Clinical and radiological features of main dementias

Aspectos clínicos e radiológicos das principais demências

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ABSTRACT

Dementia is a syndrome characterized by a decline of two or more cognitive functions, affecting social or professional life. Alzheimer's Disease is a neurodegenerative disorder that represents 53% of dementia cases; memory loss, inability to recognize faces, impaired judgement, disorientation and confusion are possible common symptoms. Vascular Dementia is responsible for 42% of dementia cases, due to cerebrovascular pathologies, and the clinical aspects are related to the extension and location of the brain injury. Lewy Bodies Dementia is a neurodegenerative disorder that represents 15% of dementia cases, and its symptoms include visual hallucinations, parkinsonism and fluctuating cognitive decline. Frontotemporal dementia is a group of clinical syndromes, divided in Behavioral-variant, characterized by disinhibition, compulsions, apathy, aberrant sexual behavior and executive dysfunction; and Primary Progressive Aphasia, which is subdivided in Nonfluent-variant and Semantic-variant. Vitamin B_{12} deficiency is a reversible cause of dementia, with a wide clinical feature, that includes psychiatric symptoms such as depression and irritability, hematological symptoms related to anemia (e.g. dyspnea and fatigue), and neurological symptoms including dementia and neuropathy. Normal pressure hydrocephalus is also reversible, presenting forgetfulness, changes in mood, decline of executive functions, reduced attention, and a lack of interest in daily activities as symptoms. The radiological findings vary depending on the etiology of dementia. For that reason, understanding neuroimaging and clinical aspects is important to diagnose effectively.

Keywords: dementia, neurology, neuroimaging.

RESUMO

A demência é uma síndrome que consiste em um declínio de um ou mais domínios cognitivos, que afeta o desempenho social ou profissional do indivíduo. A Doença de Alzheimer é um transtorno neurocognitivo que representa 53% dos casos de demência; seus sintomas podem incluir perda de memória, incapacidade de reconhecer rostos familiares, julgamento comprometido desorientação e confusão mental. A Demência Vascular é responsável por 42% dos casos de demência e é causada por doenças cerebrovasculares, seus achados clínicos são relacionados com o local e com a extensão do dano cerebral. Já a Demência por Corpos de Lewy é uma doença neurocognitiva que representa 15% dos casos de demência, cujos sintomas incluem alucinações visuais, parkinsonismo e flutuação cognitiva. A Demência Frontotemporal, por sua vez, é um grupo de síndromes, que se dividem em variante comportamental — caracterizada por desinibição, compulsão, apatia, hipersexualidade e disfunções executivas — e Afasia Progressiva Primária, subdividida em variante não-fluente e variante semântica, que cursam com disfunções da linguagem. Há, ainda, a Deficiência de Vitamina B_{12}, uma causa reversível de demência. Ela possui um quadro clínico variado, que inclui sintomas psiquiátricos, como depressão e irritabilidade, sintomas hematológicos relacionados a anemia, como dispneia e fadiga) e sintomas neurológicos, que incluem demência e neuropatias. Uma outra causa reversível é a Hidrocefalia de Pressão Normal, que se apresenta com esquecimentos, alterações de humor, perda de função executiva e redução da atenção e do interesse nas atividades cotidianas. Os achados de neuroimagem variam dependendo da etiologia da demência. Assim, compreender os aspectos clínicos e radiológicos é importante para um diagnóstico efetivo.

Palavras-chave: demência, neurologia, neuroimagem

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INTRODUCTION

According to NIH criteria, published in 2011, dementia is characterized by cognitive or behavioral symptoms affecting work or usual activities, representing a decline from previous levels of functioning and performing, when these findings are not explained by delirium or major psychiatric disorder. The diagnosis of dementia is made based on history-taking from the patient and an informant, besides mental status examination or neuropsychological testing[1].

Patients with dementia may present two or more cognitive domains impaired, which can be: ability to remember new information; judgement, handling of complex tasks and reasoning; visuospatial abilities; language; personality, behavior or comportment[1].

This syndrome usually affects elderly with neurodegenerative disorders; however young onset dementia is not considered rare[2]. There are secondary causes for dementia, therefore a series of blood and imaging exams are necessary to identify reversible diseases, such as Vitamin B_{12} deficiency, thyroidopathy or resectable tumors[3].

The overall prevalence of dementia ranges from 5 to 7%[4]. A neuropathological study in Brazil revealed Alzheimer's Disease (AD) alone or combined with other disease represents 53% of the dementia cases, followed by Vascular Dementia (VaD) unaccompanied or combined with other etiology with 42%, and Lewy Bodies Dementia (LBD) itself or in combination with other diagnoses representing 15%, while 14% of autopsied patients who had clinical criteria for dementia did not have enough neuropathological findings at autopsy[5]. It is also worth mentioning the existence of Normal Pressure Hydrocephalus (NPH), which can be one of the causes of dementia. Patients can also be diagnosed with mixed dementia, a condition in which a person has symptoms attributed to more than one type of dementia[6,7].

The clinical presentation of dementia is wide, varying according to the cause, and involves a cognitive impairment such as amnesia, loss of functional independence, behavioral disinhibition, and language changes[8]. A cognitive neurological exam and a detailed medical history obtained from both the patient and a close family member or friend are necessary to diagnose dementia[1].

Cognitive tests can be used as screening to help the examiner to make a diagnosis. Montreal Cognitive Assessment (MoCA), for example, is composed of questions and challenges evaluating 12 items. Another option is the Mini-Mental State Examination (MMSE), with 30 questions to analyze 7 different cognitive domains. Both tests range the score from 0 to 30 points[3].

Modalities of neuroimaging exams such as magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) can be relevant to classify, evaluate and help the diagnosis of dementias[3].

ALZHEIMER'S DISEASE

AD is a neurodegenerative disorder responsible for 53% of the dementia cases (5). The pathophysiology of AD involves a build-up of amyloid-ß and tau proteins. This aggregation leads to formation of neuritic plaques and neurofibrillary tangles, which causes neurodegeneration, then, consequently, synaptic and neuronal loss[9].

The typical clinical presentation of AD is an insidious loss memory with other cognitive declines, such as inability to recognize faces, impaired judgement, disorientation, confusion, and neuropsychiatric symptoms, like delusions and hallucinations, affecting the functions at work or in daily activities. Family members or friends usually report repetitive questioning, forgetfulness of recent memories and where they kept objects, besides difficulty to cook and control finances[10, 11].

MRI of AD is classically represented by hippocampal atrophy and global brain volume reduction, most evident in mesial temporal lobe (MTL)[12]. Other imaging modalities can be useful to diagnose AD as the cause of dementia. For example, single-photon emission computed tomography (SPECT) and F-fluorodeoxyglucose positron emission tomography (FDG-PET) show, respectively, a hypoperfusion and hypometabolism patterns, which are important to make a precocious diagnose and to identify AD degeneration changes in other brain areas such as inferior parietal and lateral temporal cortex, precuneus and posterior cingulate[9, 13].

VASCULAR DEMENTIA

VaD is a group of disorders that represents 42% of dementia cases, which accompanies or precedes cognitive impairment due to cerebrovascular pathologies. VaD is also frequently present in combination with AD. VaD can be originated by strokes, hemorrhages, white matter rarefaction or infarction. Its main risk factors are hypertension, dyslipidemia, diabetes, atherosclerosis, and cerebrovascular diseases[5, 14, 15].

This type of dementia has a wide clinical feature, which varies with the severity of brain injuries and its location. The clinical manifestation comprises cognitive symptoms such as forgetfulness and confusion, and neuropsychological symptoms, including depression, apathy, and changes in behavior or mood[14, 15].

VaD has many possible etiologies, such as cerebrovascular pathologies, small vessel disease, leukoaraiosis, reduced cerebral perfusion, cerebral amyloid angiopathy, mixed lesions and lacunar infarcts[15].

There are several possible findings of neuroimaging exams in VaD, which help determine the subtypes of VaD and detail the aspects of lesions. For instance, brain Computed Tomography (CT) or MRI are both able to detect atrophy and large vessel diseases, although MRI is more sensitive than CT. Brain MRI can also show white matter lesions, microinfarcts, territory of vascular injury, cerebral microbleeds (usually seen in cerebral amyloid angiopathy), contributing to determine the etiology of VaD[16, 17].

LEWY BODIES DEMENTIA

LBD is a progressive cognitive decline that represents 15% of all cases of dementia, as the second most common neurodegenerative dementia, and it is characterized by the presence of Lewy bodies (LB) and its main constituent is the protein α-synuclein[5, 18].

LBD manifests with motor, cognitive, neuropsychiatric and autonomic symptoms. The core clinical features of LBD are: recurrent visual hallucinations, one or more of the cardinal signs of parkinsonism, fluctuating cognitive decline, and REM sleep behavior disorder. Other symptoms include autonomic dysfunctions (mainly orthostatic hypotension and constipation), hypersensitivity to antipsychotics, hypersomnia, hyposmia, depression, apathy, anxiety and delusions [9, 18-22].

Parkinsonism related to LBD has an atypical pattern. Tremor is less frequent, usually classified as a postural tremor, not a resting tremor, which is frequently seen in Parkinson Disease. Moreover, there is a low response to dopaminergic treatments in parkinsonism related to LBD[18].

In order to diagnose LBD, the physicians mainly depend on its clinical features, however neuroimaging could also help. At a first sight, brain MRI and CT can reveal no significant features and it is marked by a preservation of medial temporal lobe structures and hippocampus. Nevertheless, brain MRI may reveal focal atrophy of the midbrain, and hypothalamus which indicates neuronal death due to the accumulation of LB. It also can show generalized decrease in cerebral volume, most marked in parietotemporal regions[18, 21].

SPECT and PET may provide important information, such as FDG-PET imaging usually shows presence of occipital hypometabolism. In addition, it can also observe changes in perfusion or metabolism in the occipital and parietal regions[9, 18, 21].

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) is defined as group of clinical syndromes characterized by progressive decline in executive functioning, behavior and/or language, that is associated with a series of neurodegeneration process (neuronal loss and astrocytic gliosis) of the frontal and/or temporal lobe, which results in a focal atrophy in these lobes[23].

This dementia is subdivided into three clinical subtypes: Behavioral-variant (bvFTD) and Primary Progressive Aphasia (PPA), which is subdivided in Nonfluent variant Primary Progressive Aphasia (nfvPPA) and Semantic-variant Primary Progressive Aphasia (svPPA), both having language disorders. bvFTD is the most common, and it is characterized by progressive emotional decline, changes in behavior and personality, presenting, for example, disinhibition, compulsions, apathy, aberrant sexual behavior and executive dysfunction. On the other hand, the svPPA variant patient may present a loss of knowledge of the meanings of words and compulsions. In addition, nfvPPA cases are characterized by progressive motor-speech impairment and difficulty in sentence construction[24, 25].

Neuroimaging findings on brain MRI or CT in bvFTD include frontal or anterior atrophy and on SPECT or PET, it is possible to observe hypoperfusion or hypometabolism in those same areas. Unlike bvFTD, neuroimaging findings on brain MRI in cases of nfvPPA include atrophy in the left posterior fronto-insular and perisylvian area, and on SPECT or PET is observed hypoperfusion or hypometabolism in these areas. In svPPA the findings on brain MRI are anterior temporal lobe atrophy and on SPECT/PET temporal hypoperfusion/hypometabolism can be observed[16, 23, 24].

DEMENTIA DUE TO VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} deficiency is a common reversible cause of dementia. This syndrome has a very wide clinical spectrum, which includes psychiatric symptoms (mainly depression and irritability), hematological symptoms related to anemia (e.g. dyspnea and fatigue), and other neurological symptoms including neuropathy. A retrospective study concluded that dementia due to vitamin B_{12} is characterized by behavioral changes in most cases, followed by memory loss. There is also a spinal cord manifestation, which is called subacute combined degeneration (SCD), and consists in disturbance of position sense, spastic paraparesis or tetraparesis and symmetric dysesthesia. Neurological symptoms may precede hematologic signs of vitamin B_{12} deficiency, and they are the main reason for seeking medical care[26, 28-30].

The neuroimaging of vitamin B_{12} deficiency consists in a typical myelopathy, involving the central and peripheral nervous system. FLAIR and T2-weighted MRI in involved brains show hyperintensity in periventricular white matter. In cases of SCD, it can be found a T2-weighted hyperintensity symmetrically, especially in posterior, lateral or both columns in the cervical and thoracic portions of the spinal cord[26].

NORMAL PRESSURE HYDROCEPHALUS

Normal pressure hydrocephalus (NPH) is one of the reversible and treatable causes of dementia, defined as a syndrome characterized by an abnormal presence of cerebrospinal fluid in the ventricles, cognitive impairment, gait ataxia, and urinary urgency and/or incontinence, which can be reversible. Gait impairment is usually the main clinical feature of NPH, and it is characterized as slow and broad-based, which is associated with posture and balance abnormalities. Furthermore, NPH is considered the most common type of hydrocephalus in adults[6, 31].

When enlargement of the ventricles involves prefrontal brain structures patients may present cognitive symptoms. In these cases, the clinical features of cognitive decline are presented in the subcortical form, which is characterized by forgetfulness, changes in mood, decline of executive functions, reduced attention, and a lack of interest in daily activities. In addition, visuospatial perception and visuoconstructive skills can be affected[31-33].

The Large-volume lumbar puncture (Tap Test) is a test that assesses gait and cognitive functions before and after lumbar

punctures to drain cerebrospinal fluid (CSF) in patients with NPH. The procedure can reproduce the effect of a definitive shunt. From 60% to 80% of the patients with cognitive symptoms improve after CSF shunt surgery, explaining why dementia can be reversible in such cases[6, 31, 32].

Neuroimaging findings on brain MRI or CT in NPH are enlargement of the lateral and third ventricles. The Evans' index is a ratio used to evaluate this ventricular enlargement, which compares the widest frontal horn of the lateral ventricles to the widest transverse diameter of the skull [31, 34]. This index is useful for the diagnosis of NPH, because when it is more than 0.3 it indicates enlargement of the ventricles[38].

Other neuroimaging findings can also be present, such as callosal angle of 40° or greater, enlargement of the temporal horns without hippocampal atrophy, and disproportionately enlarged subarachnoid space hydrocephalus (DESH). It can be noted by the widening of sulci near to vertex. On SPECT/PET hypometabolism and reduction of cerebral blood flow can be observed[31, 34].

Table: Prevalence, clinical features and imaging findings of some dementias.

	Prevalence	**Clinical Features**	**Imaging findings**
Alzheimer's Disease	Represents 53% of the dementia cases.*	Memory deficits, visuospatial function and language impairment. Delusions, hallucinations and depression may occur.	Brain MRI: Hippocampal atrophy and global brain volume reduction. SPECT/PET: inferior parietal and lateral temporal hypoperfusion/ hypometabolism.
Vascular Dementia	Represents 42% of the dementia cases.*	Cognitive symptoms: forgetfulness and confusion.Neuropsychological symptoms: depression, apathy, and changes in behavior or mood.	Brain CT or MRI: atrophy and large vessel diseases. White matter lesions, microinfarcts, encephalomalacia, cerebral microbleeds.
Lewy Bodies Dementia	Represents 15% of the dementia cases.*	Visual hallucinations, parkinsonism, cognitive decline, REM sleep behavior disorder, hypersomnia, hyposmia, constipation, depression, apathy, and anxiety.	Brain MRI: Atrophy of the midbrain, and hypothalamus. SPECT/PET: Occipital hypoperfusion/ hypometabolism.
Frontotemporal Dementia	Less than 14%.	BvFTD: changes in behavior and personality, disinhibition, compulsions, apathy, aberrant sexual behavior and executive dysfunction. NfvPPA: Progressive motor-speech impairment, and difficulty in sentence construction. SvPPA: Loss of knowledge of the meanings of words, and compulsions.	BvFTD MRI: Frontal or anterior atrophy. BvFTD SPECT/PET: frontal or anterior hypoperfusion/ hypometabolism nfvPPA MRI: atrophy in the left posterior fronto-insular and perisylvian area. nfvPPA SPECT/PET: left posterior fronto-insular and perisylvian hypoperfusion/ hypometabolism. svPPA MRI: Anterior temporal lobe atrophy. svPPA SPECT/PET: temporal hypoperfusion/ hypometabolism.
Dementia due to Vitamin B_{12} Deficiency	Less than 14%.	Psychiatric symptoms: depression and irritability; Hematological symptoms: dyspnea and fatigue; Neurological symptoms: neuropathy, dementia (behavioral changes and memory loss)	Typical myelopathy in the central and peripheral nervous system. FLAIR and T2-weighted MRI hyperintensity in periventricular white matter; T2-weighted hyperintensity symmetrically in posterior, lateral or both columns in the cervical and thoracic portions of the spinal cord in cases of SCD.
Normal Pressure Hydrocephalus	Less than 14%.	Cognitive impairment (forgetfulness, changes in mood, decline of executive functions, reduced attention, and lack of interest in daily activities), gait ataxia, and urinary urgency.	Brain MRI or CT: enlargement of the lateral and third ventricles, Evans' ratio > 0.3, callosal angle of 40° or greater, enlargement of the temporal horns, and Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH). SPECT/PET: Hypometabolism of periventricular regions and reduction of cerebral blood flow.

***** Prevalence data related to alone or associated with other etiologies cases found in a cross-sectional study of neuropathological findings with 1,092 patients in Brazil. This study considered patients without criteria for any neuropathological diagnose as a group that represents 14% of dementia cases, which includes Frontotemporal Dementia, Dementia due to Vitamin B12 Deficiency, and Normal Pressure Hydrocephalus5.

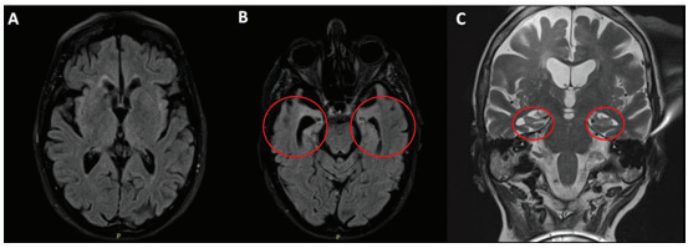

Figure 1. FLAIR axial (A and B) and T2-weighted coronal (C) brain MRI showing global brain volume reduction, predominantly in the mesial temporal lobe, characterized by increased volume of choroidal fissure and lateral ventricle temporal horn, with moderate hippocampal atrophy (circles in B and C) (Scheltens 3). There were also white-matter hyperintense signal, compatible with microangiopathy (Fazekas 2). An 80-year-old woman presenting a progressive amnesia started two years earlier. She did not remember recent events or where she placed objects. She also had poor speech with repetitive questions. At neurological examination, she had no focal neurological signs, however she obtained 22 points at the MMSE and 19 points at the MoCA, with impairment mainly in memory and visuospatial functions. Reversible dementias were ruled out after laboratory screening. These findings indicated AD as diagnosis, and donepezil was applied as treatment.

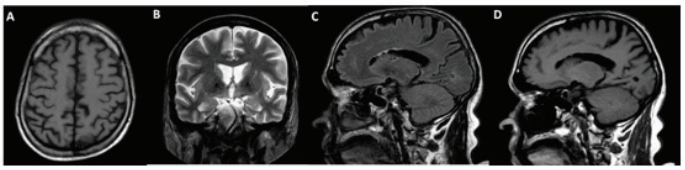

Figure 2. T1-weighted axial (A), T2-weighted coronal (B), FLAIR (C) and T1-weighted (D) sagittal brain MRI, highlighting global brain atrophy, inconspicuously more pronounced in parietotemporal regions, with enlargement of lateral ventricles. A 68-year-old man, merchant, with gradual lapses progressing for eight months. He forgets goods orders and important events, impacting work. In the last three months, he started presenting a poor speech with few words, many nightmares and visual hallucinations. These characteristics fluctuate during the day. He reached 18 points on MEEM, which reveals a decline in executive and visuospatial functions. Neurological examination showed hypomimia, bradykinesia, symmetrical cogwheel rigidity of upper limbs, reduced verbal fluency and several paraphasias. Potentially reversible dementias screening was negative. The sum of clinical and radiological characteristics allowed the diagnosis of DCL.

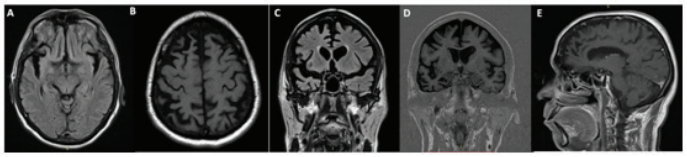

Figure 3. FLAIR (A) and T1-weighted (B) axial brain MRI, FLAIR (C) and T1-weighted IR (D) coronal brain MRI and T1-weighted sagittal brain MRI (E), showing an asymmetric global brain volume reduction, more evident in the right frontotemporal region. A 63-year-old man with a 2-year history of progressive behavioral changes, with compulsive buying disorder, which causes him many debts. In addition, increased food intake, especially consumption of sweets. In the last 9 months, the patient started to present hypersexual behavior and a small vocabulary speech. Neurological exam showed a bilateral palmomental reflex and Myerson's sign. Patient obtained 26 points on MMSE with impairment of memory and executive functions. Potentially reversible dementias screening was negative. These sets of findings allow a diagnosis of bvFTD. Then, it was proposed long term treatment with antipsychotic medication.

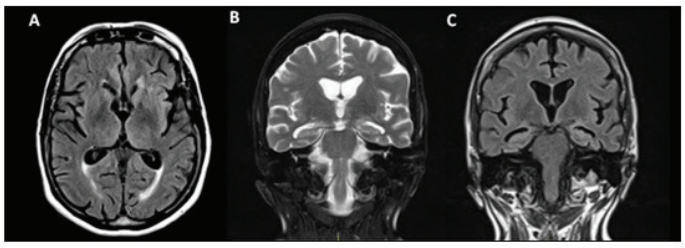

Figure 4. FLAIR axial brain MRI(A), T2-weighted (B) and FLAIR (C) coronal brain MRI, showing global brain atrophy, more evident in posterior temporal lobes and left insula and hippocampus. A 68-year-old woman, presenting language difficulties in the last two years. She started with slow and paused speeches, but comprehensible. These characteristics gradually evolved towards an unintelligible talk, ungrammatical utterance and phonological paraphasias. On neurological examination, it was found anomia and a non-fluent speech, even with efforts, however word and objects recognition were preserved. Based on these clinical features, the diagnosis of nfvPPA was made and the multidisciplinary treatment with speech therapy and music therapy was performed.

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