Dementia: Etiology and clinical presentation



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Abstract:

Dementia means persistent deterioration of intellectual and cognitive functions with little or no impairment of consciousness/awareness or perception. There are several types of dementia, but the most common in everyday practice are: Alzheimer's disease, dementia with Lewy bodies (DLT), frontotemporal dementia (FTD), vascular dementia, and dementia due to hydrocephalus. In 10-15% of cases, dementias are reversible because they arose as a clinical manifestation of some other disease that can be treated and cured. This is particularly important for doctors in primary health care, who should recognize such disorders and treat them or refer them to a secondary or tertiary health care facility. The paper presents the etiology and clinical picture of dementia, which helps establish a diagnosis. The characteristics of the most common dementias of neurodegenerative, vascular, and infectious etiology are presented.

Keywords: dementia; Alzheimer's disease; frontotemporal dementias; Huntington's disease; vascular cognitive disorder; infectious dementias

INTRODUCTION

Dementia is an acquired and permanent disorder that impairs the functionality of patients. It signifies a persistent deterioration of intellectual and cognitive functions with little or no disturbance of consciousness or perception. It involves the loss of several distinct yet overlapping intellectual abilities and presents in various combinations. There have been numerous attempts to precisely define this condition. One definition states that dementia is an acquired and persistent disorder of cognitive functions, characterized by deficits in at least three of the following cognitive domains: memory, language (speech), visuospatial abilities, personality and behavior, or other cognitive abilities (abstract thinking, calculation, judgment, planning). A key aspect of all definitions is that the cognitive changes must be acquired and sufficiently pronounced to disrupt the patient's social and professional life.

According to the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), the criteria for dementia include memory impairment and at least one of the following: aphasia, apraxia, agnosia, or impaired executive functioning. Each of these cognitive deficits causes significant impairment in social or professional functioning. Additionally, this definition requires a notable decline from a previous level of functioning and specifies that the condition does not occur exclusively during delirium [1].

The DSM-V criteria for major neurocognitive disorder (formerly dementia) involve a significant cognitive decline from previous levels in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor skills, or social cognition. The cognitive deficits interfere with independence and autonomy in daily functioning and do not occur exclusively during delirium. Additionally, it is crucial that the cognitive deficits cannot be better explained by another psychiatric disorder (such as major depressive disorder, schizophrenia, etc.).

Dementia is, therefore, an acquired disorder that impairs functionality, but over time, the understanding of which cognitive functions are affected has evolved. Contrary to earlier beliefs that memory impairment was necessary for a dementia diagnosis, it is now recognized that memory impairment is not a mandatory feature at the onset of the disease [2].

In the work of primary healthcare physicians, it is essential to recognize the early signs of dementia on time, to ensure early diagnosis and the implementation of appropriate treatment measures. This article presents the etiology and clinical features of dementia, which helps in diagnosis, as well as the characteristics of the most common types of dementia: neurodegenerative, vascular, and infectious etiologies.

ETIOLOGY OF DEMENTIA

The most common forms of dementia are Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, and dementia due to hydrocephalus. These account for nearly 99% of all dementia syndromes with a neurological etiology. Approximately 50% of dementias are caused by cerebral atrophies - primarily Alzheimer's disease, FTD, DLB, 10% multi-infarct dementia, intracranial tumors, normal-pressure hydrocephalus, Huntington's chorea, chronic drug intoxication, cerebral trauma, AIDS-related dementia, and pseudodementia [3][4][5].

In most cases, degenerative dementias can be distinguished by one or two characteristic clinical features, but these differences can be difficult to recognize in the early stages of the disease. It is not uncommon for a diagnosis of Alzheimer's dementia to be made when another type of dementia is present. In 10-15% of cases, dementia is potentially reversible and treatable, which is of great therapeutic significance. Therefore, it is essential to rule out conditions such as vitamin B12 deficiency, brain tumors, drug or toxic substance poisoning, and chronic brain infections in patients with dementia.

Although some degenerative diseases can lead to dementia, this is not always the case, as many neurodegenerative diseases do not involve cognitive impairment, nor is every dementia of neurodegenerative etiology. The earliest signs of neurodegenerative dementias may be mild and subtle, often unnoticed even by the most experienced physicians. However, individuals close to the patient may notice a certain loss of initiative, reduced interest in usual activities, including work, and withdrawal from things that previously brought pleasure. These changes are often attributed to fatigue, depression, or aging. A more common early sign of dementia is the gradual onset of forgetfulness (e.g. forgetting names, difficulty managing finances, missing appointments, or forgetting recent conversations). Later, the patient becomes easily distracted, struggles to make appropriate decisions, may feel anxious without reason, and finds it difficult to complete multiple tasks simultaneously. In some cases, an early sign may be emotional instability or affective lability. Some patients may complain of physical disturbances (dizziness, instability, vague headaches), as well as sleep disturbances. Sometimes these mental impairments become evident during an infection, surgery, head injury, or the introduction of a new medication. There may be occurrences of neglecting social norms, disregard for others, paranoia, suspicion, hallucinations, wandering, or aimless activities. As the condition progresses, memory impairment is present in most types of dementia. Apraxia, agnosia, and language disorders may appear in the early or later stages, depending on the type of dementia. In the late stages, there is also weakening and disruption of somatic functions [6][7].

Degenerative dementias are associated with obvious structural changes in the cerebral cortex, but they also involve the diencephalon and basal ganglia. Isolated lesions of the thalamus rarely cause dementia, due to its connections with the cortex, especially when memory is affected. Even when a particular disease disproportionately affects a specific part of the brain, other additional areas typically contribute to the damage. An example of this is Alzheimer's disease, where the main site of damage is the hippocampus, but degeneration is also present in the cholinergic nuclei of the basal frontal part of the brain, which project to the hippocampus and significantly enhance the deterioration of memory [8][9][10].

In dementia believed to be caused by severe cerebral trauma, lesions may be found in the gyri of the temporal and frontal poles, the *corpus callosum*, and the thalamus. In some cases, there is widespread degeneration in the deep white matter of the cerebral hemispheres due to axonal tearing. Most traumatic lesions that cause dementia are quite extensive. It is possible that critical thalamic lesions, as well as axonal tearing, play a significant role in the development of dementia.

A diffuse inflammatory process is at least partially responsible for dementia in conditions such as syphilis, cryptococcosis, other chronic meningitides, and viral infections like HIV encephalitis, HSV encephalitis, and subacute sclerosing panencephalitis. This likely involves the loss of some neurons and an inflammatory disruption of the function of the remaining neurons. Diffuse cortical neuronal loss can also be caused by prion diseases, where gliosis and spongiform changes occur, leading to a specific pattern of cognitive dysfunction. Several metabolic and toxic disorders can

affect nerve function over time and present with clinical symptoms similar to or identical to dementia.

ALZHEIMER'S DISEASE

Alzheimer's disease is the most common neurodegenerative dementia, named after the physician who first described it, Alois Alzheimer, in 1906. The prevalence of the disease is less than 1% before the age of 65, approximately 5% around the age of 65, and after the age of 60, the incidence doubles every 5 years. Around 40% of individuals over the age of 85 are affected [11].

The primary pathological changes in AD include brain atrophy, accompanied by the loss of cells and synapses, and the formation of so-called "senile plaques" and neurofibrillary tangles. These changes occur in the neocortex (especially in associative regions), the hippocampus, the amygdala complex, the nucleus basalis of Meynert, and sometimes in the medial and lateral thalamic nuclei, the dorsal tegmentum, the locus coeruleus, and the paramedial reticular area [12].

The first symptoms (except in atypical variants) typically involve memory disturbances, which are considered the leading symptom. In the early stages of the disease, episodic memory for recent events is most affected, and as the disease progresses, even memory for older events is compromised. Working and semantic memory remain intact for a long time. In the middle stages of Alzheimer's disease, apraxia, aphasia, and agnosia develop. Abstract thinking and decision-making become impaired or even impossible as the disease progresses. In the early phase, mild to moderate depression, apathy, anxiety, irritability, and anosognosia are common, while in the late stages, delusional ideas (usually paranoid), visual hallucinations, and appetite disturbances occur. Behavioral disturbances often fluctuate [13].

In addition to changes in mental status, the neurological examination is normal in the early stages of AD. In the later stages, symptoms of parkinsonism may appear, and disinhibition phenomena can also occur. In the final stage, patients become mute, incontinent, bedridden, and exhibit generalized rigidity. Myoclonic jerks and generalized epileptic seizures may develop. Death typically occurs due to infections and sepsis, malnutrition, cardiac disturbances, or pulmonary embolism. The average duration of the disease is 8 to 10 years, although there are reports of disease durations ranging from several months to 21 years. Patients with AD live longer than those with vascular dementia (6.7 years) or mixed dementia (MIX, 6.2 years).

FRONTOTEMPORAL DEMENTIAS

Frontotemporal dementias are a group of neurodegenerative disorders characterized by progressive deterioration of behavior or speech, which is associated with pathology in the frontal and temporal regions of the brain. There are six subtypes: behavioral variant (Behavioral Variant Frontotemporal Dementia, bvFTD), primary progressive aphasia (Primary Progressive Aphasias, PPAs) - semantic variant, PPA - nonfluent agrammatic variant, corticobasal syndrome, progressive supranuclear palsy (PSP), and FTD associated with motor neuron disease (MND). Variations in the clinical presentation of FTD subtypes are attributed to differences in the brain regions affected by FTD pathology. FTD typically manifests in the 50s or 60s, but cases have been reported in individuals in their 30s and or over 90 years of age. The estimated prevalence of FTD is highest in the group between 45 and 64 years of age, ranging from 15 to 22 per 100,000. Around 10% of FTD cases occur before the age of 45, and 30% of cases develop after the age of 65. It is believed that the prevalence is likely underestimated due to underrecognition and misdiagnosis of FTD by primary care physicians. FTD affects both genders equally [14].

The symptoms of FTD include disinhibition, apathy, loss of empathy, repetitive behavior, and psychotic features. A typical finding during neuropsychological testing is a deficit in executive functions, with relatively preserved memory and visuospatial abilities. However, in the early stages, many patients can still perform executive tasks well, especially those with predominantly right temporal atrophy. It is now known that some patients with bvFTD may also have significant impairment in episodic memory. They tend to perform poorly on tests of facial expression recognition, particularly when negative emotions are involved [15][16].

HUNTINGTON'S CHOREA

Huntington's chorea is a progressive disease characterized by a triad: dominant inheritance, choreoathetosis, and dementia. The disease is named after George Huntington, who first described it in 1872. The fourth and fifth decades of life are typical times for the disease to begin, but in 3-5% of cases, it starts before the age of 15, and in some cases, it starts in childhood (with a special form). Around 30% of cases begin after the age of 50, and progression is slower in older patients. Genetic testing is available to confirm the diagnosis in individuals showing symptoms. However, since there is

no cure, ethical questions arise regarding widespread use and testing in asymptomatic individuals [17].

Mental disorders often manifest in several discrete forms long before the deterioration of cognitive functioning becomes evident. In approximately half of the cases, the first noticeable changes are mild personality alterations. Patients may begin to constantly seek blame for others, complain incessantly, and become tiresome to family members with their continuous nagging. They might also become suspicious, irritable, impulsive, eccentric, disorganized, excessively religious, or exhibit a false sense of superiority. Poor self-control can manifest as bursts of temper, bouts of melancholy, carelessness, tendencies toward alcoholism, and sexual promiscuity. Mood disorders, especially depression, are common and can be the most prominent symptom in the early stages of the disease. Eventually, there is always a global decline in intellectual abilities. The patient becomes less communicative and socially withdrawn. Emotional disturbances and personality changes can reach a level where they lead to actual psychosis, with delusions or hallucinations. The inability to fulfill work responsibilities, difficulty managing household tasks, and sleep disturbances may be the reasons why medical help is sought. There are difficulties in maintaining attention, concentration, and adapting to new responsibilities. Mental flexibility decreases. At the same time, there is a loss of fine motor skills. Intelligence tests show a greater decline in verbal tests. Memory is relatively spared. This gradual decline in intellectual functions is characterized as subcortical dementia, with elements such as aphasia, apraxia, and agnosia being rarely observed, and memory impairment not being significant. Often, the process is so slow, especially in cases of late-onset, that it seems as though part of the intellectual capacity is preserved over many years. Dementia is generally more severe in cases with earlier onset (ages 15-40) compared to those with later onset (ages 55-60) [18][19].

VASCULAR COGNITIVE DISORDER

Cognitive disorders of vascular etiology are the second most common cause of dementia. Unlike most other forms of dementia, this type can be prevented and treated in many cases. It manifests after a stroke (“poststroke“) or independently of a stroke (“non-stroke“), often involving cerebrovascular disease that does not present clinical symptoms but is detected through computerized tomography or magnetic resonance imaging. Additionally, vascular cognitive impairment is a common component of mixed dementia, often associated with other neuropathological conditions, such as Alzheimer's disease [20].

The clearest circumstances in which cerebrovascular disease can be associated with cognitive impairment are in poststroke vascular cognitive impairment. The number, volume, and location of infarctions or hemorrhages are linked to the risk of poststroke cognitive impairment. Individual strokes can cause cognitive impairment, particularly regarding attention and memory. Cognitive impairment can also result from the combined effect or multiple strokes that affect brain regions, such as the prefrontal lobe, which is involved in cognitive processes. This condition is referred to as multi-infarct dementia [21].

INFECTIOUS DEMENTIAS

Infectious dementias can result from conditions such as neurolapses, AIDS dementia complex, neurosyphilis, and other disorders. Neurosyphilis encompasses several different syndromes caused by infection of the brain tissue, spinal cord, and cerebellum, and occurs in approximately 10% of untreated individuals with early syphilis. Symptomatic neurosyphilis can present in various forms depending on the affected structures of the central nervous system, and is classified into meningitic, meningovascular, and parenchymal types [22].

Lyme disease can also lead to dementia in its third stage of late persistent infection. Essentially, neuroborreliosis causes encephalopathy, which results in memory disturbances and other cognitive dysfunctions.

Cognitive disorders are well-recognized complications of chronic HIV infection, ranging from mild impairments that do not disrupt a patient’s functioning to severe dementia. AIDS dementia complex occurs in 15-30% of HIV-infected patients, usually in the advanced stages of the disease when severe immunodeficiency is present. It is characterized by a gradual development of dementia, with early symptoms including apathy, social withdrawal, slowed thinking processes, forgetfulness, and poor concentration. In rare cases, the condition remains relatively stable, but in most patients, it progresses to a severe terminal state with akinetic mutism, global cognitive decline, loss of sphincter control, and bed confinement [23].

CONCLUSION

Dementia is an acquired disorder characterized by the decline or loss of some, many, or all cognitive functions. Based on numerous etiological factors, a classification of dementia has been established. Among the various forms of dementia, those of neurodegenerative etiology are the most significant and frequent, although vascular, infectious, and other etiological factors are not negligible. From the perspective of practitioners, particularly in primary healthcare, the most critical forms are those that can be prevented and treated, arising secondarily from other (treatable and curable) diseases and disorders. A thorough understanding of the neuroanatomy and pathophysiology of this disease, as well as detailed anamnestic and hetero-anamnestic data, neuropsychological testing, and modern diagnostics, is essential for implementing adequate therapy and preventing the risk of its onset.

Declaration of interest statement

None.

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Demencija - etiologija i klinička slika

Sažetak:

Demencija označava perzistentnu deterioraciju intelektualnih i kognitivnih funkcija sa malo ili nimalo poremećaja svesti/svesnosti ili percepcije. Postoji više vrsta demencija, ali se u svakodnevnoj praksi najčešće susreću: Alchajmerova bolest (Alzheimer's Disease, AD), demencija sa Levijevim telima (Dementia with Lewy Bodies, DLB), frontotemporalna demencija (Frontotemporal Dementia, FTD), vaskularna demencija i demencija usled hidrocefalusa. U 10-15% slučajeva demencije su reverzibilne jer su nastale kao klinička manifestacija neke druge bolesti koja se može lečiti i izlečiti. Ovo je od posebnog značaja za lekare u primarnoj zdravstvenoj zaštiti koji bi trebalo da prepoznaju takve poremećaje i leče ih, ili upute na lečenje u sekundarnu ili tercijarnu zdravstvenu ustanovu. U radu je prikazana etiologija i klinička slika demencije koja pomaže u postavljanju dijagnoze. Prikazane su karakteristike najčešćih demencija neurodegenerative, vaskularne i infektivne etiologije.

Ključne reči: Alchajmerova bolest; frontotemporalne demencije; Hantingtonova bolest; vaskularni kognitivni poremećaj; infektivne demencije