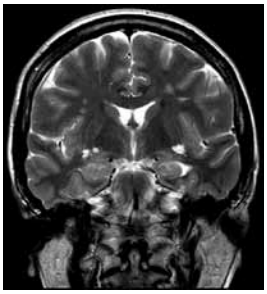

IMAGING IN DEMENTIA

IMAGEN EN DEMENCIA

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SUMMARY

Dementia is a syndrome which includes cognitive and neuropsychiatric alterations which affect at least two domains, such as memory, language, visual-spatial abilities, executive functions, personality and behavior. Regarding dementia, all these alterations represent a decrease in the prior functional level of the patient, which interferes with social tasks and daily activities. Neuroimaging techniques, especially MRI, are part of the initial study of a patient with dementia, because it serves to identify potentially reversible causes of dementia, as well as recognize vascular lesions or focal atrophy. It can also differentiate among the different types of dementia, according to the findings. Advances in the field of neuroimaging, and the use of functional neuroimaging techniques and nuclear medicine have enabled to find anatomical and functional substrates, both in the normal aging process and in advanced dementia, which has contributed to the development of new therapeutic options.

KEY WORDS (MeSH)
Magnetic resonance imaging
Alzheimer disease
Frontotemporal dementia
Vascular dementia

RESUMEN

La demencia en un síndrome que incluye alteraciones cognitivas y neuropsiquiátricas que afectan al menos dos dominios, como la memoria, el lenguaje, las habilidades visuoespaciales, las funciones ejecutivas, la personalidad y el comportamiento. Para hablar de demencia, estas alteraciones han de representar una disminución de los niveles funcionales previos e interferir con las funciones sociales y las actividades de la vida diaria. Los estudios de neuroimagen y especialmente la resonancia magnética (RM) hacen parte del estudio inicial de un paciente con un síndrome demencial, debido a que sirve para identificar causas potencialmente reversibles de la demencia, reconocer lesiones vasculares o atrofias focales y, según los hallazgos, poder diferenciar entre los diferentes tipos de demencia. Los avances en el campo de la neuroimagen y el uso de técnicas de neuroimagen funcional y metabólica han permitido encontrar sustratos anatómicos y funcionales, tanto en el envejecimiento normal como en el síndrome demencial avanzado, lo cual ha aportado al desarrollo de nuevas opciones terapéuticas.

PALABRAS CLAVE (DeCS)
Imagen por resonancia magnética
Enfermedad de Alzheimer
Demencia frontotemporal
Demencia vascular

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Introduction

Continuous development in imaging has enabled specialists to find structural and functional substrates in the encephalon for normal aging processes is as well ask for neurodegenerative processes. The present work aims to bring together the contribution of different imaging techniques to the study of dementia, particularly in the three most prevalent conditions: Alzheimer's disease, vascular dementia, and frontotemporal lobe dementia (FTLD) or frontotemporal dementia (FTD the).

Imaging techniques

A diagnostic imaging approach describes three aspects: qualitative, quantitative and advanced neuroimaging functional techniques. Computerized tomography (CT) and magnetic resonance (MR) qualitative assessments rely on visual inspection from an expert; it is highly recommended to rule out some potentially reversible causes of dementia (less than 13%) such as chronic subdural hematoma (Figure 1), hydrocephalus, strokes and neoplasias (Figure 2) (1-3).

Quantitative assessment refers to techniques that make possible to obtain numerical indexes from postprocessing (computerized manipulation) MR structural or functional images. This includes voxel-based morphometry (VBM), tensor-based morphometry (TBM), deformation-based morphometry (DBM), and volumetric techniques.

RM advanced neuroimaging techniques include diffusion, perfusion, magnetic susceptibility, and

functional RM in the strictest sense (fMRI) (4). Lastly, nuclear medicine techniques may be considered functional in the sense that they provide information on perfusion, metabolism, regional concentration of neurotransmitters or the accumulation of certain compounds in tissues.

VBM contrasts image features between groups of individuals, most commonly gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). There are, of course, some restrictions associated to working only with differences between groups. TBM and DBM comprise a set of tools that enable the study of brain shape, based on the fact that it is possible to identify necessary deformations for brain understudy to match a reference template. Therefore, while DBM allows identifying differences in volume, TBM and DBM techniques indicate differences in shape between subject groups. Furthermore, and area with gray matter volume decrease may have to undergo more deformation in order to match a reference template. The difference between the previously mentioned methods is their scope: TBM focuses on local differences whereas DBM focuses on global differences (5).

Volumetry provides estimates for certain properties (cortical thickness, area, volume, among others) of user-defined brain areas from information acquired from T1 MRI volumetric sequences (6), supplementing the neuroradiologist's expertise when detecting atrophy patterns. It is an adequate method to quantitatively evaluate longitudinal changes as it is easily repeated and replicated with different equipment and under different circumstances (7).

Diffusion-weighted images (DWI) are obtained applying the principles governing microscopic movements of free water in biological tissues (8). Even though diffusion is not visible in conventional RM images, the magnetic field can be manipulated from the equipment settings, increasing sensitivity to enable detection of this physical phenomenon. Diffusion tension imaging (DTI) employs a principle similar to that of DWI, requiring sequences sensitive to water diffusion in at least six different directions (8). These directions are used to construct a mathematic element known as tensor, which identifies the direction of maximal were diffusion on each image. DTI evaluates the integrity of white matter sectors, evidencing alterations which are not identifiable by other techniques.

With MR, it is possible to assess perfusion using a Dynamic Susceptibility Contrast-Enhanced (DSCE) technique. Recent developments in this field have facilitated brain blood flow mapping without a need for a contrast medium such as gadolinium. This technique is called Arterial Spin Labeling (ASL).

Susceptibility Weighted Imaging (SWI) products show a noticeable refinement of the classic T2 Gradient-Echo Image (GRE) and improve the sensitivity to venous blood and iron.

fMRI is built on the relationship between hemodynamics and function of the brain: increases in neuronal activity are intrinsically related to our increase in flow and volume of blood. A greater quantity of oxygenated blood generates an increase in the MR image signal, a phenomenon known as BOLD (Blood-Oxygen-Level-Dependent) effect. A series of methods allow for assessment of multiple cognitive processes, but the resultant activation patterns are not fully understood. Therefore, the role of fMRI in the diagnosis or monitoring of patients with dementia is not sufficiently clear to this day (9).

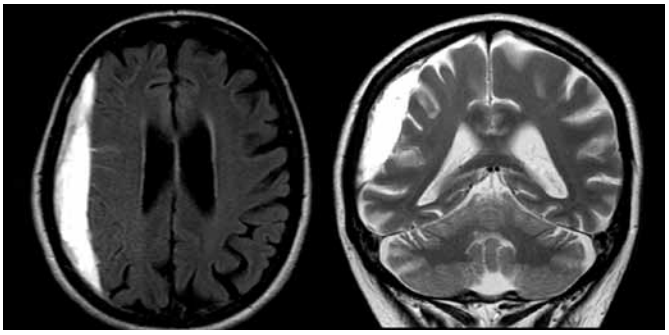

Figure 1. Cerebral MR with axial FLAIR sequences and T2 information. 65-year-old patient with demential syndrome ongoing for several weeks. A right frontoparietal extraaxial hematic accumulation is observable, corresponding to a subacute subdural hematoma.

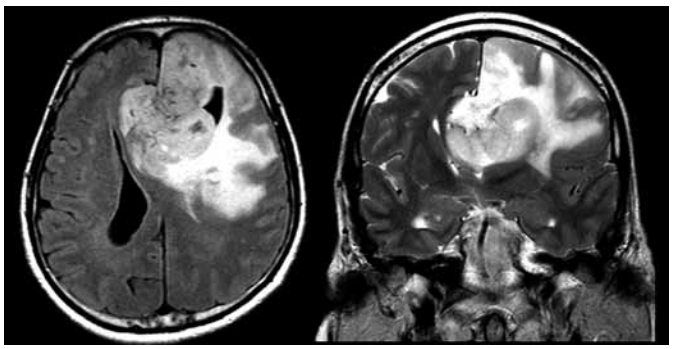

Figure 2. Cerebral MR with axial FLAIR sequences and T2 information. 60-year-old patient with behavioral alteration (frontal syndrome) for three months. There is a left frontal intraaxial mass, with surrounding vasogenic edema and signs of subfalcine and uncal herniation, consistent with an advanced glioma.

rs-fMRI, or resting state fMRI, analyzes temporal synchronization patterns in the signal obtained through BOLD effect, while the patient does not perform any task during the acquisition of images. Different methods of signal analysis report brain activation patterns that are reproducible under different acquisition conditions (10).

The basis of image generation in nuclear medicine arises from the possibility of detecting particles which are products of the radioactive decay process of a compound, called radioisotope, which accumulates in a selective manner in different regions of the brain. Available techniques in nuclear medicine are single-photon emission computerized tomography (SPECT) and positron emission tomography (PET).

PET takes advantage of active biomolecules in micro to nanomolar concentrations that have been marked with positron emitting isotopes. PET detects particles generated each time a positron emitted by the radioisotope collides with an electron. In dementia, molecules such as FDG (18F-2-fluoro-2-deoxy-D-glucose), which allows measuring local consumption of glucose are employed, as well as order imaging markers that allow for detection of amyloid and different neurotransmitters (11).

SPECT imaging employs radioisotopes that, instead of emitting positrons, emit light particles. Two molecules are broadly used: 99Tc-HMPAO (Technetium-99m complex of hexamethyl-propyleneamineoxime) and 99mTc-ECD (Technetium-99m ethyl cysteinate dimer) (12). These radioisotopes are small lipophilic compounds capable of crossing the blood-brain barrier through simple diffusion. Once they are inside the brain, their distribution is a reflection of regional brain perfusion.

Information observed by MR perfusion imaging is comparable to imaging obtained through HMPAO-SPECT, and, to a lesser degree, to FDG-PET(9).

Normal Aging

The decline of some neurological, cognitive, sensory and motor function occur during a normal aging process; while these changes may be related to systemic or neurological diseases, they may also be observed in patients who are free of these pathologies.

The term "Age-Associated Memory Impairment" was introduced in 1986 and was coined to refer to persons over 50 years old with subjective memory impairment, as well as memory testing results at least one standard deviation below a young adult but presenting a preserved intellectual capacity and no criteria for depression or dementia present. The term "Age-Associated Cognitive Impairment" refers to an impairment in different cognitive skills (executing function, language, memory, among others) when compared with young individuals. In MCI (Mild Cognitive Impairment), unlike previous ones, this is higher than expected for a given age. There are, however, studies suggesting that those patients that meets the criteria for age associated memory impairment have a risk 3 to 4 times higher of developing dementia.

There is a broad spectrum of changes normally associated to aging. Some of them overlap with demential syndrome findings; we start from the assumption that the test of choice for a patient with dementia is MR structural imaging (13).

In an in vivo study included 465 normal patients and use VBM as an analysis tool, Good's group showed a linear relationship between the changes experienced in GM, WM and CFL with age. Starting from the global decrease of GM, the relative global stability of WS, and the increase in CFL (sulci and ventricles), the following regional patterns were found:

- GM: decrease in volume of the superior parietal gyrus, pre-and postcentral gyri, insula, frontal operculum, anterior cingulum and right cerebellum (posterior lobe. Decrease in volume of the middle frontal gyrus, temporal traverse gyri and left temporal plane. Relative bilateral preservation of the thalamus, amygdala, hippocampus and entorhinal cortex volumes.
- WM: relative loss of volume in the optic radiations, frontal region and posterior arms of the internal capsule. Relative volume preservation of the posterior frontal lobes, right temporal lobe and the cerebellum.
- CFL: decreasing volume of the chiasmatic, supracerebellar and posterior cerebellomedullary cysterns, as well as the third ventricle, Sylvian and interhemispheric fissures.

We found that whenever any changes were found, they were more noticeable in males than in females, for all recorded variables (14). In a similar VBM study, a São Paulo research group published the results of an analysis of 102 individuals without dementia in their eight decade of life. They found loss of GM volume almost exclusively in males, particularly in the temporal neocortex (middle and superior gyri), the prefrontal cortex (right dorsomedial and bilateral orbitofrontal) and the medial temporal region (left parahippocampal gyrus and bilateral amygdala) (15).

Although loss of volume is detectable in young adults, it has some more noticeable effect after the seventh decade of life. In a study with 39 healthy individuals, with ages ranging from 31 to 84 years, a global volume decrease of 0.2% per year was found between ages of 30 and 50, and a decrease of 0.3 to 0.5% per year was found between ages 70 and 80. The greatest gray matter loss was described in frontal and parietal cortices. Temporal lobe and sheep camp with volume also diminishes in a continuous fashion, in a process which accelerates after age 70 (16).

Concomitantly with the loss of tissue volume, dilation of perivascular spaces is present, visible in the basal forebrain (Figure 3), subcortical white matter and the mesencephalon-thalamus interface, particularly along the perforating arteries' path. Generally speaking, their average diameter is less than 3 mm. When the finding is severe, with confluence in the basal forebrain, is known as a sieving pattern (May simulate ischemic lesions on a CT). Nonetheless, indicating this is structures using MR depends largely on the power of the magnetic field of equipment used in the study (0.2 to 3 teslas).

There is a high prevalence of white matter hyperintensities (periventricular or non-periventricular) in T2/FLAIR (Fluid-Attenuated Inversión Recovery) sequences, are eyeing from 30 to 80% of all cases (17). Practical and simple way to validate these changes is the Fazekas scale: multiple punctate lesions, early confluence of lesions, and large, diffuse lesions (18). Even if hyperintensities are considered a marker for ischemia, the first two categories may have no clinical repercussions.

Iron is found in the globus pallidus, red nucleus, dentate nucleus, black matter, subthalamic nucleus, putamen, caudate nucleus and the thalamus, between ages 20 to 60. The former four have the highest tissue concentration of this element (19). A MR will evidence these higher iron concentrations by a lower T2 signal intensity, particularly when GRE sequences are used. Note that the recently introduced SWI sequences have the greatest detection sensitivity.

The identification of macroscopic intraparenchymal hemorrhages is relevant in this context. Punctate motives, with a diameter less than 10 mm are observed in GRE as well as in SWI sequences. These represent hemosiderin during deposits in vascular walls, probably as a consequence of arteriosclerosis. In a normal brain, their prevalence should not exceed 10% (20).

Alzheimer's Disease

Alzheimer's disease (AD) is neurodegenerative condition which causes a gradual and progressive loss of episodic memory, as described by the patient or companion, of more than six months and evidenced in neuropsychological tests. This symptom may be isolated or associated with impairment in other cognitive domains, compromising the patient's day-to-day functionality. This disease affects over 37 million people in the world and its incidence is closely related to age; the risk of developing Alzheimer's doubles every five years in people over 65, and is higher than 30% in people over 85.

Among different biomarkers used in AD diagnosis, MR structural imaging enables the identification of regional atrophy in limbic structures, which is a minor reason why it has become an important analysis

tool, being included in the new diagnostic criteria proposed by Doubois and colleagues in 2007 (21).

Volume loss in regions such as the substantia innominata, anterior white, commissure, caudate nucleus, putamen, thalamus, amygdala, fornix, mammillary bodies, and precuneus has been reported and described, but the most clearly affected structure is the hippocampal formation (Figure 4) (22-28). Some signal alterations may also occur in periventricular white matter, in sequences containing T2-FLAIR information, and there may also be an increase in ventricular volume or perihippocampal fissures (29-32).

Identification of these findings is achieved through visual assessment (earlier stages) or more from metric methods (advanced stages). The loss of volume in frontomedial and temporoparietal regions has been associated to the cognitive impairment and subsequent loss of independence and ability to perform day-to-day activities an AD patient experiences (33). A meta-analysis provided evidence that hippocampal atrophy, changes in ventricular volume and generalized atrophy are among the most commonly described changes in neuroimaging as project of factors of a progression from MCI to AD (34).

We would like to emphasize that medial temporal atrophy is not exclusive to AD, being observed in other degenerative diseases as well. Therefore, it is more useful to analyze the overall pattern of brain atrophy and, overall, evaluate its progression over time. Keep in mind that young patients or non-carriers of the APOE4 gene display more posterior or parietocingular atrophy even at initial stages; this finding may be more important than affectation of the medial temporal region (20).

rs-fMRI studies were used to describe an alteration of the "default-mode" neural network, which has a anatomical base comprising the hippocampus and posterior cingulum along with the temporoparietal cortex (35).

In FDG-PET images, metabolic changes in temporoparietal association regions presenting most affectation of the angular gyri (36). Detecting changes in the posterior region of the cingulum and the precuneus in early stages of the disease is possible when employing techniques that allow comparing a patient to a control group (11, 37). MCI individuals whose FDG-PET images are within the normal limits will have a slow progression of the disease within a year, even if serious attention deficits are observed in neuropsychologic tests (38).

Besides metabolism study through FDG-PET, it is possible to obtain images of β-amyloid plaques (amyloid PET). Pittsburgh compound B (11C-PiB or [C-11]6-OH-BTA-1) has a high affinity for fibrillary β-amyloid (39). Observing 11C-PiB retention in Alzheimer patient's is possible by visual inspection. This compound is better retained in the frontal cortex, cingulum gyrus, precuneus, striatum, parietal cortex and lateral temporal cortex. Healthy individuals display a nonspecific retention of 11C-PiB compound in their white matter. Other compounds are being developed around a fluoride isotope (18F): 18F-Florbetaben and 18F-Flutemetamol, the latter aiming to surpass the 20-minute half-life offered by 11C-PiB (40).

Using amyloid PET imaging, Small and colleagues found that accumulation in medial and lateral temporal regions, the cingulum posterior region, and the parietal and frontal lateral, can predict memory impairment in around two years in patients with normal aging and MCI.

The same study showed that in subjects with MCI accumulation and frontal and parietal regions allows to predict which ones will develop AD within the following two years (41).

Vascular Dementia

Initially, but still dementia was described as a sequel of recurring strokes. Nowadays, however, a more adequate term is Vascular Cognitive Impairment (VCI), which refers to all causes of cerebrovascular disease, including risk factors such as arterial hypertension, diabetes mellitus, and atherosclerosis which results in brain damage leading to cognitive impairment, from MCI to dementia due to transitory ischemic stroke, silent strokes, strategic strokes, white matter lesions, lacunar strokes or hemorrhagic stroke. The prevalence of this condition is 1.2 to 4.2% in patients over 65 years old, with its incidence increasing with age and showing no differences between men and women.

Different criteria have been proposed for its diagnosis including the Hachinski ischemic scale, Rosen ischemic scale, DSM-III, DSM-IIIR, DSM-IV, CIE-10, ADDTC (State of California Alzheimer's Disease Diagnostic and Treatment Centers) and NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences); all please share the following foundations: to diagnose cognitive impairment through neuropsychological evaluation as well as stroke history, or clinical or neuroimaging approaches (Figure 5) (2,42).

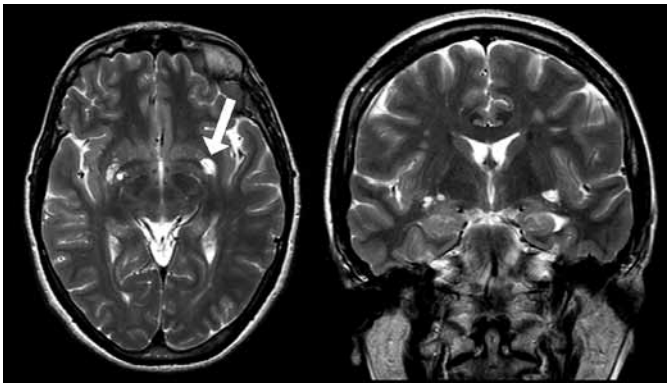

Figure 3. Cerebral MR with axial and coronal sequences with T2 information. Perivascular spaces dilation in the basal forebrain.Note the presence of a vascular structure (arrow).

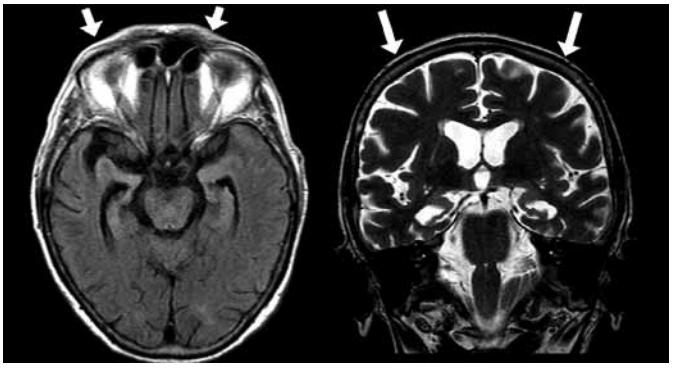

Figure 4. Cerebral MR with axial FLAIR sequences and T2 information. Loss of volume in the medial portion of the temporal lobes of a 72-year-old patient with Alzheimer's disease. Note the severity of the predominantly right hippocampal atrophy.

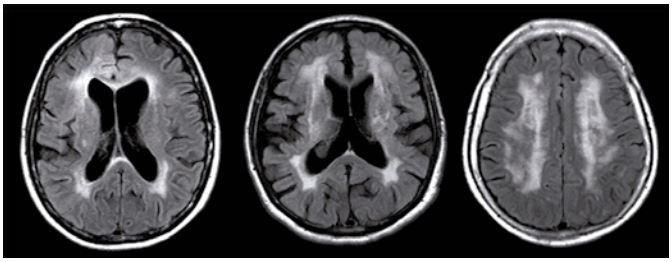

Figure 5. Cerebral MR with axial FLAIR sequences. 63-year-old patient with vascular dementia associated to severe confluent leukoencephalopathy.

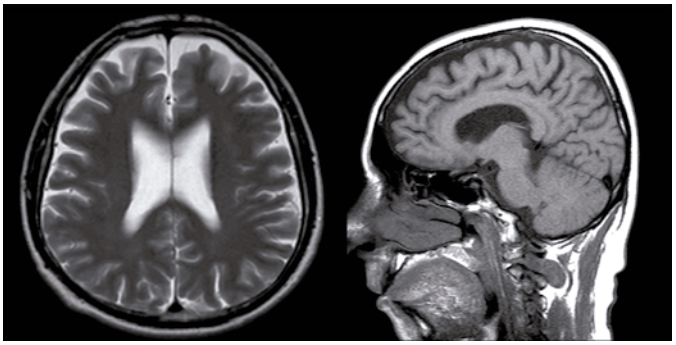

Figure 6. Cerebral MR with axial T2 and sagittal T1 sequences. Frontal atrophy evidenced in this 60-year –old patient with frontotemporal dementia.

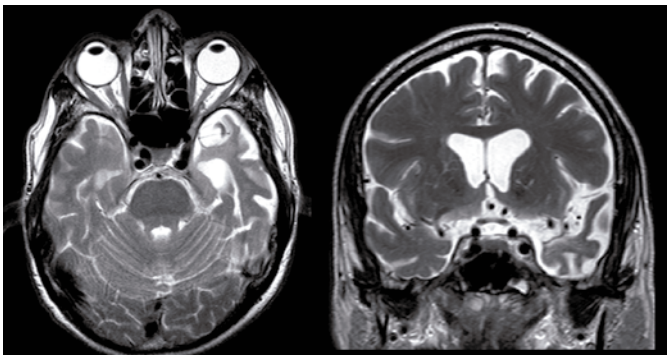

Figure 7. Cerebral MR with axial and coronal T2 sequences. Anterior temporal and left inferior atrophy observed in a 57-year-old patient with the semantic variant of a primary progressive aphasia.

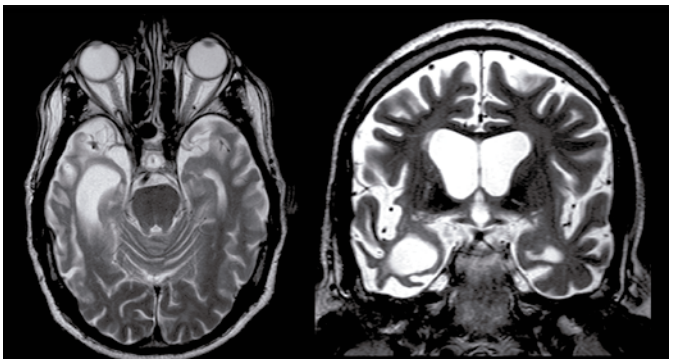

Figure 8. Cerebral MR with axial and coronal T2 sequences. Anterior temporal and right inferior atrophy observed what is likely a case of the right semantic variant of a primary progressive aphasia.

In 2003, the operative definition of VCI was released, including an operative definition of VCI including MR imaging elements (43). This definition includes two kinds of criteria, as follows;

1. Topography
   a. Large-vessel stroke (anterior cerebral, posterior cerebral, middle cerebral activity or surrounding areas).
   b. Small-vessel disease (lacunar stroke or white matter lesions, both larger than 2 mm in diameter).

2. Severity (large vessel disease of the dominant hemisphere, or bilateral; confluent leukoencephalopathy extension).

Nonetheless, these criteria are considered complex, impractical, and only reproducible by experts. When interpreting vascular changes from imaging, it's important to keep in mind that a periventricular pattern of affectation in its initial stage can be very hard to set apart from normal changes seen white matter during aging (hyper intensity with T2-FLAIR information).

In this context, assessment of vascular intracranial anatomy with angio-MR sequences obtained using a Time Offlight (TOF) technique and taking into account the presence of micro bleedings secondary to lipohyalinosis or amyloid angiopathy using GRE and SWI sequences.

Frontotemporal Lobar Degeneration/ Frontotemporal Dementia

Frontotemporal Lobar Degeneration (FTLD) is a pathological denomination comprising several clinical syndromes characterized by an alteration of behavior, language, and motor function, which collectively are the most common dementia in people below 60 years of age. Until recently, the term Frontotemporal Dementia (FTL) was used to describe the behavioral variant (bvFTL) and Primary Progressive Aphasias (PPA), which in turn may The nonfluent version (nfvPPA) and the semantic version (svPPA). However, the overlapping of these entities with other syndromes has been proven, and overlapping which includes motor neuron disease (MND), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) (44).

A common, usual finding in imaging in this context is an atrophy of frontal and temporal lobes, elements identifiable in coronal or axial T1-weighted containing FLAIR/T2 information (Figure 6).

In a group of 22 FTL patients, not discriminated by their variants, Kitagaki and colleagues (45) found increased signal in white matter using sequences with T2 and proton density information. The same study included a equally large number of healthy individuals and of patients with AD; therefore, the increase in signal in frontotemporal white matter is a diagnostic sign that allows distinction of FTL patients from subjects in the other two groups.

Frontotemporal atrophy in bcFTL follows an anterior-posterior gradient and, why is it may be bilateral, is usually asymmetrical. The first regions affected are orbitofrontal and interhemispheric cortexes. There is of the patient of the medial temporal area, but predominantly anterior (amygdala) (20).

nfvPPA displays a left perisylvian atrophy with frontinsular lesion as well as superior temporal and inferior parietal (20). On the other hand, anterior temporal (pole) and inferior (fusiform gyrus) atrophies on the left hemisphere are characteristic of svPPA (Figure 7).

Table 1. Findings summary

	Structural Alterations	Functional Alterations
Normal aging	GM overall decrease CSF overall increase increasing perivascular spaces Acceleration of the loss of volume in the temporal lobe and hippocampus after 70 years of age	Iron deposits visible through SWI in the globum pallidum, red nucleus, black matter, dentate nucleus.
AD	Hippocampus volume decrease, changes in ventricular volume, and generalized atrophy.	Metabolic changes evidenced by FDG-PET in the temporoparietal region, with greater contrast in angular gyri. Retention of 11c-PiB in the frontal cortex, cingulum gyrus, precuneus, striatum, parietal and lateral temporal cortex.
FTD bvFDT	Asymmetrical anterior-posterior atrophy, ocurring first in the orbitofrontal and interhemispheric cortexes. Amygdala involved.	PET hypometabolism or ASL hypoperfusion involving the atrophy zone.
nfvPPA FTD	Frontoinsular, superior temporal and inferior parietal atrophy.	PET hypometabolism or ASL hypoperfusion involving the atrophy zone.
svPPA FTD	Asymmetrical atrophy of the temporal pole, fusiform gyrus and amygdalohyppocampal region.	PET hypometabolism or ASL hypoperfusion involving the atrophy zone.
Logopenic FTD	A symmetric atrophy with predominance on the left posterior temporal cortex and inferior region of the parietal lobe, later affecting the posterior cingulum and anterior temporal regions, including the hippocampus.	Similar to a AD pattern.

Abbreviations: Grey matter (GM), cerebrospinal fluid (CSF), Alzheimer's disease (AD), frontotemporal dementia (FTD), behavioral variant of a frontotemporal dementia (bcFTD), non-fluent variant of a primary progressive aphasia (nfvPPA), semantic variant of a primary progressive aphasia (svPPA).

Loss of amygdalohippocampal volume is also asymmetrical, and maintains an anterior-posterior gradient (20). Nonetheless, a right variant of svPPA has also been described, where there is a right anterior temporal atrophy instead (pole, amygdala, anterior hippocampus, and fusiform gyrus) (Figure 8) (46).

Regarding superposing or overlapping syndromes, VBM tools have evidenced the following:

- PSP is found in association with mesencephalon, pons, thalamus and striatum (47).
- CBS is observed as a prefrontal cortex, striatum and brainstem atrophy (48).

Note that structure elements presented by MR may be corroborated with perfusion functional MR (ASL), SPECT or PET images, whether it is in hypoperfusion or hypometabolism conditions (20,49).

FDG-PET studies show alterations in glucose consumption in the frontal cortex, particularly in the frontomedial cortex (50). Frontal alteration predominance enables discrimination of FTL patients from AD patients. Frontal lateral and anterior temporal regions are also altered asymmetrically; this estimate is related to clinical symptoms of aphasia or semantic memory deficits (51). Although there are areas alteration which coincide both in AD and FTL, FDG-PET allows discriminating between these two conditions with 85% specificity and sensitivity. On the other hand, on the SPECT image frontal and temporal regions hypoperfusion FTL (53).

Given the spatial and temporal variability found between functional and structural data gathered by MR, the possibility of performing a multimodal analysis strengthen the results is a good idea.

A great example would be DBM morphometry and ASL perfusion (54,55)

Regarding structural quantitative techniques, frontal lobe volumetry discriminated 93% of FTL patients from subjects in a control group (56). Left amygdala and hippocampus size decrease helped distinguish patients suffering from the semantic variety from patients with the behavioral variety (57). These tools have also helped discriminate different atrophy patterns in populations with sporadic FTL, as well as mutations in the C9ORF72 gene associated to tau and gen progranulin microtubules (58).

A highly controversial FTL variant is logopenic variant, which according to postmortem findings and amyloid PET studies seems to be associated to AD (59). And our studies show part of a symmetric atrophy with left posterior temporal cortex and inferior parietal lobe predominance. As the atrophy pattern advances, it affects the posterior cingulum and anterior lip regions of the temporal lobe, including the hippocampus (19).

rs-fMRI has demonstrated that within the intrinsic connectivity networks of patients with bvFLT, the salience networks which have the anatomical basis in the anterior cingulum cortex, frontoinsula, amygdala, and striatum have been altered (35). The salience network is different, but not independent from an executing control network (60). Table 1 summarizes some of the findings presented in previous chapters.

Considerations for the future

Future implementation of ultrahigh-field MR (greater than 3 teslas) will facilitate obtaining. Applicable details on microscopic scale, a fundamental element in the assessment of structures such as the hippocampus (61).

As an example, thickness reduction in the CA1 region of the campus discriminates patients with AD from control patients (62).

This reduction in the CA1 region as well as the subiculum is also present in patients with AD, in contrast with patients suffering of other dementias (63). It's worth noting that, to date, there are likely more than 50 machines capable of working at 7 teslas, usually restricted to a research environment (64).

Refinement of computer sciences will provide advances to facilitate routine, quick and detailed analysis of structural or functional imaging studies, from a population level to an individual level.

In the nearby future, amyloid PET imaging will be available to supplements clinical evolution and provide support in matching patients with available therapies. FDG-PET and MR quantitative assessment will be useful when defining patients' patterns of evolution. When dealing with AD, it is necessary to find other marker biomolecules that may provide insights on important pathogenetic processes: soluble β-amyloid measurement, tau protein, acetylcholine and brain swelling (65).

Although some authors have criticized the large amount of money required to perform neuroimaging studies in populations with dementia, there is consensus in that many of the tools currently being explored will eventually reach clinical application; an excellent example is β-amyloid PET (66). Likewise, as highly important to keep in mind that all these investigations not boldly 04 insights on their way a neurodegenerative disease affects the patient's functionality, but also generate new hypotheses on the structure and function of cerebral networks in healthy individuals (67)

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