Clinical Differences among Four Common Dementia Syndromes

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Cases of dementia are increasing due to longer life expectancy of the world population. Physicians should be able to recognize common dementia syndromes. After excluding reversible causes of dementia, there are four common dementia syndromes, which are Alzheimer's disease, vascular dementia, dementia with Lewy body, and frontotemporal dementia. The key points of clinical differences of these dementia syndromes are summarized in this article.

Key words: *Alzheimer's disease, vascular dementia, dementia with Lewy body, frontotemporal dementia, Parkinson's disease*

Introduction

There are four clinical dementia syndromes accounting for 90% of all cases after excluding other common reversible causes of cognitive impairment.[1] These four major diseases are Alzheimer's disease (AD) and vascular dementia (VaD), which together account for approximately 80% of dementias, dementia with Lewy body (DLB), and frontotemporal dementia (FTD). The four common diseases have different clinical characteristics, and there are diagnostic criteria for each of them. These criteria bear review as physicians who deal with dementia might not always recall them in detail. As AD is the most common cause of dementia, accounting for 50–60% of cases, physicians should be familiar with the clinical difference between AD and other diseases.[2,3] This article will focus on the clinical difference between AD and other common dementia syndromes.

Alzheimer's Disease

A 70-year-old man presented with a 3-year history of progressive memory loss, which mainly affected his short term memory. He needed his daughter to remind him of his appointments and some day-to-day activities. He had problems with driving alone as he became confused with the routes, though he had used them for a long time. He could not manage his bills as usual. The physical examination was unremarkable. The Mini Mental State Examination (MMSE) was 20 out of 30.

Alzheimer's disease is the most common cause of dementia among older adults. The major pathogenesis is the production and accumulation of beta-amyloid peptide, bringing about the formation of neurofibrillary tangles, oxidation and lipid peroxidation, glutaminergic excitotoxicity, inflammation, and activation of the cascade of apoptotic cell death. Furthermore, the other hypothesis regarding the pathophysiology of AD stresses tau-protein abnormalities, heavy metals, vascular factors, and viral infections.[4] The natural course of AD averages 10 years. The cardinal features are insidious onset, progressive course, and early memory loss; at least one other cognitive impairment such as language dysfunction, apraxia, agnosia, visuospatial disorder, as well as executive dysfunction, must be seen. These impairments should constitute a decline from the previous level of cognitive functioning, interfering with daily activities.

Memory decline is the hallmark of cognitive change in AD. It is characterized as a storage deficit, meaning that material cannot be recalled with cue. In the early stage, memory impairment for recent events is common whereas long-term memory remains intact. As the disease progresses, individuals with AD are increasingly unable to recall more distant memories. Typically, the motor signs are absent early in the course. Likewise, sensory abnormalities, seizures, and gait difficulties are uncommon until the late phase of disease.[2,4] Behavioural changes, including depression, anxiety, apathy, aggression, agitation, wandering, vocalization, disinhibition, and abnormal eating, are common thereafter and cause caregiver stress as well as greater use of health care service.[5]

Table 1: Clinical Differences between Vascular Dementia and Alzheimer's Disease

Clinical features	Vascular Dementia	Alzheimer's Disease
History of atherosclerotic diseases	Transient ischemic attack, strokes, atherosclerotic risk factors e.g., diabetes mellitus, hypertension	Less common
Onset	Sudden or gradual	Gradual
Progression	Slow or stepwise progression	Slow, progressive decline
Neurological examination	Neurological deficits	Normal
Gait	Often disturbed early	Usually normal
Memory	Mild impairment in early phase	Prominent in early phase
Executive function	Marked impairment and early	Impaired later
Type of dementia	Subcortical	Cortical
Hachinski Ischemic Score	≥ 7	≤ 4
Neuroimaging	Infarction or white matter lesions	Normal or hippocampal atrophy

Source: Roman GC, 2003;[11] Muangpaisan W et al., 2005.[18]

Vascular Dementia

A 65-year-old man with hypertension, diabetes mellitus, and coronary artery disease developed sudden left hemiparesis and dysarthria 6 months ago. Three months later, his wife noticed that he could not name the only two grandchildren he had and could not remember to take his medications. He could neither operate a remote control nor cook meals as usual. On examination, there was only slight pronator drift on his left arm and hyperreflexia of the left extremities.

There are several clinical syndromes of vascular dementia (VaD), which are categorized into multi-infarct dementia, single strategic infarct (single brain infarct damaging functionally critical areas of the brain such as angular gyrus, thalamus, basal forebrain, posterior cerebral artery, and anterior cerebral artery territories), lacunar state, Binswanger's disease, genetic forms (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), and hypoxic ischemic encephalopathy.[6–8] A number of mechanisms causing these clinical syndromes are hemorrhage, ischemia/thrombosis, vasospasm, low perfusion, hematologic and rheological problems.

Since cases do not share common etiology and mechanism, patients may have different clinical presentations. For example, the onset may be abrupt or insidious. The progression may be stepwise, fluctuating, or marked by continuous worsening.[9–11] Frequently, individuals with VaD present with gradual and progressive cognitive decline without any stroke events. However, typical cases of VaD are usually seen with atherosclerotic comorbidities (diabetes mellitus, hypertension, coronary heart disease, and peripheral artery disease). The onset of cognitive decline is either subtle or abrupt, and there is psychomotor slowing, executive dysfunction, focal cognitive deficits and motor signs. The temporal association between the cerebrovascular event and the onset of dementia should be within 3 months. Nevertheless, as VaD is variable, sometimes the temporal association cannot be demonstrated easily due to an unclear onset of vascular event. Table 1 summarizes the clinical characteristics of AD and VaD.

Dementia with Lewy Bodies

A 72-year-old man with a 6-month history of cognitive impairment and visual hallucination presented to an emergency room after repeated falls a few days ago. His wife felt that he had been slow in thinking, speaking, and performing his routine activities for a few months. On examination, he had bilateral rigidity, parkinsonian gait, and masked face. No history of medication could be elicited.

Dementia with Lewy bodies (DLB) is a clinically defined syndrome and is claimed to be the second most common type of degenerative dementia among older adults, accounting for 10–15% of cases at autopsy. The criteria for diagnosis of DLB are highly specific but not sensitive. Core clinical features are fluctuating cognitive impairment (50–75%), visual hallucinations, and parkinsonism (seen in 25–50% of patients at diagnosis).[12] Its supportive features are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusion, hallucination of other modalities, REM

Table 2: Clincial Differences between Dementia with Lewy Bodies and Alzheimer's Disease

Clinical features	DLB	AD
Isolated memory impairment	93.8%	31.3%
Parkinsonism	More common	Less common and usually develops later in the course
Psychiatric symptoms	More likely to occur with dementia symptoms early in the course	Less likely
Fluctuation of cognitive function	50–75%	When delirious
Verbal memory	Better	Worse
Type of memory impairment	Semantic memory	Episodic memory
Executive function	Poor early in the course	Less severe in early phase
Attention, visuospatial function, constructional abilities	More impairment	Less impairment
Visual hallucinations	Common since early phase	Less prominent in early course
Autonomic involvement	Common	Less common
Neuroleptics response	Extrapyramidal side effect; may cause mortality	Behavioural response

Source: Bolla LR, et al. 2000;[1] McKeith I, et al., 2004;[12] Muangpaisan W, et al., 2005;[18] Leverenz JB, et al., 2002;[19] Stewart JT, 2003.[20]

sleep behaviour disorder, and depression. Physicians frequently encounter patients with dementia and parkinsonism, and a number of differential diagnoses should be raised such as multi-infarct dementia, normal pressure hydrocephalus, and Parkinson-plus syndrome.

In terms of making a diagnosis, the two most confusing diseases are DLB and Parkinson's disease with dementia (PDD) because the clinical features are similar. There are some clinical manifestations used to separate these two similar neuropathologic diseases. First, the temporal course of the disease is always used to distinguish these two overlapping syndromes. If the onset of dementia is within 12 months of parkinsonism's onset, it is likely to be DLB. By contrast, if the onset of parkinsonism is more than 12 months earlier than dementia onset, it should be PDD. Secondly, individuals with DLB usually have extrapyramidal signs in axial structures such as postural instability and masked face, whereas tremor is less prominent than among those with

Table 3: Clinical Differences between Dementia with Lewy Bodies and Parkinson's Disease with Dementia

Clinical features	DLB	PDD
Tremor	Less common	Common
Motor symptoms	Bilateral	Unilateral predominant
Axial predominant such as postural instability, gait difficulty, and masked face	Common	Less common
Parkinsonism at dementia diagnosis	25–50%	100%
Response to levodopa	Poor	Good
Cognitive impairment	Before or within 1 year of motor symptoms	Usually developed after motor symptoms 4–5 years (at least 1 year)

Source: McKeith I, et al., 2004;[12] McKeith IG, 2004;[13] Muangpaisan W, et al., 2005;[18] Leverenz JB, et al., 2002.[19]

Table 4: Clinical Differences between Frontotemporal Dementia and Alzheimer's Disease

Clinical features	FTD	AD
Age at onset	Rarely > 75 years	Increases markedly with age
Early behavioural problems	Common	Unusual
Socially inappropriate behaviours	Common early in the course	Usually in severe case
Memory impairment	Less prominent in early course	Early and profound impairment
Language problems	May have isolated language problems without memory impairment (in progressive nonfluent aphasia type)	Usually associated with memory impairment
Visuospatial defect	Rare in mild to moderately impaired case	Common
Motor signs	More common (in FTD with motor neuron disease)	Less common
Mood	Marked irritability, anhedonia, withdrawal, alexithymia (difficulties in understanding, processing, or describing emotions), euphoria, lack of guilty, apathy or suicidal ideation	Sadness, tears, anhedonia, apathy, guilt
Psychotic features	Rare persecutory delusion, usually jealous, somatic, religious, and bizarre behaviours	Usually have delusion of misidentification or persecutory type and usually occur in middle or late stage
Appetite, dietary change	Increased appetite, carbohydrate craving 80%, weight gain	Less common: anorexia and weight loss

Source: McKhann MG, et al. 2001;[15] Muangpaisan W, et al. 2003;[16] Muangpaisan W, et al. 2005;[18] Gregory CA, et al. 1996;[21] Mendez M, et al. 1993.[22]

PDD. Finally, all individuals with PDD have parkinsonian features at the time of dementia diagnosis, whereas only 25–50% of those with DLB have parkinsonism at the time of diagnosis. However, 80–100% of individuals with DLB develop some parkinsonism during its natural course.[13] Potential predictors for the development of cognitive decline and dementia in PD include older age at the onset of motor symptoms, bradykinesis, akinetic-rigid parkinsonism, bilateral onset of parkinsonism, depression, early visual hallucinations, and declining response to levodopa. The clinical differences between DLB and AD are shown in Table 2 and the clinical differences of DLB and PDD are presented in Table 3.

Frontotemporal Dementia

A 50-year-old woman presented with behavioural change over the course of two years. She had less concentration to accomplish her assigned tasks and was less responsible to her job. She had begun eating more and had gained 20 pounds in 5 months. She told lies and dirty jokes, stole office stationary, and picked up objects within reach and sight. She had poor personal hygiene and refused to take a bath. Apart from grasp, and palmomental reflexes, the physical examination did not reveal any other abnormality. Her MMSE was 29/ 30, but her performance on the clock drawing test was poor.

The clinical features of frontotemporal dementia (FTD) are described with the emphasis on prominent personality and behavioural changes with less prominent memory loss early in the course (Table 4).[14–16] Frequently, FTD is misdiagnosed as personality disorders or late-onset psychiatric disorders. Common behaviour and conduct disturbances are loss of personal awareness, loss of social comportment, disinhibition, impulsivity, distractibility, hyperorality (e.g., excessive eating), social withdrawal, stereotyped or preservative behaviour, and speech output change (e.g., reduction of speech, stereotype of speech, and echolalia). The physical examination usually reveals early prominent primitive or frontal reflexes. One-half of patients have a family history of dementia in a first-degree relative. There are three principal varieties of FTD: frontal variant FTD, semantic dementia, and progressive nonfluent aphasia.[17] Physicians usually misdiagnose FTD if semantic dementia and progressive nonfluent aphasia are present because these two subtypes do not have prominent behavioural or personality disturbance like the frontal variant FTD.

Key points

Prevalence of dementia is increasing due to longer life expectancy.

Exclude reversible causes of dementia first.

The common dementia syndromes in clinical practice are Alzheimer's disease, vascular dementia, dementia with Lewy body, and frontotemporal dementia.

Primary care physicians should be familiar with the clinical differences among these four dementia syndromes.

Conclusion

Failure to recognize dementia syndromes remains common. Different types of dementia require different approaches and management. Among a long list of the differential diagnosis of dementia, four common diseases (Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia should come to mind just from the history, physical examination, and simple neuropsychological batteries. Further investigations may be needed to confirm the provisional diagnosis and rule out some mimics in complicated cases.

No competing financial interests declared.

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