Distinguishing Different Dementias

Diagnosing dementia, and its many types, can be challenging for physicians. Patients can exhibit a broad range of symptoms which can overlap with other age-related disorders. Diagnosis is, of course, the important first step in treating and managing dementia. This article reviews diagnostic criteria for the most common dementias, as well as their differential features.

by Richard Camicioli, MD, FRCPC

Introduction

Alzheimer's disease (AD) is the most common dementia, accounting for the majority of cases in the elderly. Differentiation of AD from other common dementias is important in order to implement an appropriate treatment plan and to provide prognostic information for patients and their families.

Criteria for distinguishing types of dementias include: demographics, risk factors, clinical course, examination features and laboratory findings. Complicating the differential diagnosis of dementia is the fact that neurodegenerative and other age-related disorders (such as ischemic disease) can overlap. Also, advanced dementias may resemble each other. In a minority of cases, an accurate diagnosis cannot be made in living patients. This highlights the importance of obtaining an autopsy for deceased dementia patients. This article first reviews diagnostic criteria for the most common dementias (see Table 1, Figure 1) and briefly discusses the differential features of various dementias (see Table 2).

Dr. Camicioli is an Associate Professor, Department of Medicine (Neurology), at the University of Alberta, Edmonton.
He is also on staff at the Glenrose Rehabilitation Hospital, Edmonton, Alberta.

Common Dementias

AD is characterized by an insidious onset of progressive impairment of memory, as well as other areas of cognition, including orientation, language, visuospatial function and praxis.[1] Personality change and marked impairment in attention and executive function raise, however, the possibility of other causes of dementia, such as the frontotemporal dementias (FTDs).[2] Occasionally, AD presents with focal features.[3] Marked early motor impairment, including abnormal gait, while common in the later stage of AD,[4] is unusual in the early stage of AD and raises the possibility of vascular dementia (VaD) or dementia with Lewy bodies (DLB). Diagnostic criteria are available for VaD,[5,6] DLB,[7] and FTD but are still being developed for Parkinson's disease with dementia (PDD).[8,9]

Vascular dementia. VaD, dementia caused by cerebrovascular disease, is the second most common form of dementia, accounting for 10% to 20% of cases of dementia in the elderly. "Pure" VaD is relatively uncommon. VaD can be caused by multiple cerebral infarctions, which can be cortical (the left angular gyrus, the frontal lobes and the medial temporal lobes) or subcortical (thalamus, genu of the internal capsule, and caudate nucleus), single strategic infarctions, or diffuse white matter disease.

Cerebrovascular disease is a risk factor for AD, but can also coexist with AD.[10] In fact, a combination of AD and cerebrovascular disease is more likely than VaD. An acute onset, stepwise decline, focal neurological signs, gait impairment and urinary difficulties are suggestive of VaD, especially in the setting of vascular risk factors. Cerebrovascular events can, however, be clinically silent and dementia can progress insidiously.[11]

The Hachinski Scale and the National Institute of Neurological Disorders and Stroke Association –*Association Internationale pour l'Enseignement en Neurosciences* (NINDS-AIREN) criteria are specific to identifying multi-infarct dementia, but are insensitive.[12,13] The California Alzheimer Disease Diagnosis and Treatment Centers (ADDTC) criteria,[5] and Mayo Clinic criteria[14] have improved sensitivity and reasonable specificity.

The term "subcortical dementia," first described in progressive supranuclear palsy (PSP) refers to a dementia where cognitive slowing, apathy, executive dysfunction and pseudobulbar palsy are prominent features in the absence of "cortical" dementia features (aphasia, apraxia and agnosia). Recent studies, comparing cognitive impairment between subcortical VaD and AD, have found that patients with vascular cognitive impairment have relative sparing of memory and worse executive function compared to AD,[15] though imaging changes can overlap with normals.[16]

Parkinson's disease dementia and dementia with Lewy bodies. Cortical Lewy bodies are found in both PDD and DLB. In PDD, parkinsonism precedes cognitive changes by one year or longer, whereas in DLB, dementia and parkinsonism co-occur within a year of each other. Both can exhibit coexistent AD pathology, which influences the clinical presentation.

Table 1

Non-AD Dementias

Vascular Dementia
- Multi-infarct dementia
  - cortical
  - sub-cortical
- Subcortical vascular dementia
- Strategic infarct-related dementia
- Mixed dementia: Alzheimer/Vascular
- Amyloid angiopathy
- Hereditary vascular dementias
  - cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy (CADASIL)

Dementia with Lewy Bodies
- Dementia with Lewy bodies (DLB)
  - pure DLB
  - mixed Alzheimer/DLB
- Parkinson's disease with dementia

Frontotemporal dementia
- Behavioral variant
- Progressive non-fluent aphasia
- Semantic dementia
- Frontotemporal dementia with motor neuron disease

Other focal neurodegenerative syndromes
- Progressive apraxia
  - corticobasalganglionic degeneration
  - Alzheimer's disease
- Progressive visuospatial impairment
  - Alzheimer's disease
  - subcortical gliosis
  - Creutzfeld Jakob disease

Toxins
- Alcohol

Normal Pressure Hydrocephalus

Dementia related to structural pathology
- malignant tumors
- benign tumors (depends on location)
- absesses

Inflammatory disorders
- Multiple sclerosis
- Vasculitis
  - with systemic involvement
  - without systemic involvement
- Systemic lupus erythematosis
- Sjogren's syndrome
- Sarcoidosis
- Bechet's disease
- Non-vasculitic autoimmune encephalomyelitis (NAIM)

Infection-related dementias
- Creutzfeldt Jakob disease
- HIV-related dementia
- Syphillis
- Whipple's disease
- Herpes encephalitis and other viral encephalitides
- Chronic meningitis
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis

Metabolic-related dementias
- B12 deficiency
- Thyroid disease
- Parathyroid disease

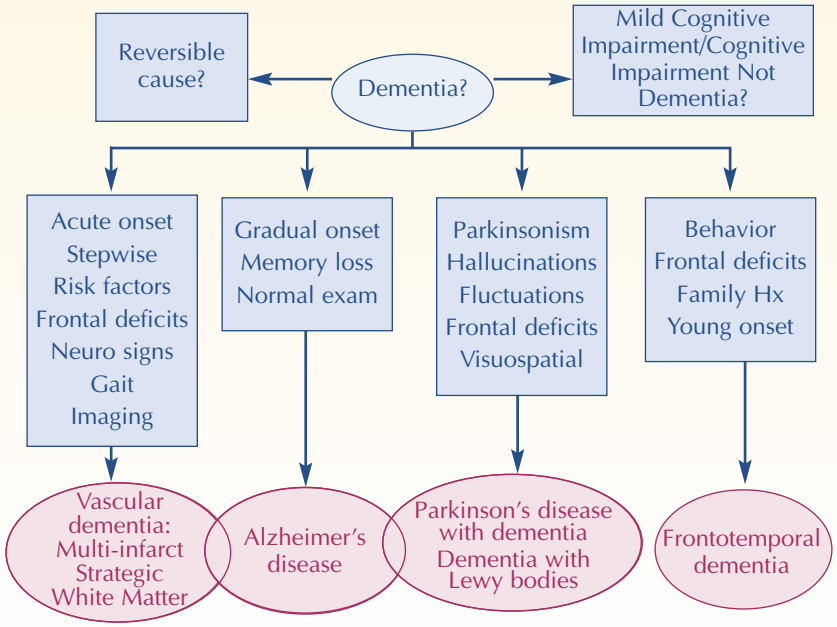
Hereditary dementias

Diagnostic features of DLB include visual hallucinations, fluctuating cognition and parkinsonism; two of these three features must be exhibited for a diagnosis of probable DLB, while one of these exhibited features is sufficient for a diagnosis of possible DLB. Sensitivity might be improved by considering secondary symptoms such as syncope, falls, psychosis and visuospatial problems on examination.[17]

Patients with Parkinson's disease develop dementia at a rate of up to 10% per year,[18] with a prevalence of 20% to 30%.[19] PDD and DLB

Figure 1

Differential Diagnostic Consideration for Common Dementias



patients exhibit attention, executive and visuospatial impairment.[7] Sleep disturbance, specifically rapid-eye-movement sleep disorder, is strongly associated with synuclein pathology, including diffuse Lewy bodies.[7] Hallucinations and fluctuations are more common in DLB, but occur in PDD, and are more common in DLB than in AD.[7] Although extra-pyramidal signs may be less severe in DLB compared with PDD, response to levodopa may be better in PDD.[7]

Frontotemporal dementias. FTDs are characterized by behavioral and personality changes and cognitive deficits predominantly affecting executive function and language. Compared with AD, FTD patients exhibit a greater degree of behavioral and executive impairment with relative sparing of episodic memory and visuospatial function.[20] Behavioral difficulties including decreased insight, decreased attention to personal care, disinhibition, and inappropriate behavior are prominent in behavioral variant FTD, but also occur in other subtypes of FTD.[21] Language problems seen in FTD variants—primary progressive aphasia and semantic dementia—occasionally lead to diagnostic confusion. Diverse clinical presentations can be imperfectly matched to a variety of pathologies that include tau-positive (ballooned neurons, Pick bodies) or tau-negative changes (ubiquitin-positive inclusions or neuronal loss with gliosis).[22] Tau-negative, ubiquitin-positive inclusions are seen in FTD and in motor neuron disease.

Normal pressure hydrocephalus (NPH). NPH is a potentially treatable syndrome defined by dementia and associated with gait impairment and urinary urgency or incontinence.[23] If one suspects NPH, differential diagnostic considerations include obstructive hydrocephalus, multiple system atrophy (associated with ataxia and incontinence) and vascular dementia with gait impairment. The clinical triad, along with hydrocephalus on imaging, is predictive of shunt responders.[24] Clinical features associated with a positive response include a shorter duration of illness, lack of cortical cognitive deficits and positive response to removal of cerebrospinal fluid, by external or internal lumbar drainage, or by single or repeated lumbar puncture. While duration of cognitive impairment and other features predict poor response, patients may respond despite negative predictors.

Clinical Features and Differential Diagnosis

Age of onset. Age of onset can help in the differential diagnosis of dementia. In a study, Huntington's disease (HD) was the most prevalent cause of dementia in people aged 45 to 65 years, with 18 cases per 100,000, followed by AD and FTD which both had a prevalence of 15 cases per 100,000.[25] VaD accounted for 8.2 cases and DLB accounted for 6.9 cases per 100,000. A second study found that AD was most common with 41 cases per

100,000, followed by 17.9 cases of VaD, 15.4 cases of FTD and 13.6 cases of alcohol-related dementia per 100,000.[26] Futhermore, a study of people aged 65 years and older found the proportion of dementias to be: AD 31.3%; VaD 21.9%; DLB 10.9% and FTD 7.8%.[27] This is also consistent with a Finnish study of people aged 75 years and older.[28] In addition, early-onset adult dementias can occur due to a genetic or metabolic disorder of childhood onset presenting with a later onset.[29-31]

Family history. The presence of a family history can provide clues to the etiology of dementia. While familial AD is well-known, a family history of dementia is even more likely in FTD. The most common definable inheritance pattern in FTD is autosomal dominant, occurring in 10% to 20% or more of cases, depending on the population studied.[32] Family history without a clear inheritance pattern is also common, and can be found in up to 40% of cases. HD is common among early-onset dementias associated with an autosomal dominant family history. A family history is common in AD, and can also occur in DLB. A positive family history is less common in VaD, except in the autosomal dominant VaDs such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Table 2

Neurologic Features and Selected Differential Dementia Diagnoses

Cranial Nerve Findings
- Whipple's disease
- Progressive supranuclear palsy
- Nieman Pick Type C

Pyramidal signs
- Amyotrophic lateral sclerosis
- Vascular cognitive impairment/dementia
- Hereditary spastic paraplegia with dementia
  - familial Alzheimer's disease with spastic paraplegia
- Leukodystrophies
  - adrenoleukodystrophy
  - metachromatic leukodystrophy
  - orthochromatic leukodysrophy
  - Krabbe disease
  - Pelizaeus-Merzbacher disease

Parkinsonism
- Early/late
- Parkinson's disease and dementia
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Alzheimer's disease
- Frontotemporal dementia

Ataxia
- Creutzfeld Jakob disease
- Celiac disease
- Hashimoto encephalitis
- Multiple system atrophy
- Spinocerebellar degeneration
- Alcohol

Apraxia
- Corticobasal ganglionic degeneration
- Alzheimer's disease

Gait impairment
- Vascular cognitive impairment/dementia
- Normal pressure hydrocephalus

Neuropathy
- HIV
- Creutzfeld Jakob disease
- Paraneoplastic Syndromes
- Vitamin B12 deficiency
- Alcohol
- Inflammatory disorders
  - Sarcoidosis
  - Sjogren's syndrome
  - Systemic lupus erythematosis
- Hereditary neuropathy with dementia
  - leukodystrophies
  - mitochondrial disorders
  - polyglucosan body disease

Seizures/Myoclonus
- Creutzfeldt Jakob disease
- Late Alzheimer's disease
- Whipple's disease

Metabolic disorders (with seizure and myoclonus)
- Mitochondrial encephalopathies
- Baltic myoclonus (Unverricht Lundborg disease)
- Lafora disease
- Ceroid lipofuscinosis
- Sialidosis
- GM2 gangliosidosis

Clinical Course

Acute onset. An acute onset may be consistent with VaD. Delirium should be considered when there is an acute onset associated with fluctuations in level of consciousness, especially in the setting of an underlying cause. Dramatic fluctuations in the level of consciousness are characteristic of DLB.[7] Delirium and dementia commonly co-occur; and are risk factors for each other.[33]

Rapidly progressive dementias and Creutzfeldt Jakob disease (CJD). A rapidly progressive dementia raises the possibility of CJD, but can be seen in AD and DLB as well.[34] CJD is a rapidly progressive dementia that can only be definitively diagnosed by a brain tissue examination showing prion proteins with associated spongiform changes. It is a reportable disease in Canada (visit *www.phcaspc.gc.ca/hcaiiamss/-cjdmcj/index.html*). CJD can be sporadic, familial or transmissible. Transmissible forms of CJD include iatrogenic and variant CJD. Criteria for probable CJD include typical electroencephalogram (EEG) features with at least two of the following: myoclonus, visual or cerebellar signs, pyramidal or extra-pyramidal signs, or akinetic mutism (visit *www.eurocjd.ed.ac.uk/-def.html*). Clinical diagnosis can also be made with a history of a rapidly progressive dementia with duration of less than 2 years, and at least two clinical features, with a positive 14-3-3 test on cerebrospinal fluid (CSF) examination. False positives on the 14-3-3 test include AD, VaD and encephalitis. False negatives can also be seen, especially in slowly progressive CJD.[35] Diffusion-weighted magnetic resonance imaging (MRI) may have superior sensitivity compared with EEG and a CSF examination.[36]

Sporadic CJD is inexorably progressive, usually resulting in death within a year; however, the course can be longer.[37] A long duration is common in familial prion diseases. Variant CJD is a progressive neuropsychiatric disorder ultimately leading to ataxia, dementia and myoclonus (or chorea) without the typical EEG appearance of CJD or the proportion with elevation in the 14-3-3 protein.[38] Young onset sporadic CJD cases have a long neuropsychiatric prodrome.[39]

Other rapidly progressive dementias. Dementia associated with motor neuron disease can also run a rapid course. Syndromes that should be considered in the differential diagnosis of a rapidly progressive dementia include viral encephalitis, paraneoplastic (limbic) encephalitis, central nervous system cancer, Hashimoto's encephalitis, other disorders (including antiphospholipid syndrome, systemic lupus erythematosis, sarcoidosis and non-vasculitic autoimmune meningoencephalitis),[40,41] autoimmune infections and metabolic disorders.

Clinical and Neurological Exam Features

Weight loss and or other systemic complaints raise the concern of an underlying neoplasm that might directly (metastasis or carcinomatous meningitis) or indirectly (paraneoplastic) lead to cognitive decline. Clues to an acute and subacute central nervous system infection include headache, fever, seizures, systemic complaints, infection of peripheral tissue, rapid progression of symptoms, focal neurological features (abscess with parenchymal involvement) and travel to endemic areas. Specific features such as rash and arthritis raise the concern of infection or autoimmune processes.

Dementia with motor impairment. Supranuclear gaze palsy and a history of early falls are characteristic of PSP, but can be seen in corticobasalganglionic degeneration, which leads to progressive apraxia and FTD.[42] Not all PSP patients exhibit abnormal eye movements. Impaired saccades can be seen in HD, CBDG, PSP and FTD. Also, unusual rhythmic ocular and associated cranial movements—oculomasticatory myorhythmia—are seen in Whipple's disease.[43]

DLB and PDD are characterized by parkinsonism (tremor, bradykinesia, rigidity). Dysfunction of the extra-pyramidal system is evident in HD (chorea), PSP (impaired postural reflexes), CBDG (myoclonus, dystonia) and FTD (parkinsonism). Chorea and peripheral neuropathy are seen in neuroacanthocytosis which can be associated with dementia. Gait disorder is characteristic of NPH and VaD. Pantothenate kinase-associated neurodegeneration, a disorder of brain iron accumulation (seen on MRI) can occur in adults where it can present as a progressive movement disorder with chorea and dementia. In the setting of a younger patient with dementia, dystonia or another movement disorder, Wilson's disease should be excluded given the potential for treatment.

Pyramidal system dysfunction is seen in cerebrovascular disease and associated VaD. Leukodystrophies, in particular adrenoleukodystrophy and metachromatic leukodystrophy, are associated with cognitive decline and spasticity. Vitamin B12 deficiency can lead to a myelopathy with upper motor neuron signs and peripheral neuropathy (decreased ankle jerks and sensory loss).

Mixed upper and lower motor neuron signs are seen in amyotrophic lateral sclerosis (ALS), which is commonly associated with cognitive impairment and less frequently associated with dementia. Conversely, motor neuron disease is also seen in FTD, where it is associated with a worse prognosis.

Cerebellar ataxia may be seen in patients with prion disease. Superficial siderosis causes dementia and progressive neurological deficits, including pyramidal signs and ataxia.[44] Central nervous system microbleeds, which can be identified using T2*-weighted gradient echo MRI scans, are found in amyloid angiopathy,[45] CADASIL and AD. Hereditary ataxia-dementia syndromes include dentatorubral-pallidoluysian atrophy and other spinocerebellar ataxias. Celiac disease, paraneoplastic syndromes, and Hashimoto encephalitis are examples of acquired and potentially treatable ataxia-dementia syndromes. Recently the fragile X premutation has been found to be a relatively common disorder associated with ataxia, tremor, parkinsonism and dementia.[46] Multiple system atrophy is associated with subcortical cognitive deficits.

Seizures and myoclonus. Seizures and myoclonus are relatively rare in dementia patients. Myoclonus is characteristic of CJD, and common in AD, especially late in the course. Focal myoclonus is also evident in CBGD. A number of young-onset dementias are associated with seizures and myoclonus. Recurrent non-convulsive seizures can sometimes be associated with cognitive impairment, mimicking dementia.

Reversible Dementias

While completely reversible dementias are rare,[47,48] common co-morbid conditions may exacerbate symptoms. Intracranial pathology (*i.e.,* cerebrovascular disease, tumors, and hydrocephalus) is often accompanied by associated signs and a progressive course. Head trauma can usually be identified by history. Seizures, seen in DLB, are associated with fluctuating symptoms. Depression often co-occurs with dementia and depressive symptoms should be treated regardless of whether or not they are considered the primary cause of cognitive impairment. Vitamin B12 deficiency and thyroid disease can be clinically silent except for cognitive impairment. Alcohol is the most common toxin associated with cognitive impairment. Rarer entities, including autoimmune disorders, can cause dementia syndromes.

HIV is associated with a subcortical dementia and is an important consideration, especially in individuals with risk factors or known HIV.[49] Neurosyphilis remains an important cause of dementia to identify because it is potentially treatable.[50] Viral encephalitis can present in an indolent fashion, unpredictably leaving dementia patients. Furthermore, worldwide tuberculosis and neurocysticercosis are common infections that have a predilection for the central nervous system. Lyme disease is an infection associated with dementia that should be considered in individuals with appropriate symptoms, such as a rash and polyarthritis, from an endemic area. Immunosupression predisposes to infections in general, and specific disorders, such as progressive multifocal leukoencephalopathy, are important to consider in this setting.

Laboratory Investigations

Guidelines exist for the evaluation of dementia.[51,52] It is important to rule out anemia, renal or hepatic dysfunction, electrolyte abnormalities, and abnormal glucose, as these problems can interfere with cognitive function. Most recommendations include checking a vitamin B12 level and thyroid function since these can be associated with

insidious cognitive decline. Calcium or phosphate abnormalities raise the concern of parathyroid dysfunction, which is associated with cognitive impairment, parkinsonism and depression.

Neuroimaging. Mass lesions and hydrocephalus are identified by imaging. White matter changes lead to circumscribed diagnostic considerations. Contrast enhancement raises the possibility of infiltrative, infectious or inflammatory disorders. While AD is associated with medial temporal atrophy compared to controls, FTD and CBDG are associated with asymmetric or frontal atrophy on computed tomography (CT) or MRI scans or perfusion deficits on single photon emission computed tomography (SPECT) and metabolic deficits on positron emission tomography (PET) scans.[53] PSP patients have midbrain and frontal atrophy.

Lumbar puncture. Specific tests, including CSF examination, are useful in the appropriate clinical setting. This should prompt investigations targeted by the clinical picture. Infections have abnormalities on CSF examination, including elevated protein, pleiocytosis and evidence for microorganism on examination or culture. The polymerase chain reaction is useful for amplifying genomic material for specific infections, including herpes simplex and Whipple's disease. While elevation in peripheral anti-neuronal bodies (*i.e.,* anti-Hu, anti-Yo) may be found in paraneoplastic syndromes, these may be absent; hence a targeted assessment for cancer is a first step in evaluating patients with a suspected paraneoplastic syndrome.[54] Of note, limbic encephalitis can have an autoimmune basis in the absence of a neoplasm. Inflammatory disorders of the brain often lead to elevated protein and may lead to elevated cell counts. Multiple sclerosis and other inflammatory disorders can lead to an elevated immunoglobulin index and oligoclonal bands. Serum or CSF angiotensin-converting enzyme can be elevated in sarcoidosis.

Peripheral biopsy. Skin and muscle biopsy may be helpful in some dementias and may obviate a brain biopsy if diagnostic. Skin changes may be evident in some dementias such as Sneddon's syndrome. Vasculitis may be evident in skin or muscle biopsy. An angiopathy characteristic of CADASIL can be diagnosed on skin biopsy and might be pursued in rapidly progressive dementia with white matter disease.[55] Skin biopsy can be helpful in the diagnosis of ceroid lipofuscinosis or Lafora's disease, young-onset disorders associated with dementia. Polyglucosan body disease is a disorder associated with urinary incontinence, gait impairment and neuropathy, with periodic acid-Schiff (PAS) positive inclusions on nerve or sweat gland biopsy. Salivary gland biopsies are helpful in diagnosing Sjogren's syndrome.

Brain biopsy. Brain biopsy is reserved for cases where there is diagnostic uncertainty and is particularly important in cases where therapeutics may be instituted or altered on the basis of a biopsy.[56] Biopsies may be complicated by seizures, delirium, pneumonia and wound infections. Diagnoses that might lead to specific treatments include: inflammatory disorders, including vasculitis, sarcoidosis, or non-vasculititic autoimminune meningoencephalitis. Parenchymal or perivascular infiltrative disorders may also be diagnosed definitively via brain biopsy. Whipple's disease and infections by other fastidious organisms can sometimes be diagnosed by biopsy alone. While the identification of a non-treatable degenerative syndrome can often assist families in decision making, justifying brain biopsies in some atypical or rapidly progressive cases, biopsies are often non-specific—43% in a study by Warren et al.[56]

Summary

In summary, physicians conducting a careful clinical approach should differentiate typical AD from other dementias. Of course, diagnostic uncertainty will remain in a minority of cases. The challenge in such a situation, is to identify diagnoses for patients for which there are treatments available.

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