The aim of this study was to review, summarize and analyze recent findings relevant to the contribution of neuroimaging to the diagnosis of Alzheimer’s disease (AD) and vascular dementia (VaD). Computerized tomography (CT) or magnetic resonance imaging (MRI) provide accurate demonstration of the location and rate of progression of atrophic changes affecting the brain in AD and the different types of vascular lesions observed in mixed dementias and in pure VaD. Quantification of cortical thickness allows early diagnosis and rate of progression from mild cognitive impairment (MCI) to dementia. White matter involvement can also be quantified with diffusion tensor imaging (DTI) and functional methods including fMRI, functional connectivity, and MR spectroscopy (MRS). Isotope-based techniques such as positron emission tomography (PET) allow measurement of regional cerebral glucose metabolism using $^{18}$F-2-fluoro-deoxy-D-glucose (FDG). Cerebral blood flow can be measured using PET with $^{15}$O or with single photon emission computerized tomography (SPECT) with technetium ($^{99m}$Tc-HMPAO) or, more recently, arterial spin label (ASL) imaging. There are isotope markers for amyloid-beta ($^{11}$O-PIB, $^{18}$F-florbetapir), tau ($^{18}$F-DONP) and activated microglia ($^{1}$C-PK11195). Neuroimaging markers are particularly useful at the early symptomatic and preclinical asymptomatic phases of AD, as well as serving as endpoints in clinical trials.

Key Words: Neuroimaging, Alzheimer’s disease, Vascular dementia, Computerized tomography, Magnetic resonance imaging, Diffusion tensor imaging, Positron emission tomography, Single photon emission computerized tomography.

Introduction

A decade ago, the American Academy of Neurology (1) recommended the mandatory use of brain imaging for evaluation of patients with dementia because it often identifies the pathological cause of the dementing syndrome. Likewise, the current Guidelines of the European Federation of Neurological Societies (2) state: Structural imaging, which should be performed at least once in the diagnostic work-up of patients with cognitive impairment, serves to exclude other potentially treatable diseases; to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia. Although typical cases of dementia may not benefit from routine functional imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural imaging work-up and in particular clinical settings. For instance, CT or MRI may immediately disclose an unsuspected frontal brain tumor, metastases, stroke, subdural hematoma, or hydrocephalus as the cause of the dementia (1,2). Moreover, imaging provides accurate demonstration of pathological processes occurring in the brain as a result of dementing disorders such as neoplastic infiltration in lymphomas (3) or the typical high-signal intensity on $T_2$-weighted MR images in the pulvinar nucleus and medial thalamus in Creutzfeldt-Jakob disease (4). However, these patients represent a minority (<8%) of patients presenting with...
memory complaints to a memory clinic (5). CT and MRI usually provide clear evidence of cerebrovascular disease (CVD) in patients with vascular dementia (VaD). Nonetheless, for the large majority of patients with neurodegenerative dementias—both pure forms or dementias mixed with CVD—structural studies using quantitative structural MRI or functional imaging with positron emission tomography (PET) using isotopes such as 18F-2-fluoro-deoxy-D-glucose (FDG), H215O, or 11C-Pittsburgh compound B (PIB) as well as single photon emission computerized tomography (SPECT) with technetium (99mTc-HMPAO) or even magnetic resonance spectroscopy (MRS) have become the tests of choice for the differential diagnosis of senile dementias, in particular for the symptomatic, preclinical phase of Alzheimer’s disease (AD), in addition to being highly sensitive endpoints in clinical trials.

**Historical Aspects**

Since first used in the 1890s to visualize bones and other body structures, the in vivo imaging of the brain using X-rays was a major problem for almost 100 years given the fact that the skull provides the brain with solid bone shielding from the radiation. Earlier techniques to overcome this problem included the injection of air into the cerebrospinal fluid spaces to visualize the contours of the brain or pneumoencephalography, a technique developed by Walter Dandy in 1919 and cerebral arteriography, first used by Egas Moniz (Nobel Prize in Medicine in 1949) and still in use today; arteriography requires the intra-arterial injection of contrast agents into the cerebral arteries. These are, of course, indirect methods of determining the anatomic structure of the brain. Actual structural images of the brain parenchyma only became possible in 1972 with the development of CT of the brain by Cormack and Hounsfield (who shared the Nobel Prize in Medicine in 1979). More recently, Lauterbur and Mansfield received the Nobel Prize in Medicine in 2003 for their invention of MRI. The use of isotopes in emission tomography was pioneered by Kuhl, Chapman and Edwards in the 1950s at the University of Pennsylvania; in the early 1960s, the Danish researcher Niels Lassen began using inhaled 133Xe or 18F-2-fluoro-deoxy-D-glucose (FDG), a glucose analogue. A noncontrast brain CT obtained concurrently defines the 3D images of tracer cerebral blood flow. The current trend is towards the development of functional and highly sensitive multimodal brain imaging techniques such as subsecond fMRI and fast diffusion imaging (6) or a combination of automated structural MRI measures including regional volumes and regional cortical thickness measures combined with proton (1H) MRS measures in the hippocampus (7). Using multivariate data analysis the latter method had 97% sensitivity and 94% specificity compared to MRI or MRS alone in separating AD from normal controls (7). It is conceivable that the simultaneous use of multiple modalities will become a useful technique in the early diagnosis of AD.

**Imaging in Neurodegenerative Dementias**

The two basic imaging methods currently used in the diagnosis of dementias are structural brain imaging (CT/MRI) and metabolic imaging (PET/SPECT). CT uses X-rays and the resulting images depend on the electron density and rates of absorption of X-rays by different tissues. MRI uses the changes induced by the magnetic field to alter the rate of spin of the hydrogen atom about its own axis; this change of the electromagnetic properties of protons in water molecules in the tissue added to the small difference in energy produced by the change of spin of the protons is detected and used for the anatomic threedimensional (3D) reconstruction of the tissue. More recently, perfusion MR imaging uses radiofrequency pulses to label water proton spins in blood flowing through the carotid and vertebral arteries (arterial-spin labeling or ASL) in order to measure cerebral blood flow (8) without the use of contrast agents. MRS is based on a similar principle using predominantly the phosphorus (31P) nucleus, 1H (proton studies), and 13C to provide metabolic information. Other MR modalities include diffusion MRI that measures alterations of white matter and functional MRI (fMRI) that determines brain function using BOLD contrast.

As indicated above, CT is useful in determining the presence of treatable, reversible or modifiable causes of dementia (1–3) but has less spatial and anatomic resolution than MRI and is, therefore, less sensitive to detect atrophy and early or mild cerebrovascular disease particularly in the white matter, with the exception of presence of blood in the brain parenchyma. CT is also more sensitive than MRI in detecting the presence of calcifications or bony lesions. Moreover, CT/MRI continue to be used clinically to determine ventricular volume in patients with AD (9,10) and in suspected cases of normal pressure hydrocephalus (11). Overall, MRI has higher anatomic resolution and better soft tissue definition and grey-white matter contrast than CT.

Currently, PET scan is the metabolic brain imaging system most frequently utilized. It produces 3D images of the brain by detecting pairs of gamma rays emitted indirectly by a positron-emitting isotope radionuclide carried in a biologically active molecule, most often 18F-2-fluoro-deoxy-D-glucose (FDG), a glucose analogue. A noncontrast brain CT obtained concurrently defines the 3D images of tracer concentration. These images reflect regional brain metabolic activity defined by the tissue uptake of glucose.

**Pathological—Radiological Correlations**

The neuropathological changes that identify most neurodegenerative dementias were clearly defined by the end of the last century. These include gray matter alterations, particularly of the brain cortex, neuronal loss and atrophy accompanied by inflammatory and degenerative lesions, and vascular changes, along with deposits of abnormally
misfolded proteins. In 1991, Braak and Braak (12) described the typical progression of deposition of neurofibrillary tangles in AD as a hierarchical sequence that begins in the nucleus basalis of Meynert (13) and then involves sequentially the entorhinal cortex, the hippocampal formation, the amygdala, neocortical association areas and eventually frontal areas (14). The clinical challenge for the neuroimaging specialists has been the noninvasive identification of these changes occurring in the brain parenchyma.

The neuropathological progression in AD was confirmed in vivo with the use of neuroimaging (15), mostly with development of computational techniques of regions of interest (ROI) using MRI. These techniques demonstrated progressive hippocampal atrophy with decrease volume of the hippocampus (15,16) along with cortical thinning of entorhinal cortex (17,18) with sparing of the sensorimotor cortex and occipital lobes (19,20). Also, atrophy and decreased connectivity on resting state fMRI in the precuneus appears to be an early change in AD (21).

### Visual Rating of Structural Neuroimaging (CT/MRI) in the Clinic

According to Wattjes (22), the following elements must be evaluated visually in the CT/MRI of patients with suspected dementia: cortical atrophy and medial temporal atrophy.

The 4-point scale (0–3) of Pasquier and colleagues (23) is quite useful and can be applied for local or regional cortical atrophy as follows: grade 0 = normal; grade 1 = widened sulci; grade 2 = widened sulci and volume loss of gyri; grade 3 = knife blade atrophy.

Medial temporal atrophy is evaluated in coronal views on T1-weighted sequences using the 5-point scale designed by Scheltens and colleagues (24) to measure the width of the choroid fissure, the temporal horn, and the hippocampal volume as follows: normal = no lesions; grade 1 = width choroid fissure; grade 2 = width of the choroid fissure, width of the temporal horn; grade 3 = width of the choroid fissure, width of the temporal horn, volume loss hippocampus; grade 4 = width of the choroid fissure, width of the temporal horn, volume loss of hippocampus. Evidence-based data (15) has confirmed that visual evaluation of the anteromedial temporal lobe for atrophy on MRI has a sensitivity of 83–85% and a specificity of 96–98% to differentiate patients with AD from those without AD. Volumetric measurements of structural neuroimaging provide far greater diagnostic precision than visual evaluation (15), especially in mild cognitive impairment and early symptomatic, predementia cases of AD.

### Functional Neuroimaging

The main functional neuroimaging techniques used in AD are SPECT and PET. FDG PET provides measurements of regional glucose metabolism, whereas SPECT measures regional cerebral perfusion. In AD, FDG-PET measures the presence of a temporoparietal decline in glucose metabolism (Figure 1), whereas SPECT defines a concurrent decrease in blood flow in the temporal and parietal lobes (25) relative to healthy controls. However, the sensitivity (63%) and specificity (82%) of the temporoparietal metabolic decline on PET in separating pathologically confirmed AD from healthy individuals is similar to the sensitivity (63%) of the clinical diagnosis but lower than the specificity (100%) in this cohort (15,26).

MRS provides biochemical information of hydrogen proton-containing metabolites in the brain (1H MRS), particularly of the ratio of the neuronal metabolite N-acetyl aspartate to myoinositol (NAA/MI); 1H MRS distinguished patients with AD from healthy individuals with a sensitivity of 83% and specificity of 98% in a clinically confirmed cohort (15,27). In brief, the diagnostic accuracy of PET, SPECT, 1H MRS, and MRI volumetry of the hippocampus is similar to the accuracy of a pathologically confirmed clinical diagnosis of AD (15). Sensitive neuroimaging in AD has been used as an endpoint in controlled clinical trials, reducing the need for large numbers of subjects in the trial, reducing costs and accelerating the results.

### AD Stages and Biomarkers

Based on findings from a dominantly inherited AD cohort, Bateman et al. (28) concluded that the earliest biomarker is the decrease in the concentration of amyloid-beta (Aβ42) in the cerebrospinal fluid (CSF) that begins to decline 25 years before expected symptom onset. This is followed 15 years before symptom onset by Aβ deposition in the precuneus measured by PET with 11C-PiB and by elevation of CSF tau protein. Impaired cerebral metabolism in the precuneus measured with 18FDG-PET and onset of episodic memory problems were observed 10 years before expected symptom onset. Based on this and other studies, the new guidelines of the National Institutes of Aging (29) now divide AD into three phases: dementia phase in which clinical symptoms are present; symptomatic, predementia phase presenting with mild cognitive impairment (MCI) consistent with AD; and a preclinical asymptomatic phase diagnosed with genetic, imaging and CSF markers.

Atrophy of gray matter in AD can be quantified with automated methods to measure cortical thickness; in patients with MCI, thinning of the temporal cortex and precuneus is a predictor of worsening towards dementia (30). In AD, loss of cortical neurons is accompanied by atrophy of white matter due to axonal disconnection and loss of anisotropy of affected axonal bundles. Two fMRI techniques are used as imaging markers in the preclinical phase of AD to determine impairment of synaptic function of brain networks: diffusion tensor imaging (DTI) based on the detection of water diffusion longitudinally inside axons that provides imaging of the anatomy of axonal bundles and...
**Functional Connectivity**

Based on the relative synchrony of the blood-oxygen-level dependent (BOLD) signal across brain regions linked together during resting state. Of interest, increased connectivity is a compensatory mechanism observed in individuals at risk for developing AD (30) but with progression of the disease both activity and connectivity decline to levels lower than in healthy controls. Early white matter abnormalities in MCI/AD detected with DTI affect the cingulum, particularly the parahippocampal cingulum, the uncinate fasciculus, the corpus callosum, and the superior longitudinal fasciculus (30).

**Amyloid Beta (Aβ) and Tau Protein Imaging**

PET imaging of Aβ in amyloid plaques has been obtained with a number of PET ligands (31) including 18F-FDDNP (32), a compound that binds to Aβ and tau, 11C-CSB-13 (33) and 11C-PIB (34). These ligands have provided the first direct in vivo visualization of brain amyloid deposition (30,31). The compound most widely used has been 11C-PIB, a positron-emitting isotope with a half-life of only 20.4 min. Recently, two new PET Aβ-binding agents (flutemetamol and florbetapir) utilize the 18F isotope with a half-life of 109.8 min that allows wider use of these compounds (30). 18F-florbetapir showed good concordance of Aβ load images with postmortem histology (35). As a result, the FDA approved this compound in April 2012.

**Inflammation**

Activated brain microglia in AD can be imaged with 11C-PK11195, a less than ideal compound. Second-generation radioligands for activated microglia are being studied and astrocytosis has been detected in AD with 11C-DED PET (30).

**Neuroimaging in Vascular Dementia**

Neuroimaging plays a key role in the diagnosis of VaD (22,36). In most cases, CT and MRI provide evidence of vascular lesions in order to confirm the diagnosis of VaD. Also, the specific vascular cause can be defined based on structural images. For instance, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is characterized by subcortical white matter lesions affecting the pole of the temporal lobes (37) along with hyperintensity signals on T2-weighted images in the brain stem, particularly in the pons. Absence of low-density T1 signals in deep brain stem and cerebellar structures are also noted (38).

The NINDS-AIREN criteria (36) for research studies of VaD emphasize that neuroimaging studies are essential for the diagnostic process of VaD. The imaging lesions of CVD include those types causing small-vessel disease, usually affecting at least 25% of the white matter along with multiple basal ganglia and frontal white matter lacunes, and bilateral thalamic lesions. Other forms of CVD include large vessel strokes and watershed infarcts (39).

Vascular lesions of the white matter are important in VaD and also contribute to AD and other mixed forms of dementia (40). The Fazekas scale (41) provides two scores rated 0–3 on FLAIR MRI images to quantify white matter hyperintensities as a marker of small vessel vascular damage, as follows:

- Periventricular hyperintensities: 0 = absence; 1 = caps or pencil-thinning; 2 = smooth halo; 3 = irregular, extending into deep white matter.
- White matter hyperintensities: 0 = absence; 1 = punctate foci; 2 = early confluence of foci (Figure 2); 3 = large confluent areas.

The scale was modified by Scheltens et al. (42) to include regional changes including periventricular, lobar white matter and basal ganglia hyperintensities, and infratentorial foci of hyperintensity.

Lacunes are other important markers of small vessel disease, included within the NINDS-AIREN criteria for VaD (36) and should be counted and localized. Thalamic lacunes significantly increase the risk of dementia (43).

Often, elderly patients with dementia who fulfill diagnostic criteria for VaD also show changes consistent with AD pathology or mixed dementia (AD + VaD). A practical consequence is that the clinical response to donepezil...
treatment in patients with hippocampal atrophy is different from those without atrophy (44).

To determine the resemblance of the FDG PET pattern of VaD to that of AD, Pascual and colleagues (45) studied demented and nondemented patients with severe microvascular brain disease with white matter lesions on both hemispheres. Neuropsychological testing separated subjects with dementia and without dementia. Patients with AD and healthy controls matched by age, gender, and educational level were also studied. FDG distribution was analyzed using both voxel-based and volume of interest methods. Patients with AD had the characteristic PET FDG pattern of bilaterally decreased metabolism in the parietotemporal association cortex and precuneus. In contrast, patients with microvascular disease of the white matter, with and without dementia, had a similar anatomic pattern with metabolic abnormalities, particularly in the frontal lobes and deep nuclei. This pattern was more severe in those with VaD than in nondemented cases (45).

Neuroimaging is also crucial in identifying potentially treatable, early vascular damage leading to VaD (46,47) including predisposing conditions such as obstructive sleep apnea (48).

In conclusion, the current trend is towards the development of functional and highly sensitive multimodal brain imaging techniques. It is conceivable that the simultaneous use of multiple modalities will become a useful technique in the early diagnosis of AD. Neuroimaging markers are particularly useful at the early symptomatic and preclinical asymptomatic phases of AD as well as serving as endpoints in clinical trials.

References


