Special Article

Atypical Dementia: When It Is Not Alzheimer's Disease

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Dementia represents the most common neurodegenerative disorders affecting approximately 5% of the elderly population over age 65 years. At present, different forms of dementia are distinguished, including Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal dementia, and dementia secondary to diseases, such as AIDS dementia. Unlike AD, these atypical dementias are often associated with neurological symptoms, reflecting the localization of the degenerative process rather than the nature of the underlying histopathology. The present article provides an overview of the clinical evaluation of patients with atypical dementia and reviews distinguishing features of atypical dementias that may be confused with AD. The laboratory and imaging evaluation of various types of dementias are described. Current practice guidelines and practice parameters are reviewed as relevant for primary care practitioner.

Keywords: *Dementia, Vascular dementia, Diffuse Lewy body dementia, Parkinson disease dementia*

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"Dementia" is a generic term that describes a loss of mental function. It is an acquired, persistent impairment in multiple areas of intellectual function, which are not due to delirium. Operationally, it is impairment in three or more of the following nine domains of mental activity, including memory, language, perception (especially visuospatial), praxis, calculations, conceptual, or semantic knowledge, executive functions, personality or social behavior, and expression. Most definitions, such as those of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), require that the intellectual deficits be of sufficient severity to impair social and occupational functions[1]. Different criteria in the above definition emphasize the characteristics of dementia, distinguishing from its mimics. For example, acquired nature separates dementia from the congenital mental retard syndromes. The persistent intellectual impairment of dementia distinguishes itself from delirium, which is an acute disorder of cognition, characterized by a disturbance in attention. Finally, multiple intellectual deficits exclude patients with isolated neuropsychological disturbances, such as aphasia or amnesia due to focal brain lesions.

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Once the dementia is recognized, the second step is to identify the etiology or specific type of dementing syndromes. The diagnostic evaluations, with special attention to temporal, cognitive, behavioral, and neurological features, are helpful in distinguishing between Alzheimer's disease (AD) and many other etiologies. While most studies indicate that 55-70% of cases of dementia in developed countries have AD-type pathologic changes, the actual proportion of dementia patients with pure AD is far less[2]. Indeed, more recent studies suggested that as many as half of those with AD patients have concomitant vascular disease or cortical Lewy bodies[3]. As a result, cerebrovascular disease with or without AD-type pathology has led to the second most common cause of dementia, comprising 10-30% of all dementing diseases in western countries[4]. While other forms of dementias are increasingly recognized, the prevalence of those illnesses is still not as clear and many patients are still undiagnosed. Therefore, physicians should become aware of clues to diagnose less common dementias (Table 1), such as the presence of focal neurological findings that suggest structural lesions, including stroke, subdural hematoma, or vascular dementia. The early onset of behavioral abnormalities, language dysfunction, or rigidity suggests frontotemporal dementia (FTP). Parkinsonian features suggest the presence of Parkinson's disease with dementia (PDD). Fluctuations

Table 1. Classification of some dementing disorders based on suggestive features[7]

Dementing disorders	Suggestive features
Vascular dementia (VaD)	- Stepwise deterioration (< 50%) - Focal neurologic signs - Neuroimaging evidence of cerebrovascular insufficiency
Dementia with Lewy bodies (DLB)	- Fluctuations in performance - Visual hallucinations, delusions - Bilateral symmetric parkinsonism - Neuroleptic hypersensitivity
Frontotemporal dementia (FTD)	- Early personality change - Frontal dysexecutive syndromes - Early language dysfunction - Relatively preserved memory and visuospatial function
Parkinson's disease dementia (PDD)	- Asymmetric parkinsonian features - Later onset of dementia, at least 1 year after the onset of parkinsonian features - Subcortical dementia with impairment of frontal-executive functions

in performance or the presence of visual hallucinations suggests dementia with Lewy bodies (DLB). While different forms of dementias are recognized, therapeutic approaches of these dementias are made more complex by the current lack of consensus on appropriate clinical criteria, biomarkers, and nosological boundaries. Based on common underlying neuropathological and neurochemical findings, current potential treatment approaches have arisen that focus on enhancement of neurotransmitter function. However, these treatments are expensive and no formal therapeutic guidelines have been established. In the present article, the author will provide an overview of different types of less common dementias, other than AD (VaD, FTD, DLB, PDD), and review distinguishing features among these different forms as well as discussing current clinical practice guidelines and practice parameters for the primary care practitioner. The laboratory and imaging findings of various causes of dementia will also be discussed.

Vascular dementia (VaD)

Vascular dementia (VaD) refers to a group of heterogeneous disorders due to a variety of cerebrovascular insufficiency. After AD, VaD is the second most common dementing illness, accounting for 10-30% for all dementia[5] VaD is associated with advancing age, male gender, and known strokes. VaD may even be more common than AD among African-Americans in the United States or other Asian countries[6]. Although most literatures focus on AD and VaD as separate clinical entities, there is increasing evidence that the brain lesions associated with AD and VaD often occur together and that AD and VaD brain lesions interact in important ways to increase the likelihood of cognitive decline. The coexistence of AD and VaD pathology is often termed mixed dementia[7].

VaD can result from ischemic or hemorrhagic brain damage and there are several major subtypes of VaD. Of these, the three most common mechanisms causing VaD are recognized, including single strategic stroke (such as in the anteromedial thalamus), multiple infarcts due to thrombosis or emboli of the large or medium size arteries, and subcortical small-vessel disease. In the last category, multiple lacunes and extensive white matter lesions or Binswanger's disease involving one-fourth or more of white matter are responsible for about two-thirds of VaD and are more likely than large or medium vessel thromboembolism to lead to progressive dementia (Fig. 1A, 1B). Because of a variety of pathogenic mechanism and locations, clinical manifestations are heterogeneous and depend on the size, location, and type of damage. However, common focal neurological signs include hemiparesis, visual field defects, pseudobulbar palsy, and hemisensory loss.

Different diagnostic criteria have been proposed for VaD. The most widely used criterions are those in the DSM-IV, the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences

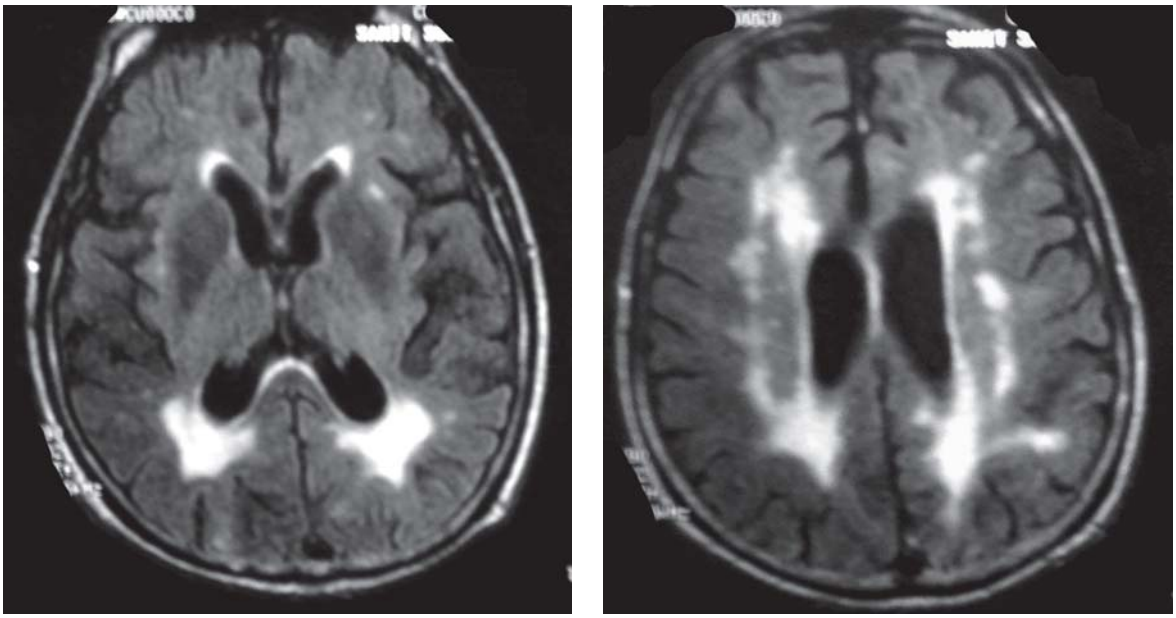

Fig. 1 MRI (1A and 1B: FLAIR) images of a patient with extensive white matter disease

(NINDS-AIREN) (Table 2), and the international classification of diseases, 10th revision (ICD-10). All the current criteria depend on recognizing dementia, cerebrovascular disease, and a probable association between the two, but differ among themselves, not interchangeable, and lack sensitivity, particularly for the effects of white matter lesions. White matter lesions or leukoaraiosis, are present in the majority of patients of VaD and may be the sole finding in 40% of patients. The term "subcortical vascular dementia" has been used to incorporate the old entities of lacunar state and Binswanger's disease[8]. Patients in this group often have a history

Table 2. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia[10]

Probable VaD
1) Dementia. Impairment of memory and > 2 consecutive domains
2) Cerebrovascular disease:
   - Focal signs on neurologic examination (hemiparesis, lower facial weakness, Babinski's sign, sensory deficit, hemianopia, and dysarthria)
   - Evidence of relevant cerebrovascular disease by brain imaging: large vessel infarcts, single strategically placed infarction, multiple basal ganglia and white matter lacunes, extensive white matter lesions, or combination thereof
3) A relationship between the above disorders indicated by the presence of ≥ 1 of the following:
   - Onset of dementia within 3 months after a recognized stroke
   - Abrupt deterioration in cognitive functions
   - Fluctuating, stepwise progression of cognitive deficits
4) Clinical features consistent with the diagnosis of probable VaD:
   - Early presence of a gait disturbance, history of unsteadiness or frequent unprovoked falls, early urinary incontinence, pseudobulbar palsy, personality and mood changes

Possible VaD
1) Dementia with focal neurologic signs but without neuroimaging confirmation of the definite cerebrovascular disease, or
2) Dementia with focal signs but without a clear temporal relationship between dementia and stroke
3) Dementia and focal signs but with a subtle onset and variable course of cognitive deficits

of multiple vascular disorders, including arterial hypertension, diabetes, and ischemic heart disease. Strokes or TIA episodes may occur, but they are frequently unrecognized. The onset is insidious in over half of patients and the course is usually continuous and slowly progressive. The classic sudden onset with stepwise deterioration is present in less than half of cases. The cognitive syndrome in subcortical vascular dementia, based on lesions affecting the prefrontal-subcortical circuit, is referred to as 'dysexecutive syndrome', which includes slowed information processing, impairment in planning, formulation, organization, and executing. The memory deficits are generally mild and do not predominate.

Because some cases with VaD are clinically silent, it is important to obtain neuroimaging in all cases of dementia. In addition, the American Academy of Neurology now recognizes the use of neuroimaging in the initial evaluation of patients with dementia as appropriate[9]. The NINDS-AIREN criteria also cite findings on neuroimaging as evidence of relevant cerebrovascular disease[10]. On neuroimaging, white matter lesions or leukoaraiosis consist of ill-defined regions with altered signal around the frontal and occipital horns of the lateral ventricles, often extending into the centrum semiovale. Extensive white matter lesions, with thickened irregular periventricular margins, prominent ventricular capping, and large or coalesced lesions in the hemispheric white matter, result in VaD that is often referred to as Binswanger's disease (Fig. 1)[11]. Binswanger's disease has its onset in the sixth or seventh decade and is associated with hypertension. Reduced speed of information is the common manifestation, related to the degree of white matter lesions on neuroimaging. In addition, patients with Binswanger's disease have decreased spontaneity, apathy, abulia, and emotional bluntness. Falls are also frequent, associated with mild extrapyramidal features and frontal grasp reflexes or other release signs.

The clinical differentiation of VaD from AD with cerebrovascular disease can be difficult. Indeed, over 60% of older patients with AD present with incomplete white matter infarction, suggesting strong association between AD and vascular risk factors[12]. The term AD + VaD or AD + cerebrovascular disease or 'mixed dementia' has been used for dementia with vascular pathology in combination with AD changes. However, disagreement on the clinical diagnosis remains a major problem and as yet, no formal diagnostic criteria have been formulated. Therefore, questions remain as to what amount of cerebrovascular lesions can be regarded as unrelated to dementia in patients with AD and what the threshold should be. With all the existing vascular risk factors for dementia, including AD, it is possible that dementia commonly arises from a combination of vascular risk factors and AD pathology[13]. It is also possible that two disorders (AD and VaD) come on at the same time in the same patient without the disorders having any causal relation.

Frontotemporal dementia (FTD)

Frontotemporal lobar degeneration (FTLD) is a heterogeneous disorder comprising of dementing disorders with degeneration of the frontal lobes, anterior temporal lobes, or both. Frontotemporal dementia (FTD) is the main FTLD syndrome, constituting up to 10% of all the neuropathological diagnoses of dementia[14]. Patients with FTD frequently present with prominent personality and behavioral disturbances. In the past, many physicians referred to FTD patients as having Pick's disease but on neuropathological examination, most FTD patients lack the pathognomonic Pick bodies. While Pick's bodies were observed in only 20-25% of FTD patients[15], another feature of Pick's disease, the balloon cell, is more common. As a result, the current FTLD spectrum disorders have expanded including FTD, Pick's disease (FTLD-Pick), FTD lacking distinctive pathology, and progressive aphasias. Converging evidence also suggests that some of these disorders are "tauopathies" from tau protein abnormalities, for example corticobasal degeneration (CBD), and familial tauopathies linked to chromosome 17[16].

FTD is considered as a part of presenile dementia syndromes with the age of onset around 57 years (range 51-63 years). It is the most frequent clinical phenotype of lobar degenerations affecting the frontal and temporal cortex, and the third most common neurodegenerative dementia syndrome after AD and DLB (not including vascular dementia). Personality change is usually the most prominent symptoms and tends to precede their cognitive disabilities. Frequently, a decline in social interpersonal conduct is the earliest observed symptom by families or friends, manifesting as disinhibition, irritability, impulsivity, or lack of empathy[17]. These behavioral changes provide the most important clue allowing the differentiation of this condition from AD. Changes in personality are also evident with a tendency to neglect or loss of interest in personal hygiene with failure to wash, bathe, groom, or dress appropriately. Patients with FTD may present unkempt and partially clothed, or they may urinate or defecate in front of others. Language is also

affected early with a progressive loss of meaning of words, objects and faces that contrasts with fluent verbal output. Deficits in insight, abstraction, planning, and problems solving are frequently observed, in keeping with a frontal dysexecutive syndromes. Kluver-Bucy syndrome may present with hyperorality. Later, behavior becomes increasingly stereotyped and ritualistic whereas memory, orientation, and visuospatial function remain relatively well preserved until the late stages. Activities of daily living are also maintained over long periods of the course. Gradually, however, symptoms progress to profound dementia.

To distinguish between FTD and AD, the sequence of symptoms during the clinical course is important. In early AD, there is amnesia with preserved social skills and personal propriety; in early FTD, there are interpersonal or personality changes with loss of executive abilities and relative preservation of memory. It is an episodic memory or new learning, and not retrograde autobiographical memory that is impaired in AD and spared in FTD. Disturbed behaviors, such as compulsive or obstinate acts, verbal sterotypies, and changes in eating preferences are also more common in FTD than in AD. Additionally, clinical criteria for diagnosing FTD, including Lund and Master criteria, and the most recent consensus criteria have been developed (Table 3)[18,19].

There is no laboratory pathognomonic of FTD and, for the time being, clinical criteria remain the mainstay of diagnosis. However, laboratory investigations can be helpful in ruling out other disorders that can mimic FTD. While not sensitive to early clinical changes, the majority of FTD patients show bifrontal and anterior temporal atrophy with enlargement of sylvian fissures and volume loss of hippocampus and entorhinal cortex on MRI. However, the degree of hippocampal atrophy in FTD is less severe than in AD. Further differentiation between FTD and AD is assisted by functional imaging, demonstrating frontotemporal hypoperfusion on single photon emission tomography (SPECT) or hypometabolism on positron emission tomography (PET) in typical cases of FTD, which contrasts to temporo-parietal deficits in AD[20]. In addition, the changes are often asymmetric. The lack of specificity of both structural MRI and functional imaging limits their contribution for diagnosis[21]. In addition to imaging studies, genetic tests may be of value in evaluating FTD patients. Chow et al[22] found that there are secondary cases among first-degree relatives in 30-50% of FTD patients, suggesting autosomal dominant transmission in approximately half of these pedigrees. Although apolipoprotein e4 allele is not a risk factor for FTD, there is an association of FTD with an increased frequency of the e4 allele, but not as strong as for AD[23].

Primary progressive aphasia is usually seen as part of FTLD[24]. Patients with progressive aphasia often present with difficulty in verbal expression,

Table 3. The consensus clinical diagnostic features of frontotemporal dementia[16]

1) Core diagnostic features (all must be present)
   - Insidious onset and gradual progression
   - Early decline in social interpersonal conduct
   - Early impairment in regulation of personal conduct
   - Early emotional blunting
   - Early loss of insight
2) Supportive diagnostic features:
   A. Behavior disorders
      - Decline in personal hygiene and grooming
      - Mental rigidity and inflexibility
      - Distractibility and impersistence
      - Hyperorality and dietary changes
      - Perserveration and stereotyped behavior
      - Utilization behavior
   B. Speech and language: altered speech output (aspontaneity and economy of speech, press of speech), stereotypy of speech, echolalia, preserveration, mutism
   C. Physical signs: primitive reflexes, incontinence, akinesia, rigidity, tremor, low and labile blood pressure
   D. Investigations:
      - Neuropsychology: impaired frontal lobe tests, no amnesia or perceptual deficit
      - EEG: normal on conventional EEG despite clinically evident dementia
      - Brain imaging: predominant frontal and/or anterior temporal abnormality

anomia, and shortened phrase length in the presence of relative preservation of comprehension. Speech is hesitant, broken, dysarthric, and effortful. Due to particular difficulty with verbs and sentence processing, some patients have to learn sign language, and some find it useful to carry laminated cards that provide information to assist themselves and others in specific situations. On neuroimaging, the atrophy is often asymmetric, involving mainly the left frontotemporal lobe. Despite its rarity, primary progressive aphasia should be considered when language is the only area of prominent dysfunction for at least the first two years of the disease; and other mental faculties, such as memory of daily events, visual and spatial skills, and behavior remain relatively intact.

Dementia with lewy bodies

Dementia with Lewy bodies describes a parkinsonian dementia with widespread Lewy bodies. DLB is considered the second most common cause of dementia, accounting for 14-20% of patients, after AD. Most DLB patients are over 65 years of age, and two-thirds of them are male[25]. The prevalence of clinically diagnosed DLB in a Finnish population aged 75 years or older was found to be 5%, comprising 22% of all demented subjects[26].

The hallmark pathological finding of DLB is the presence of cortical Lewy bodies[27,28]. Lewy bodies (LBs) are intracytoplasmic aggregates of a-synuclein and other proteins (Fig. 2). LBs can be detected on routine hematoxylin and eosin staining, but immunological stains are more sensitive, a synuclein stains being more superior to ubiquitin stains. In addition to DLB, cortical LBs may be found in the majority of patients with PD, with or without dementia. Therefore, the distinction between DLB and PDD as two distinct clinical phenotypes has been criticized by some experts who regard different clinical presentations in these two disorders as simply representing different points on a common spectrum of LB disease. On the contrary, other experts distinguish DLB from PDD, based on the temporal sequence of appearance of symptoms. DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism and PDD should be used to describe dementia that occurs in the context of well-established PD[29]. Furthermore, most patients with DLB have associated AD pathology that consists mainly of senile plaques with fewer neurofibrillary tangles than that in "pure" AD. Therefore, dividing lines between these disorders are somewhat arbitrary and dementias associated with LBs comprise a spectrum of diseases, including PD with Lewy body pathologic changes limited to the brainstem, dementia with LBs associated with LBs in the cerebral cortex, and AD associated with cortical LBs as well as typical Alzheimer pathologic findings.

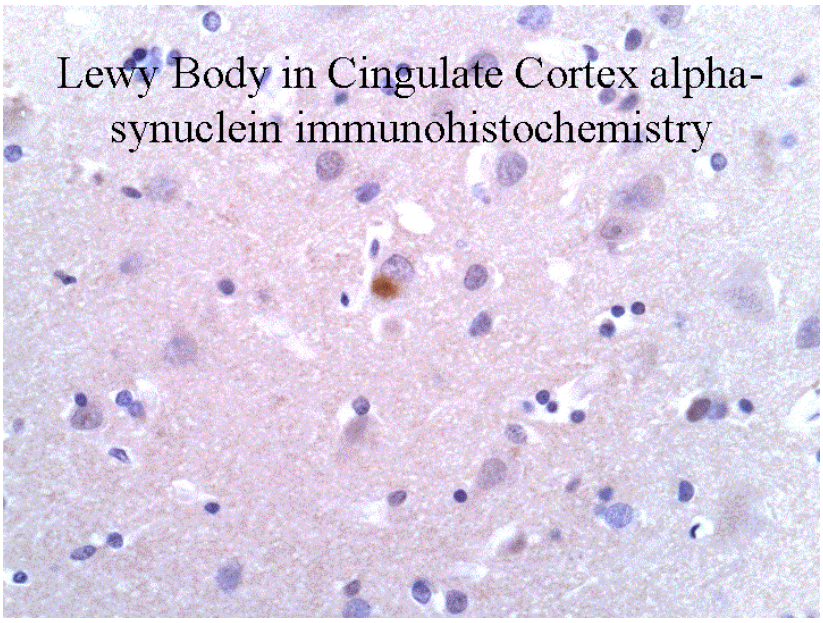

Fig. 2 Lewy body in the cingulated cortex with alpha synuclein immunohistochemistry

The main clinical feature of DLB is a progressive cognitive decline of sufficient magnitude to interfere with normal occupational or social functions, along with three additional core features: parkinsonism, cognitive fluctuations, and visual hallucinations (Table 4)[30]. Parkinsonism, which consists of rigidity, bradykinesia, and disturbances of postures and equilibrium, tends to be bilateral, symmetric and milder than in PD. Tremor in DLB is also less common than in PD. Cognitive fluctuations, described as "sundowning" or "intermittent delirium", is present in 80% or more in cases. Excessive daytime drowsiness with transient confusion on waking also occurs commonly. These episodes can last from a few seconds to several hours and often be confused with diagnosis of a transient ischemic attack or a seizure disorder. Visual hallucinations are the presenting symptom in 33% of cases, and often present early in the course of illness, although tactile, auditory, and olfactory hallucinations may occur. Visual hallucinations in DLB are often well-formed, detailed, and of animated figures, which provoke varying emotional responses from fear to amusement and indifference, usually with some insight into the unreality of the episode once it is over[31]. Visual hallucinations

Table 4. Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)[24]

1) Central feature (essential for a diagnosis of possible or probable DLB)
   - Dementia per definition
   - Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression
   - Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent
2) Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)
   - Fluctuating cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism
3) Suggestive features (if one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made; in the absence of any core features, one or more suggestive features is sufficient for possible DLB; probable DLB should not be diagnosed on the basis of suggestive features alone)
   - REM sleep behavior disorder
   - Severe neuroleptic sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
4) Supportive features (commonly present but not proven to have diagnostic specificity)
   - Repeated falls and syncope
   - Transient, unexplained loss of consciousness
   - Severe autonomic dysfunction, e g. orthostasis hypotension, urinary incontinence
   - Hallucinations in other modalities
   - Depression
   - Relative preserveration of medial temporal lobe structures on CT/MRI scan
   - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
   - Abnormal (low uptake) MIBG myocardial scintigraphy
   - Prominent slow wave activity on EEG with temporal lobe transient sharp waves
5) A diagnosis of DLB is less likely
   - In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging
   - In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture
   - If parkinsonism only appears for the first time at a stage of severe dementia
6) Temporal sequence of symptoms

   DLB should be diagnosed when dementia occurs before on concurrently with parkinsonism (if it is present); the term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease; in a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful; in research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended; adoption of other time periods will simply confound data pooling or comparison between studies; in other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy

in DLB correlate strongly with LB density in parahippocampal and inferior temporal lobe cortices[32]. Delusions can occur in about half of the patients. Unlike the poorly formed, mundane ideas in AD that are based on forgetfulness and confabulation, delusions in DLB are often bizarre, fixed, and complex.

Sleep disturbances are also common in DLB, as are daytime drowsiness and confusion on waking. REM sleep behavior disorder (RBD) is frequently associated with DLB, manifested by vivid and often frightening dreams during REM sleep without muscle atonia. Patients, therefore, appear to "act out their dreams" vocalizing, flailing limbs, and moving around their beds violently. In addition to the history of the bed partner, the diagnosis of RBD may be confirmed by polysomnography. Although a positive history of severe neuroleptic sensitivity is strongly suggestive of DLB, a history of neuroleptic tolerance do not exclude the diagnosis since approximately half of DLB patients do not react adversely to dopamine receptor blocking agents.

No specific studies or investigations are yet available to increase diagnostic accuracy for DLB[33]. Since most DLB cases are sporadic, genetic tests cannot be recommended in routine clinical practice. MRI generally discloses whole brain atrophy, but with relative preservation of the hippocampal and medial temporal lobe, compared to AD. Findings on HMPAO SPECT or PET revealed bilateral temporoparietal hypometabolism similar to, but milder than that seen in AD[34]. Imaging findings are neither sensitive nor specific enough to distinguish DLB from AD. The hypometabolism in the primary visual cortex in DLB may be associated with the visual hallucinations.

Parkinson's disease with dementia (PDD)

Estimates of the incidence and prevalence of dementia in PD vary widely due in part to differing operational definitions of dementia and to varying study designs. However, PDD is generally used when dementia occurs in the context of well-established PD, beginning at least 1 year after the onset of movement disorders[29,30,35]. With this operating definition, the proportion of PD patients who develop dementia ranges from 30 to 40%, particularly common in those aged 65 years and over[36,37]. Other clinical characteristics of PD that are linked to subsequent dementia include increased severity of bradykinesia, increased disease duration, and a family history of dementia. PD patients can have a long period of subtle cognitive change preceding the development of dementia, but classically, PDD has been described as a "subcortical" dementia in which psychomotor retardation, memory abnormalities, cognitive impairment, and mood disturbances are considered cardinal features. However, the most sensitive cognitive deficits are in frontal-executive functions[38]. There is deterioration in abstraction, concept formation, problem solving, and categorization accuracy. PDD patients also develop problems with specific aspects of memory involving immediate (short-term) memory and retrieval of information, which is improved by recognition cues. Moreover, they have markedly reduced rates of information processing and fail to initiate activities spontaneously.

The pathological findings in PDD have been quite varied and inconsistent[39,40]. Older pathological studies of PDD generally reported a significant loss of neurons in the nucleus basalis of Meynert associated with extensive reductions of choline acetyltransferase in cortical regions. These findings suggest that PDD may be in part related to the same cholinergic defect that is seen in AD, further supporting a relationship between PDD and AD. However, more recent studies revealed that cortical LBs positive for a-synuclein are the most sensitive and specific markers for PDD, with amyloid plaques and neurofibrillary tangles being present only inconsistently[41]. Therefore, PDD may have heterogeneous causes, including subclinical AD changes, cortical LBs, decreased activity of cholinergic and other neurotransmitters, and dopaminergic loss from substantia nigra and caudate nuclei[42]

PD patients are prone to other neuropsychiatric features, which can further contribute to cognitive dysfunction. Depression, occurring in 30-40% of PD patients, is more common among those with cognitive impairment or dementia[36]. PD patients have a tendency to anxiety disorders, particularly generalized anxiety, panic, or agorophobia. Psychosis, delusions, and visual hallucinations may occur because of a combination of cognitive dysfunction and antiparkinsonian medications. Indeed, psychosis is the most common indication of nursing home placement in PD patients.

In addition to PD, dementia can develop in other neurodegenerative parkinsonian disorders. Among those conditions, Parkinson-plus syndromes are neurodegenerative disorders, which are characterized by parkinsonism and at least one other non-parkinsonian neurological manifestations. For example, progressive supranuclear palsy is characterized by axial parkinsonism and supranuclear vertical gaze palsy. Other Parkinson-plus syndromes are corticobasal

degeneration, multiple system atrophy, and amyotrophic lateral sclerosis/parkinsonism dementia complex in which the details of each condition are beyond the scope of this review.

During the past decade, the author has seen a considerable resurgence of interest in non-Alzheimer form of neurodegenerative dementia. The major non-AD dementias present different challenges to caregivers and healthcare providers. In addition, much of the conceptual basis of these disorders has significantly changed in the past decade. Although AD, VaD, and DLB pathology overlap, the peculiarities of the non-AD dementias may not be sufficiently familiar to practitioners. Therefore, physicians must be vigilant to less common causes of dementia and are aware of clues to diagnose less common conditions, such as focal neurological findings, which may suggest VaD; early onset of behavioral abnormalities and language dysfunction that point to FTD; and Parkinsonian features, which may be suggestive of PDD or dementia related to Parkinson-plus syndromes. Furthermore, a growing understanding of AD is critically important as it allows us to define better distinctions and similarities between AD and the major non-AD dementias.

References

1. Association AP. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: American Psychiatric Association; 1994.
2. Mendez MF, Mastri AR, Sung JH, Zander BA, Frey WH. Neuropathologically confirmed Alzheimer's disease: clinical diagnoses in 394 cases. J Geriatr Psychiatry Neurol 1991; 4: 26-9.
3. Londos E, Passant U, Risberg J, Gustafson L, Brun A. Contributions of other brain pathologies in dementia with lewy bodies. Dement Geriatr Cogn Disord 2002; 13: 130-48.
4. Roman GC, Goldstein M. A population-based study of dementia in 85-year-olds. N Engl J Med 1993; 329: 63-4.
5. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000; 54(11 Suppl 5): S10-5.
6. Fratiglioni L, De Ronchi D, Aguero-Torres H. Worldwide prevalence and incidence of dementia. Drugs Aging 1999; 15: 365-75.
7. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. J Am Geriatr Soc 2002; 50: 1431-8.
8. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1: 426-36.
9. Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56: 1143-53.
10. Pohjasvaara T, Mantyla R, Ylikoski R, Kaste M, Erkinjuntti T. Comparison of different clinical criteria (DSM-III, ADDTC, ICD-10, NINDS-AIREN, DSM-IV) for the diagnosis of vascular dementia. National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Stroke 2000; 31: 2952-7.
11. Hurley RA, Tomimoto H, Akiguchi I, Fisher RE, Taber KH. Binswanger's disease: an ongoing controversy. J Neuropsychiatry Clin Neurosci 2000; 12: 301-4.
12. Englund E, Brun A, Persson B. Correlations between histopathologic white matter changes and proton MR relaxation times in dementia. Alzheimer Dis Assoc Disord 1987; 1: 156-70.
13. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimer Dis Assoc Disord 1999; 13(Suppl 3): S115-23.
14. Jellinger KA. Diagnostic accuracy of Alzheimer's disease: a clinicopathological study. Acta Neuropathol (Berl) 1996; 91: 219-20.
15. Mendez MF, Selwood A, Mastri AR, Frey WH. Pick's disease versus Alzheimer's disease: a comparison of clinical characteristics. Neurology 1993; 43: 289-92.
16. Spillantini MG, Yoshida H, Rizzini C, Lantos PL, Khan N, Rossor MN, et al. A novel tau mutation (N296N) in familial dementia with swollen achromatic neurons and corticobasal inclusion bodies. Ann Neurol 2000; 48: 939-43.
17. Greicius MD, Geschwind MD, Miller BL. Presenile dementia syndromes: an update on taxonomy and diagnosis. J Neurol Neurosurg Psychiatry 2002; 72: 691-700.
18. The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994; 57: 416-8.
19. Neary D, Snowden JS, Gustafson L, Passant U,

Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546-54.
20. Miller BL, Gearhart R. Neuroimaging in the diagnosis of frontotemporal dementia. Dement Geriatr Cogn Disord 1999; 10 Suppl 1: 71-4.
21. Pasquier F, Lavenu I, Lebert F, Jacob B, Steinling M, Petit H. The use of SPECT in a multidisciplinary memory clinic. Dement Geriatr Cogn Disord 1997; 8: 85-91.
22. Chow TW, Miller BL, Hayashi VN, Geschwind DH. Inheritance of frontotemporal dementia. Arch Neurol 1999; 56: 817-22.
23. Gustafson L, Abrahamson M, Grubb A, Nilsson K, Fex G. Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia. Dement Geriatr Cogn Disord 1997; 8: 240-3.
24. Mesulam MM. Primary progressive aphasia - a language-based dementia. N Engl J Med 2003; 349: 1535-42.
25. Barber R, Panikkar A, McKeith IG. Dementia with Lewy bodies: diagnosis and management. Int J Geriatr Psychiatry 2001; 16(Suppl 1): S12-8.
26. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, Sulkava R. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry 2003; 74: 720-4.
27. Gibb WR, Esiri MM, Lees AJ. Clinical and pathological features of diffuse cortical Lewy body disease (Lewy body dementia). Brain 1987; 110: 1131-53.
28. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. J Alzheimers Dis 2006; 9: 417-23.
29. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007; 68: 812-9.
30. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65: 1863-72.
31. Ballard C, McKeith I, Harrison R, O'Brien J, Thompson P, Lowery K, et al. A detailed phenomenological comparison of complex visual hallucinations in dementia with Lewy bodies and Alzheimer's disease. Int Psychogeriatr 1997; 9: 381-8.
32. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain 2002; 125: 391-403.
33. Hohl U, Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. Diagnostic accuracy of dementia with Lewy bodies. Arch Neurol 2000; 57: 347-51.
34. Colloby SJ, Fenwick JD, Williams ED, Paling SM, Lobotesis K, Ballard C, et al. A comparison of (99m)Tc-HMPAO SPET changes in dementia with Lewy bodies and Alzheimer's disease using statistical parametric mapping. Eur J Nucl Med Mol Imaging 2002; 29: 615-22.
35. Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2006; 66: 996-1002.
36. Aarsland D, Tandberg E, Larsen JP, Cummings JL. Frequency of dementia in Parkinson disease. Arch Neurol 1996; 53: 538-42.
37. Cummings JL. Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol 1988; 1: 24-36.
38. Elias JW, Treland JE. Executive function in Parkinson's disease and subcortical disorders. Semin Clin Neuropsychiatry 1999; 4: 34-40.
39. Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005; 64: 1404-10.
40. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005; 58: 773-6.
41. Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 2000; 54: 1916-21.
42. Burn DJ. Cortical Lewy body disease and Parkinson's disease dementia. Curr Opin Neurol 2006; 19: 572-9.

กลุ่มโรคสมองเสื่อมที่นอกเหนือจากโรคอัลไซเมอร์

รุ่งโรจน์ พิทยศิริ

โรคสมองเสื่อม เป็นโรคความเสื่อมของระบบประสาทที่มีสาเหตุได้หลายอย่าง ถึงแม้ว่าในปัจจุบันจะพบว่าสาเหตุส่วนใหญ่ของโรคสมองเสื่อม เกิดขึ้นเนื่องจากโรคอัลไซเมอร์ ซึ่งมีมากถึง 55-70% ผู้ป่วยที่มีแต่อาการของโรคอัลไซเมอร์แต่เพียงอย่างเดียวพบได้น้อย ในทางกลับกัน ผู้ป่วยที่มีอาการของโรคอัลไซเมอร์ มักมีพยาธิสภาพอย่างอื่นร่วมด้วย ดังเช่น โรคหลอดเลือดสมอง นอกจากนี้สาเหตุของโรคสมองเสื่อม ยังรวมถึงสาเหตุอื่น ๆ ที่นอกเหนือจากโรคอัลไซเมอร์ ดังเช่น โรคสมองเสื่อมที่เกิดจากหลอดเลือดสมอง โรคสมองเสื่อมลูวีบอดี้ โรคสมองเสื่อมฟรอนโตเทมปอราล และโรคสมองเสื่อมในโรคพาร์กินสัน เนื่องจากในปัจจุบันมีผู้ป่วยที่ได้รับการวินิจฉัยในโรคกลุ่มนี้เพิ่มขึ้น บทความนี้จะกล่าวถึงภาวะสมองเสื่อมต่าง ๆ ที่นอกเหนือจากโรคอัลไซเมอร์ ทั้งในด้านอาการทางคลินิกพยาธิวิทยา โดยเน้นถึงการวินิจฉัยแยกโรคสมองเสื่อมต่าง ๆ ออกจากโรคอัลไซเมอร์