Cognitive disorders. Alzheimer's disease and other dementias.

Dr. Rafa G. Carretero
Internal Medicine Department
Hospital Universitario de Móstoles

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1 Introduction

The definition of dementia has been updated. The old term Dementia is now called Major Neurocognitive Disorder (MND). However, due to the common use of the term dementia in society and medical literature, it will be referred to as both Dementia and Major Neurocognitive Disorder. It is worth noting the limitations of using the term dementia, including its common association exclusively with older patients, and that it is often used synonymously with Alzheimer disease. Major neurocognitive disorder can affect younger individuals and does not always imply Alzheimer disease as the etiology of cognitive decline.

Major neurocognitive disorder is characterized by:

- A significant decline in at least one of the domains of cognition which include executive function, complex attention, language, learning, memory, perceptual-motor, or social cognition.
- The decline represents a change from a patient's prior level of cognitive ability.
- The decline is persistent and progressive over time, and is not associated exclusively with an episode of delirium.
- In addition to the cognitive decline, there must also be a decline in the patient's ability to function and perform everyday tasks. That means that the decline interferes with independence in everyday activities.

The everyday function of a patient is often evaluated in terms of the ability to perform instrumental activities of daily living, such as managing finances or medications, or feeding oneself. It is often a progressive disorder, and individuals often do not have insight into their deficits. Currently, no cure exists for any of the causes of dementia.

2 Epidemiology and etiology

The prevalence of dementia is expected to continue to increase along with the increasing numbers of the aging population. Currently, 47 million people in the world have dementia, and the number is expected to increase to 131 million by 2050. Alzheimer disease is the 5th leading cause of death for people over the age of 65 in the United States. Dementia is a significant public health burden and significantly increases the costs of care, both to the individual and society.

Several conditions can cause major neurocognitive disorder. Dementia can be causes by several etiological subtypes that indicate the possible etiology of the disorder. These subtypes include Alzheimer disease, vascular disease, frontotemporal lobar degeneration, Lewy body disease, Parkinson disease, HIV infection, Huntington disease, prion disease, substance and or medication use, traumatic brain injury, another medical condition, multiple etiologies, and unspecified. A patient may have more than one etiology contributing to dementia. For example, there may be a mixed picture of Alzheimer disease with vascular disease in the same patient. Other medical conditions that can lead to dementia include progressive supranuclear palsy, corticobasal syndrome, and, less commonly, multiple system atrophy. It often takes time to distinguish the etiology and can be aided by many factors, including the results of imaging studies, lab studies, genetic markers, patient comorbidities, medical and family history, and clinical findings.

Alzheimer disease is the most common cause of dementia, as it is responsible for 70 to 80% of all cases of dementia. It can occur sporadically or be familial. Alzheimer's disease is a gradual and progressive neurodegenerative disease caused by neuronal cell death. There is a genetic role identified for both early and late-onset Alzheimer's disease. Several risk factors have been associated with Alzheimer's disease, but increasing age is the most important risk factor for Alzheimer's disease. The incidence of Alzheimer's disease doubles every 5 years, after the age of 65. Prevalence rates increase from 10% after the age of 65 to 40% after the age of 85.

Vascular dementia accounts for approximately 15% of all dementia cases. Its incidence increases with age. Risk factors for vascular dementia include hypercholesteremia, diabetes mellitus, hypertension, and smoking.

Lewy body dementia accounts for approximately 5% of dementia cases. Other causes of dementia contribute in a minor for: Parkinson disease dementia, Frontotemporal dementia, Creutzfeldt-Jakob disease.

3 Pathophysiology

The pathophysiology of major neurocognitive disorder, or dementia, varies depending on the subtype. Most types of dementia, except vascular dementia, are caused by the accumulation of native proteins in the brain. Therefore, causes can be degenerative (such as Alzheimer disease), vascular, mixed (vascular and degenerative), metabolopathies (rare), or genetic (predisposition to be degenerative).

Alzheimer disease is characterized by widespread atrophy of the cortex and deposition of amyloid plaques, and neurofibrillary tangles of hyperphosphorylated tau protein in neurons which contribute to their degeneration.

Lewy body dementia and Parkinson disease dementia are characterized by the intracellular accumulation of Lewy bodies, which are insoluble aggregates of alpha-synuclein protein in the brain.

Frontotemporal dementia is characterized by various mutations leading to the deposition of ubiquitinated TDP-43 and hyperphosphorylated tau proteins in the frontal and temporal lobes leading to dementia, early personality, behavioral changes, and aphasia depending on the subtype.

Huntington disease is caused by an autosomal dominant inherited gene mutation.

Prion-related dementias are caused by misfolded prions, which are proteinaceous particles that are infectious in nature and self-spreading. Prion dementias include Creutzfeldt-Jakob disease and kuru, among other syndromes.

HIV infection is associated with the development of neurocognitive disorders, in part due to the activation of macrophages and toxic inflammation leading to neurodegeneration in the brain.

Alcohol consumption, particularly high dose and prolonged use, is associated with multiple cytotoxic processes within the brain.

Vascular dementia is caused by ischemic injury to the brain (e.g., stroke or multiple transient ischemic attacks), leading to permanent neuronal death.

The pathological changes in the brain of patients with different types of dementia can be varied. However, there is often overlap and mixed presentations and findings. Overall, neurodegeneration and vascular changes are seen in the brains of patients with dementia.

In the case of vascular dementia, the findings can vary and are related to the underlying etiology of vascular compromise, including lacunar infarcts, hemorrhagic lesions, and microvascular disease.

In the case of degenerative causes, such as Lewy body and Parkinson disease, or even Alzheimer disease, there can be presence of Lewy bodies throughout the neocortex, brainstem, and limbic regions of the brain. Lewy bodies are intracellular aggregates of proteins. There is also a loss of midbrain dopaminergic neurons. Additionally, there are neuritic plaques made up of amyloid and neurofibrillary tangles, similar to Alzheimer disease.

Alzheimer disease is characterized by extracellular amyloid beta protein deposition and neurofibrillary tangles composed of tau proteins.

Frontotemporal dementia is characterized by atrophy in the frontal and temporal lobes. There is neuronal loss, microvacuolation, and loss of myelin. Degeneration is found in the cortical and basal ganglia.

Cruetzfield Jakob disease will show loss of neurons, spongiform degeneration (vacuoles in the intraneuronal space).

4 Differential diagnosis and terminology

Most patients with dementia do not present with a self-complaint of memory loss; it is often a relative (wife, husband) or other informant who brings the problem to the clinician's attention. Self-reported memory loss does not appear to correlate with the subsequent development of dementia, while informant-reported memory loss is a much better predictor of the current presence and future development of dementia. Nevertheless, family members are often delayed in recognizing the signs of dementia, many of which are inaccurately ascribed to aging.

An essential aspect of dementia is that the cognitive impairment represents a change from baseline. With most of the dementia syndromes, the change is gradual and progresses over time; however, that aspect may not be appreciated by family members. By the time the patient has stopped driving or managing finances, subtle but worsening clinical manifestations have often been present for at least a few years.

Memory difficulty is the most common chief complaint; in addition, patients with dementia also have difficulty with one or more of the following: - Retaining new information (eg, trouble remembering events) - Handling complex tasks (eg, balancing a checkbook) - Reasoning (eg, unable to cope with unexpected events) - Spatial ability and orientation (eg, getting lost in familiar places) - Language (eg, word finding) - Behavior

It is mandatory to differentiate some diagnoses that can **mimic** dementia. Cognitive impairment related to dementia must be distinguished from acute cerebrovascular disease (stroke or TIA), delirium and depression:

- Dementia
- Acute cerebrovascular disease
- (Acute) delirium
- Depression

Dementia Gradual onset of short-term memory loss (ie, loss of memory for recent events) and functional impairment in more than one domain:

1. Executive function (finances, shopping, cooking, laundry, transportation)
2. Basic activities of daily living (feeding, dressing, bathing, toileting, transfers)

Cerebrovascular disease Sudden deterioration in cognition; episodes of confusion, aphasia, slurred speech, focal weakness.

Delirium It is an acute cognitive impairment with clouded sensorium, difficulty with attention, and hypersomnolence. It is is usually acute in onset and is associated with prominent deficits in attention. Patients have fluctuations in their level of consciousness and have difficulty maintaining concentration. The distinction between delirium and dementia can be difficult and sometimes impossible in acute presentations. Dementia is a significant risk factor for delirium, and thus, delirium and dementia can co-occur.

Depression Patients with depression are often more likely to complain about memory loss than those with dementia; the latter are frequently brought to clinicians by their families or caregivers, while depressed patients may present by themselves. The presentation of depression as dementia has been called *pseudodementia* or, more recently, "dementia of depression." Patients with depression may have signs of psychomotor slowing and give poor effort on testing (*I just can't do this*), while those with dementia often try hard but respond with incorrect answers. It is important for the clinician and/or test administrator to estimate the effort given by the patient. It is also important to realize that depression and dementia can occur in the same patient and that patients with dementia present with depression as a presenting complaint.

5 Clinical presentation

History must be obtained from the patient and their close friends, family members, or caregivers. Patients may present with symptoms of changes in behavior, getting lost in familiar neighborhoods, memory loss, mood changes, aggression, social withdrawal, self-neglect, cognitive difficulty, personality changes, difficulty performing tasks, forgetfulness, difficulty in communication, loss of independence, etc. A detailed history should include past medical, family, medication, and substance use history and defining observed symptoms of cognitive decline.

It is important to evaluate their current functional abilities and any changes in their ability to perform daily tasks and whether there are some concerns arising from the cognitive changes: Is the patient still driving? Have there been any episodes of wandering or getting lost? Can they handle money or go on shopping safely?

In addition to symptoms of dementia, the following symptoms may be seen in the following conditions:

- In Parkinson and Lewy body dementia, the patient can have visual hallucinations, and parkinsonian symptoms (bradykinesia, resting tremor, and muscle rigidity), and fluctuating cognition, attention, and alertness.
- In frontotemporal dementia, the patient can have behavior changes, including disinhibition and apathy
- In Creutzfeld-Jakob disease, the patient can have myoclonus, ataxia, and memory and behavior changes.

6 Diagnosis

All domains of cognition must be assessed. There are multiple cognitive evaluation tools available for use in a clinical setting, including the Mini-mental status examination (MMSE), Montreal Cognitive Assessment (MoCA), Saint Louis University Mental Status (SLUMS), and so on. These studies can be repeated over time to document the progression of decline. They can give an idea of the severity of the deficit along with specific cognitive domains that are affected.

Laboratory tests to check in all patients during the evaluation of dementia include complete blood count, urinalysis, metabolic panel, vitamin B12, folic acid, thyroid function tests, and serological tests for syphilis and HIV. These test can rule out other causes of dementina, such as HIV-related dementia or vitamin B-12 deficit.

Regarding neuroimaging, a brain MRI (magnetic resonance imaging) without contrast is often the initial test ordered. It is valuable for evaluating signs of vascular or ischemic disease, as well as localized regions or global atrophy that may be seen. A DaTscan uses a radiotracer to highlight dopamine transporter proteins in a SPECT scan on the presynaptic dopaminergic neurons. Other advances functional brain imaging techniques are PET, SPECT, and functional MRIm that can help in the early diagnosis and monitoring of patients with dementia.

7 Treatment

There are medications to improve cognitive function, such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and memantine. Cholinesterase inhibitors aim to slow or delay the worsening of symptoms. The benefits seen with the use modest, and ofthen in the early stages of the disease, when the cognitive impairment is mild.

Behavioral symptoms include irritability, anxiety, and depression. Antidepressants and sometimes antipsychotics can help with these symptoms. In addition, non-drug approaches like supportive care, memory training, physical exercise programs, and mental and social stimulation can be employed in symptom control.

8 Prognosis

The prognosis of dementia is poor. Dementia is often a progressive condition with no cure or treatment. The 1-year mortality rate was 30 to 40%, while the 5-year mortality rate

was 60 to 65%. Men had a higher risk than women.

There are some complications that can arise during the course of the disease, such as malnutrition, repiratory infections due to dysphagia, inability to perform self-care tasks, apathy, agitation, and do on.