensitivities.[31] The CSF Ig Index and oligoclonal bands are also important CSF studies, as they may be elevated in inflammatory or autoimmune neurologic diseases. Cerebrospinal fluid cell count, protein, glucose, and a Venereal Disease Research Laboratory test (VDRL) should be performed on all patients, and herpes simplex virus polymerase chain reaction (HSV PCR) must be considered if encephalitis is suspected.

A first tier of blood tests to consider in patients with RPD might include a complete blood count, a basic metabolic panel (including magnesium, phosphorus, and calcium), liver function testing, ammonia, thyroid function testing (thyroid-stimulating hormone [TSH] and free T4), B12 level (with methylmalonic acid and homocysteine), a basic rheumatologic panel (antinuclear antibody [ANA], erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], rheumatoid factor (RF), antineutrophil cytoplasmic antibodies [ANCAs]), rapid plasmin reagin (RPR), human immunodeficiency virus (HIV) serology (or viral load if acute infection is suspected). Additional studies should be ordered based on clinical suspicion, including Lyme serologies and PCR, a search for other tick-borne illnesses, Wilson's disease studies, and an extended panel for connective tissue disease.[29] If considering an autoimmunomediated encephalopathy, a complete a panel of autoantibodies should be sent.

There is currently no effective treatment to slow the progression of prion disease, and treatment chiefly involves supportive care. Depression and anxiety may be treated with SSRIs. Psychosis, agitation, and aggression may be managed judiciously with small doses of an atypical antipsychotic, such as quetiapine. Severe and debilitating myoclonus may response to low doses of clonazepam or antiseizure medications such as valproic acid or levetiracetam.

Disclosures

Dr. Geschwind serves on the board of directors for San Francisco Bay Area Physicians for Social Responsibility, on the editorial board of *Dementia & Neuropsychologia*, and serves or has served as a consultant for Best Doctors, Inc; the Gerson Lehrman Group, Inc; Guidepoint Global, LLC; Lewis Brisbois Bisgaard & Smith LLP; Lundbeck Inc; MEDACorp; NeuroPhage Pharmaceuticals; and Quest Diagnostics. He receives research support from CurePSP, the Michael J. Homer Family Fund, the National Institute on Aging (R01 AG AG031189), Quest Diagnostics, and the Tau Consortium.

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References

1 Galasko D. The diagnostic evaluation of a patient with dementia. Continuum (Minneap Minn) 2013;19(2 Dementia):397–410
2 Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11(3):332–384
3 McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263–269
4 Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009;66(2):216–225
5 Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev 2015;4:CD006489
6 Migliaccio R, Agosta F, Possin KL, et al. Mapping the progression of atrophy in early- and late-onset Alzheimer's disease. J Alzheimers Dis 2015;46(2):351–364
7 Ossenkoppele R, Pijnenburg YA, Perry DC, et al. The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. Brain 2015;138(Pt 9):2732–2749
8 Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012;11(2):170–178
9 Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord 2015;30(12):1600–1611
10 McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65(12):1863–1872
11 Lim SM, Katsifis A, Villemagne VL, et al. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. J Nucl Med 2009;50(10):1638–1645
12 Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol 2001;50(3):358–365
13 Graff-Radford J, Murray ME, Lowe VJ, et al. Dementia with Lewy bodies: basis of cingulate island sign. Neurology 2014;83(9):801–809
14 Guidi M, Paciaroni L, Paolini S, De Padova S, Scarpino O. Differences and similarities in the neuropsychological profile of dementia with Lewy bodies and Alzheimer's disease in the early stage. J Neurol Sci 2006;248(1–2):120–123
15 McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000;356(9247):2031–2036
16 Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134(Pt 9):2456–2477
17 Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology 2002;59(7):1077–1079
18 Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry 2007;15(1):84–87

19 Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47(1):1–9
20 Kim YE, Kang SY, Ma HI, Ju YS, Kim YJ. A visual rating scale for the hummingbird sign with adjustable diagnostic validity. J Parkinsons Dis 2015;5(3):605–612
21 Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009;8(3):270–279
22 Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80(5):496–503
23 Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. Ann Neurol 2011;70(2):327–340
24 Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011; 76(11):1006–1014
25 Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann Neurol 2008;64(1):97–108
26 Sala I, Marquié M, Sánchez-Saudinós MB, et al. Rapidly progressive dementia: experience in a tertiary care medical center. Alzheimer Dis Assoc Disord 2012;26(3):267–271
27 Papageorgiou SG, Kontaxis T, Bonakis A, Karahalios G, Kalfakis N, Vassilopoulos D. Rapidly progressive dementia: causes found in a Greek tertiary referral center in Athens. Alzheimer Dis Assoc Disord 2009;23(4):337–346
28 Rabinovici GD, Wang PN, Levin J, et al. First symptom in sporadic Creutzfeldt-Jakob disease. Neurology 2006;66(2):286–287
29 Paterson RW, Takada LT, Geschwind MD. Diagnosis and treatment of rapidly progressive dementias. Neurol Clin Pract 2012;2(3): 187–200
30 Takada LT, Geschwind MD. Prion diseases. Semin Neurol 2013; 33(4):348–356
31 Geschwind MD. Prion diseases. Continuum (Minneap Minn) 2015; 21(6 Neuroinfectious Disease):1612–1638
32 Carswell C, Thompson A, Lukic A, et al. MRI findings are often missed in the diagnosis of Creutzfeldt-Jakob disease. BMC Neurol 2012;12(1):153
33 Geschwind MK, Kuryan C, Cattaruzza T, et al. Brain MRI in sporadic Jakob-Creutzfeldt disease is often misread. Neurology 2010;74 (Suppl 2):A213
34 Vitali P, Migliaccio R, Agosta F, Rosen HJ, Geschwind MD. Neuroimaging in dementia. Semin Neurol 2008;28(4): 467–483