NEUROIMAGING OF DISORDERS CAUSING DEMENTIA

Joseph C. Masdeu, M.D., Ph.D.

Section on Integrative Neuroimaging, NIH, Bethesda, USA

Few areas in Medicine are evolving as quickly as our ability to image the human brain. The rapid development of neuroimaging tools in the past few years has provided the physician with a panoply of imaging modalities, each with a somewhat complex technology and with specific applications. A learning need exists to update the knowledge of neurologists and other physicians on the current role of imaging in the management of dementia, one of the most prevalent neurological disorders. Currently around 24 million people have dementia in the world, with the number being projected to double every 20 years. Moreover, therapeutic intervention is likely to be most effective in the preclinical stages of the dementing process, or at least in the early stages of cognitive impairment, when the halting of progressive neuronal loss seems most feasible. At these early stages of the process, neuroimaging provides key information to determine whether the patient has a degenerative dementing disease and which type, particularly when neuroimaging is combined with genetics.

NON-DEGENERATIVE DISORDERS

Potentially reversible neurological or psychiatric conditions leading to cognitive impairment may be diagnosed with the help of neuroimaging. For this reason, the 1994 American Academy of Neurology (AAN) guideline on the management of dementia, which did not require the use of imaging to diagnose a degenerative dementia in a patient with progressive memory loss and no motor or sensory findings or epilepsy, was changed to require structural imaging (CT or MRI) in the 2001 guideline. To this change contributed the report of patients with a clinical picture of progressive memory loss caused by tumors or subdural hematomas. Unless a tumor infiltrates the cortex, for instance in the case of very rare lymphomas or metastases from malignant melanoma, a CT without contrast is enough to rule out potentially reversible structural brain lesions. The European guidelines for the work up of dementia suggest that, if possible, an MRI be performed to increase specificity, given that MRI provides additional information on vascular causes of dementia and to distinguish the various degenerative dementias.

Symptomatic hydrocephalus in an older person presents with gait impairment and urinary incontinence, which generally are more prominent than cognitive impairment. When present, cognitive impairment is characterized by psychomotor slowing and impaired executive function and memory, but with preserved naming. Cortical sulci may be large and ballooned in symptomatic hydrocephalus. This finding should not be confused with the sulcal dilatation observed in hydrocephalus “ex vacuo,” caused by atrophy of the brain.

The role of vascular disease as a cause of dementia continues to need further definition. Small vessel infarction, of the subcortical type, seems more likely to contribute to dementia than large cortical infarctions. The effect of vascular and degenerative changes is cumulative. When vascular disease is the primary cause of dementia, multiple infarctions are generally present on CT or MRI, particularly involving the thalamic nuclei bilaterally.
By contrast, the extent of white matter involvement on T2-weighted images does not correlate with cognitive impairment in many studies. Medial temporal atrophy, a feature of Alzheimer’s disease (AD), also correlates with cognitive impairment in vascular dementia. Cognitive impairment is a prominent feature of cerebral amyloid angiopathy (CAA), which presents with white matter hyperintensity on T2 MRI and cortical microhemorrhages, best seen on gradient echo MRI sequences. Amyloid deposition in CAA can now be imaged with $^{11}$C PIB PET. In rare cases, CAA can be worsened by regional inflammation, susceptible to immunesuppressiver treatment. Involvement of the white matter of the frontal and temporal poles may help differentiate on MRI cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) from sporadic subcortical arteriosclerotic encephalopathy.

**Prion diseases** may present as a rather rapidly progressive dementing process, often accompanied by clinical manifestations of basal ganglia or cerebellar involvement. Imaging is very helpful and tends to be abnormal before the onset of any characteristic EEG pattern. Bilateral caudate or thalamic areas of high signal intensity on diffusion-weighted or FLAIR MRI imaging are characteristic. The cortical ribbon is often affected, particularly in the paramedial regions of the frontal lobes. The same regions have reduced metabolism on FDG PET.

Most cognitive impairment from *depression or mania* can be readily diagnosed from the clinical findings and response to therapy. However, in some older patients making these diagnoses may not be straightforward. In a patient with impairment in various areas of cognition, likely to be attributable to an attentional deficit, and with a normal structural imaging study, a negative PET or SPECT study may help decrease the probability of a neurodegenerative disorder. A normal $^{18}$F fluorodeoxyglucose (FDG) PET study lowers the probability of the patient presenting a neurodegenerative disorder in the following few years to about 10%. The 67% probability of a pathologically confirmed diagnosis of AD with a clinical diagnosis of possible AD, was lowered to a 52% with a negative SPECT. The findings characteristic of neurodegenerative dementia on PET and SPECT will be reviewed below. A negative $^{11}$C Pittsburgh Compound B (PiB) PET will decrease the probability of AD and dementia with Lewy bodies (DLB), but not of having a frontotemporal dementia.

**DEGENERATIVE DEMENTING PROCESSES**

In this section I will review the most characteristic imaging findings in the most frequent types of neurodegenerative dementia. Many of the disorders that now we consider diseases, such as Alzheimer’s, may turn out to be caused by a variety of genetic and environmental conditions. As an example, the genetic heterogeneity of the fronto-temporal dementias has become apparent in the past few years. From an imaging / neuropathology perspective, the advent of compounds, such as PiB, to image amyloid deposition in the brain allows us to separate dementias with amyloid deposition (AD, DLB) from dementias without amyloid deposition (frontotemporal and other dementias).
**ALZHEIMER’S DISEASE (AD)**

**Structural Imaging (MRI and CT)**

Most cases of AD start with mesial temporal atrophy, which can be appreciated by a dilation of the temporal horn of the lateral ventricle on CT or by atrophy of the entorhinal and hippocampal cortex on MRI. The same is true of MCI leading to AD. As the disease progresses, atrophy extends from the limbic cortex to the neocortex, particularly in regions posterior to the rolandic sulcus. Medial temporal atrophy is not specific for AD and happens in frontotemporal dementia (FTD) and vascular dementia as well. Greater bilateral symmetry and predominantly posterior atrophy tend to suggest AD over FTD. In some patients, early atrophy of areas in the parietal, occipital or posterior temporal lobe can be prominent, giving rise to presentations such as Balint’s syndrome. In such cases, regional atrophy may be determined by automated methods, such as voxel-based morphometry now available in some clinical units. By facilitating the comparison of two or more studies, automated methods greatly simplify the determination of the annual rate of volume change in temporal cortex, which distinguishes AD from controls with greater sensitivity and specificity than one-time measurements. Whereas the volume loss in normal aging is less than 1%, rates as high as 4% occur in early AD.

**Table 2 Scheltens Scale for the Visual Assessment of Medial Temporal-Lobe Atrophy**

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of Choroid Fissure</th>
<th>Width of Temporal Horn</th>
<th>Height of Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

↑ = increased, ↓ = decreased.


**Regional Cerebral Metabolism Studied with PET**

Regional cerebral metabolism studies with PET have used \(^{18}\)F-2-deoxy-2-fluoro-D-glucose (FDG) as a metabolic marker. The most typical pattern found in early AD is decreased metabolism bilaterally in the parieto-temporal association cortex and posterior cingulate gyrus, as well as the medial temporal region. As the disease progresses, frontal association
cortex becomes involved, while the paracentral cortex (primary motor-sensory areas) remains preserved. The specificity and sensitivity of these findings continue to be debated. In studies with neuropathological confirmation the sensitivity (84 - 95%) has been higher than the specificity (71 - 74%), that is, a normal study is seldom associated with AD. FDG-PET improves diagnostic accuracy over the clinical evaluation in separating histologically-proven AD from frontotemporal dementia. This clinical application of FDG-PET has been approved by the Centers for Medicare & Medicaid Services (CMS, USA) since 2004. Among persons with MCI, the most likely to progress to AD have metabolic findings similar to AD.

**Amyloid Imaging**

Until very recently, brain amyloid could be imaged only with $^{11}$C “Pittsburgh Compound B” (PIB), helping separate the dementias with marked amyloid deposition from the rest. Now, at least two similar compounds are labeled with $^{18}$F, a much more versatile isotope, which will greatly facilitate the clinical application of this technique. In April 2012, the FDA approved the use of one of them (florbetapir, Amivid) for clinical use.

**LEWY-BODY DEMENTIA (LBD)**

There are very few neuropathologically-confirmed imaging studies of LBD. More occipital atrophy in LBD than in AD has been reported by a group with a good diagnostic record. In agreement is the finding of decreased metabolism in occipital association cortex. As PIB binds with much greater affinity to beta amyloid than to alfa synuclein, positive PIB studies in LBD probably reflect amyloid binding.

**FRONTOTEMPORAL DEMENTIAS (FTD), CORTICOBASAL DEGENERATION (CBD)**

Clinically, neuropathologically and genetically, FTD comprises a heterogeneous group of disorders. It can present with a frontotemporal syndrome, characterized by impulsivity and disinhibition, or as a progressive aphasia, either semantic or non-fluent. Atrophy on MRI or decreased metabolism on FDG-PET tends to be regional and corresponds well to the area preferentially affected by the pathology. Except for rare cases with motor neuron involvement, these disorders tend to affect association cortex, rather than primary motor or sensory cortices. Clinical, imaging and neuropathological findings are summarized in Table 3. The most common clinical variety, frontotemporal dementia, is also the most neuropathologically and genetically heterogeneous, as is the more recently characterized hippocampal sclerosis dementia. Fronto-temporal abnormalities on FDG-PET / SPECT may antedate the atrophy that eventually becomes obvious on MRI. For this reason, PET has been approved for FTD diagnosis by the Centers for Medicare & Medicaid Services (CMS, USA). Amyloid imaging is negative in the frontotemporal dementias.

In corticobasal degeneration FDG-PET shows decreased metabolism in the affected hemisphere, ipsilateral lenticular nucleus and ipsilateral thalamus.
Table 3 Nonamyloid Dementias

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Clinical Findings</th>
<th>Atrophy (MRI) ↓</th>
<th>Metabolism (PET) ↓</th>
<th>Perfusion (SPECT) ↓</th>
<th>Motor Neuron Disease</th>
<th>Ubiquitinated Bodies (TDP-43)</th>
<th>Tau</th>
<th>Known Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral variant frontotemporal dementia (bvFTD)</td>
<td>Behavioral and personality changes and executive dysfunction</td>
<td>Bilateral frontotemporal atrophy, hypometabolism, and hypoperfusion</td>
<td>20%</td>
<td>50%</td>
<td>50%</td>
<td>Progranulin (PGRN) and microtubule-associated protein tau (MAPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia with motor neuron disease</td>
<td>Similar to bvFTD</td>
<td>Frontal &gt; temporal lobe atrophy, hypometabolism, and hypoperfusion</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>Possible chromosome 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic dementia</td>
<td>Anomic aphasia, loss of comprehension, surface dyslexia</td>
<td>Bilateral (left &gt; right) anterior temporal, atrophy, hypometabolism, and hypoperfusion</td>
<td>&lt; 5%</td>
<td>80%</td>
<td>20%</td>
<td>None determined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive nonfluent aphasia</td>
<td>Nonfluent speech with agrammatism</td>
<td>Left perisylvian association cortex atrophy, hypometabolism, and hypoperfusion</td>
<td>&lt; 5%</td>
<td>20%</td>
<td>80%</td>
<td>PGRN and MAPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticobasal syndrome</td>
<td>Apraxia, rigidity</td>
<td>Asymmetric frontoparietal, lenticular and thalamic atrophy, hypometabolism, and hypoperfusion</td>
<td>&lt; 5%</td>
<td>5%</td>
<td>95%</td>
<td>MAPT H1 haplotype and PGRN (four families)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive supranuclear palsy syndrome</td>
<td>Vertical supranuclear palsy, apathy, symmetric parkinsonism</td>
<td>Midbrain atrophy; mild frontal lobe atrophy, hypometabolism, and hypoperfusion</td>
<td>&lt; 1%</td>
<td>1%</td>
<td>99%</td>
<td>MAPT H1 haplotype</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


References