

IMAGING DEMENTING ILLNESSES

PART I: ALZHEIMER DISEASE AND VASCULAR DEMENTIA

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Dementia is an impairment of mental ability representing a decline from that level previously reached by the individual, and results in the inability to appropriately interact with one's environment. Dementias may be static, progressive, or reversible, and have many etiologies. One percent of the population above age 40 suffers from dementia and this figure rises to 7% above age 80 and 50% above age 90. Forty-five percent of dementias are due to Alzheimer disease (AD) followed closely by vascular dementia.

A stage along the way to dementia is mild cognitive impairment (MCI). There are various definitions but the simplest ones refer to a person who has some memory problems but can continue to live independently. It is a precursor of Alzheimer disease. Recognition of MCI clinically is important for institution of therapy, although there has not yet been an effective therapy developed. MCI has decreased FA and increased ADC in WM of frontal and temporal lobes and corpus callosum. Cortical thickness was decreased in GM regions of the frontal, temporal, and parietal lobes in patients with MCI. DTI and cortical thickness analyses may differentiate MCI from normal aging.

Predicting that conversion of MCI to Alzheimer disease

Therefore, one of the prime goals of imaging is identification of mild cognitive impairment and identifying those cases, which are likely to progress to Alzheimer disease. Early studies with CT showed low density in the hippocampal formations was highly sensitive for predicting conversion. Hippocampal and amygdala atrophy are highly sensitive in predicting the change as is atrophy of the entorhinal cortex, reduced glucose metabolism on PETT scanning, decreased size of the corpus callosum, functional MR imaging with cholinergic challenge, MR spectroscopy, and transverse relaxation rate. Converters have more left parietal atrophy and left lateral temporal lobe atrophy than non-converters. A new PETT ligand, [11C] PIB, and elevated values of apparent diffusion coefficients are newer methods that predict this conversion.

Alzheimer disease is primarily one of neuronal loss, amyloid containing neuritic plaques, neurofibrillary tangles in frontal, temporal, and parietal cortex, and granulovacuolar degeneration in the hippocampus. Amyloid beta peptide and Tau protein are felt to be important pathologic factors and among the chromosomes implicated in pathogenesis of the disease are 1, 14, 19, and 21. The significant increase in neuritic plaques, but not NF tangles in patients with even mild AD at death, compared with controls, suggests that *only* plaques are associated with the earliest symptoms of Alzheimer disease. The presence of CSF tau protein and amyloid beta peptide₄₂ had a predictive value of greater than 90% for Alzheimer disease. The findings on CT relate somewhat to the presence, but not to the degree of dementia. Its main role is to rule out the possibility of treatable or reversible dementias.

Cholinergic neurons are intimately involved in cognitive functions, especially memory. Such neurons are found in "association areas" of the brain. As a result, extensive studies of the association areas such as the amygdala, hippocampus, basal forebrain nuclei and the frontal and temporal cortex are current areas of study. While the size of the temporal horns, Sylvian fissures, and anterior temporal gyri have some predictive value, CT studies of the medial temporal lobe, looking specifically at hippocampal sulcus CSF, provide sensitive predictors of decline in elderly patients with mild impairment.

The advent of magnetic resonance imaging provided an opportunity to directly visualize the gray and white matter structures in the medial temporal lobe. The hippocampal formation, choroidal fissures, and the amygdala were readily visible and gave rise to a number of volumetric studies of the hippocampal formations. These again were highly accurate in separating *groups* of elderly control patients from those of elderly patients with Alzheimer disease. Entorhinal cortex volume, measured on MR, is comparable in discriminative power to hippocampal volume in diagnosing Alzheimer disease. It is felt that AD pathology begins in the entorhinal cortex. AD patients have 2.5 times greater whole brain atrophy rates than controls and more than 5 times greater rates of entorhinal cortex and hippocampal atrophy and these measures are more sensitive than ventricle or whole brain measures for detecting AD progression.

Temporal lobe volume loss may begin as early as six years before the onset of dementia. Hippocampal atrophy (HA) has been reported even in AD patients with the mildest dementia. Serum HDL-cholesterol, but not LDL- or total cholesterol, is associated with hippocampal volume and dementia.

Right hippocampal volume is 31% lower in the demented twins compared to the non-demented twin, and 6% lower when the demented twin is compared to controls. This may indicate preclinical AD in non demented twins. HA is not limited to Alzheimer disease and may also be seen in vascular dementia and Parkinson disease with dementia. The volume of the entorhinal cortex is diminished in AD but not in normal aging. The total cross-sectional area of corpus callosum is significantly reduced in patients with AD, with the most prominent changes in the rostrum and splenium and relative sparing of the body of the corpus callosum.

Several individuals have reported loss of large neurons in the basal forebrain particularly from the nucleus basalis of Meynert (NBM). This lies in the basal forebrain, above the optic tracts and below the anterior commissure. However, this area has a homogeneous appearance on magnetic resonance scan and the precise size and position the NBM within the basal forebrain has still not been described. However, there is height loss in the substantia innominata of patients with AD. Neuronal loss in the locus coeruleus is greater than that in the basal nucleus of Meynert in AD.

White matter hyperintensities in AD patients are superimposed phenomena of vascular origin. Measurement of tissue volumes in AD demonstrates that WMH are significantly related to cortical atrophy and neuropsychological impairment. They contribute to specific neurological and neuropsychiatric manifestations, but global cognitive impairment is more closely associated with atrophy.

MR spectroscopy (MRS) in Alzheimer disease shows decrease in the neuronal marker, NAA, and an increased myoinositol peak. In general, spectroscopy shows that NAA/Cr is decreased in dementias characterized by neuron loss (AD, FTLN, VascD), MI/Cr is elevated in dementias characterized by gliosis (AD, FTLN), and Cho/Cr is elevated in dementias characterized by profound cholinergic deficit (AD, DLB). MRS can be an excellent predictor of the conversion from MCI to AD. Occipital NAA/Creatine ratio <1.61 predicted conversion to dementia from MCI with 100% sensitivity and 75% specificity.

Hippocampal ADC is higher in patients with mild cognitive impairment and AD patients than in controls. This is felt to represent early ultrastructural changes in the progression of AD. PET scanning claims to be 93% sensitive as an indicator of AD in patients with cognitive symptoms of dementia. Posterior cingulate hypoperfusion on Tc-99m HMPAO SPECT was found in 65% of AD patients, 25% of SDAT patients and in none of the other dementias. It is therefore felt to be useful to diagnose AD, less useful to diagnose earlier stages of AD and not useful to diagnose other dementias. The posterior cingulate sign was present in 80% of pathologically proved AD cases, but only in 5% of cases of frontotemporal dementia suggesting that it is a means of discriminating between the two entities. SPECT also correlates with aggressiveness in AD. Compared with non-aggressive AD patients, aggressive patients showed marked right medial temporal hypoperfusion, an important neural correlate of aggression.

Studies are underway to directly visualize amyloid in vivo. Most efforts at in vivo imaging of amyloid plaques have been directed toward developing radioactive ligands that can be detected by PET or SPECT. *2-(1-{6-[2-¹⁸F]fluoroethyl} (methyl) amino]-2-naphthyl}-ethylidene) malononitrile* is also referred to as ¹⁸FDDNP. This probe labels amyloid in living humans. It shows good correlation with FDG PET and MRI in AD. It correlates with MMSE scores in AD. B-amyloid plaques are an integral part of the early pathophysiology of AD, and amyloid imaging agents may help in earlier diagnosis and effective management of Alzheimer disease. DDNP detected by PET in living AD patients shows greater accumulation and slower clearance observed in amyloid plaque and NFT-dense brain areas and correlated with lower memory performance scores. [¹¹C]SB-13 is a B-Amyloid specific PET tracer. When injected into AD and control patients, AD patients show increased retention in frontal and posterior temporal and inferior parietal lobes. Cortical PIB binding is elevated in Alzheimer disease subjects, and generally less in subjects with dementia with Lewy bodies, and absent in frontotemporal dementia. Subjects with mild cognitive impairment, generally show an Alzheimer disease-like pattern. Binding is greatest in the pre-cuneus/posterior cingulate, temporal cortex, caudate nuclei, and lateral temporal and parietal cortices. 22% of normal subjects showed cortical uptake. The degree of PIB binding did not correlate with the severity of the dementia.

Reduced risk of AD in highly educated people may reflect “cognitive reserve”. Using PIB, it has been shown that there is more pronounced amyloid accumulation in high educated compared to low educated patients with mild AD. This suggests “cognitive reserve and delayed clinical expression of AD in high educated patients with marked AD pathology

Vascular and ischemic degenerative diseases

To make a diagnosis of **vascular dementia** (VaD), a patient must have evidence of cerebral vascular disease by examination and imaging, and the patient must be demented. Vascular dementia encompasses all forms of cognitive loss due to cerebrovascular disease. Criteria for diagnosis rely on CT or MR for confirmation of vascular lesions although they do not require the lesions to correlate with cognitive or functional deficits. The dementia and onset of cerebral vascular disease must be temporally related. Vascular dementias may be secondary to thrombosis, embolus and hypotension and do not necessarily require that there be infarction. Patients should have the usual risk factors of hypertension, heart disease, smoking, diabetes, alcohol and hyperlipidemia. Vascular dementia comprises 54-65% of dementias diagnosed in Japan and in Italy was noted to be more prevalent than Alzheimer disease over the age of 70. Mixed Alzheimer disease and cerebrovascular dementia (mixed dementia) is most common in the oldest patients.

A new theory is that Alzheimer disease is actually a vascular disorder. This is based on the fact that:

- All risk factors for AD have a vascular component that reduces cerebral perfusion
- Risk factor association between AD and VaD
- Neuroimaging shows regional cerebral hypoperfusion in AD
- Pharmacotherapy that improves AD improves cerebral perfusion WMH often precedes cognitive change
- Overlap of AD and VaD symptoms
- Similarity of cerebrovascular lesions in both diseases
- Cerebral hypoperfusion precedes cerebral hypometabolism and cognitive decline in AD.
- Hypertension may cause protein leakage into the brain.

- Poor circulation prevents B-amyloid clearance from the brain.
- Heterogenous and multifactorial nature of AD, probably from diverse presence of vascular risk factors.

It has been hypothesized that hypertension creates a vulnerability state for the development of neurodegenerative disorders, especially Alzheimer disease. Vascular dementia may be associated with large vessel or small vessel occlusive disease. The subtypes of vascular dementia are:

- Post-stroke vascular dementia is characterized by abrupt onset of signs and symptoms and cortical cognitive impairment such as aphasia, apraxia or agnosia.
- Single strategic infarct dementia is due to small infarcts in thalamus, basal forebrain, or caudate. Memory, executive function and consciousness may be impaired.
- Subcortical ischemic vascular disease results from small vessel disease, lacunes and incomplete white matter ischemia. There is slow onset with psychomotor slowing, problems with activities of daily living, abstract thought, but not necessarily memory.

Stroke is followed by significant decline in cognitive performance when pre-stroke and post-stroke measurements are compared, although it is difficult to relate the degree of dementia to imaging findings. Dementia develops in 19% of stroke patients and 11% of controls indicating that stroke almost doubles the risk of dementia. The total volume of infarcted brain has some correlation. Global cerebral edema and left sided infarction are important risk factors for cognitive dysfunction after subarachnoid hemorrhage. Stroke patients with pre-existing medial temporal lobe atrophy are more likely to develop post-stroke dementia than those without. Sixteen percent of patients admitted with stroke have pre-existing dementia, and therefore, the effects of stroke in causing dementia must be interpreted in light of this fact. As mortality from stroke declines, the rate of diagnosed dementia increases, and improved survival from stroke may contribute to this trend. Other contributing factors may include better diagnostics, an increased propensity to make the diagnosis, and increasing dementia risk attributable to factors other than stroke. In post stroke patients with cognitive impairment, gray matter volume reductions were seen mostly in the thalamus with smaller reductions in the cingulate gyrus and frontal, temporal, parietal, and occipital lobes. This suggests a central role for the thalamus in the development of cognitive impairment.

A study which rated the intensity of white matter hyperintensities showed that they are directly related to lower scores on tests of fluid type intelligence, the ability to solve problems, often with the pressure of time. WMHV is related to poor performance in cognitive domains related to frontal and medial temporal lobes. Subjects with chronic respiratory disease had deeper WMHs. White matter hyperintensity as affecting more than 0.75% of cranial volume had significantly slower performance on a task of cognitive flexibility and sensorimotor ability. White matter hyperintensity volume is greater in amyloid angiopathy, and Alzheimer disease/MCI than in normal aging. However, there were no differences in spatial distributions. When controlling for total white matter hyperintensity volume, the hyperintensities were most frequent in the deep periventricular white matter in all three groups. This suggests that white matter hyperintensities were most common in regions of relatively lower normal cerebral perfusion. Decreased lung function is related to poorer cognitive function and increased subcortical atrophy in mid-adult life. Presence of chronic respiratory disease may be related to deep WMHs in men. Total white matter lesions strongly predict executive impairments. These are primarily due to deep white matter lesions but not necessarily to peri-ventricular lesions. It has been hypothesized that these lesions preferentially disrupt frontal-sub cortical circuits. It has also been shown that cerebral microbleeds are an important factor that causes cognitive impairment in subcortical vascular dementia. ESRD patients have lower FA values in white matter than controls. FA and duration of dialysis relate to decreased cognitive function.

Elderly people with silent brain infarcts have an increased risk of dementia and a steeper decline in cognitive function than those without such lesions. Lacunar infarcts increase the risk of dementia 20 fold in AD, and damage to frontal circuits compounds the early hippocampal lesions of AD. 1/5th of 85 year olds have infarcts on CT and half of them are clinically silent. These infarcts relate to an increased rate of dementia and three year mortality.

Small strategically placed infarcts may cause serious dementia, and therefore location is more important than size. As an example, the Papez circuit involves the fornix, mamillary bodies, mammillothalamic tracts, anterior thalami, cingulate cortex and cingulate bundles. Lesions of the major components of the circuit, especially the anterior thalamic nuclei, disrupt memory in humans. Lesions outside the circuit, especially in the dorsal medial and pulvinar nuclei of the thalamus may also cause severe cognitive and behavioral changes in

spite of the small size of the lesions. Imaging such small lesions of the thalamus has shown that T2 and FLAIR sequences detected 97 % of small thalamic infarcts, but FLAIR alone detected only 51% of ischemic lesions and 60 % of microbleeds indicating the need for both sequences in examining for small strategically placed infarcts. Total serum homocysteine (tHcy) is a risk factor for stroke and dementia. 259 subjects had pixel based quantitative MR to determine total WMHV. Higher levels of tHcy correlated with WMHV suggesting that tHcy is a risk factor for white matter damage. . In the Cardiovascular Health Study, it was shown that use of any antidepressant during the period of the study was associated with worsening of white matter hyperintensity volume, especially with the use of tricyclic antidepressants.

Besides arteriosclerotic cerebrovascular disease, there are a number of other reported vascular causes of dementia. **Dural arteriovenous fistula and intracerebral arteriovenous fistulae** may cause severe venous hypertension and venous outflow obstruction. This may be associated with thalamic venous infarction and subsequent dementia.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) is a familial disease with imaging features resembling Binswanger encephalopathy. The disease presents with gait abnormality, Parkinson-like symptoms and progressive dementia. MR shows white matter T2 hyperintensities and T1 cystic hypointensities and cystic lesions in the basal ganglia. Onset is usually earlier than Binswanger disease, and patients often do not have risk factors such as hypertension or other cerebrovascular disease risk factors. Granular amorphous deposits are found in vessel walls, a finding not associated with Binswanger or hypertensive encephalopathy. White matter hyperintensity load and micro hemorrhages are not associated with cognitive dysfunction. Mean apparent diffusion coefficient and lacunar infarcts are the most important magnetic resonance parameters associated with cognitive dysfunction, in CADASIL.

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