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The WCC Note™

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Alzheimer's Disease: Diagnosis and MRI Imaging

The first day a person walks or rides on a bike becomes a celebrated moment in any family's history. But the final time a person fills out a crossword puzzle or charts a stock ledger usually goes unnoticed. No photographs capture the last stroke of a pencil; such monumental losses slip by without fanfare.

The silent deposition of amyloid β occurs the same way, insidiously laying down and killing brain cells without heralding its presence. How, then, do we know Alzheimer's disease is taking hold in a life? This issue of *The WCC Note* examines recent literature on the diagnosis and biomarkers of Alzheimer's disease. ■

DIAGNOSIS

How Is Alzheimer's Disease Diagnosed?

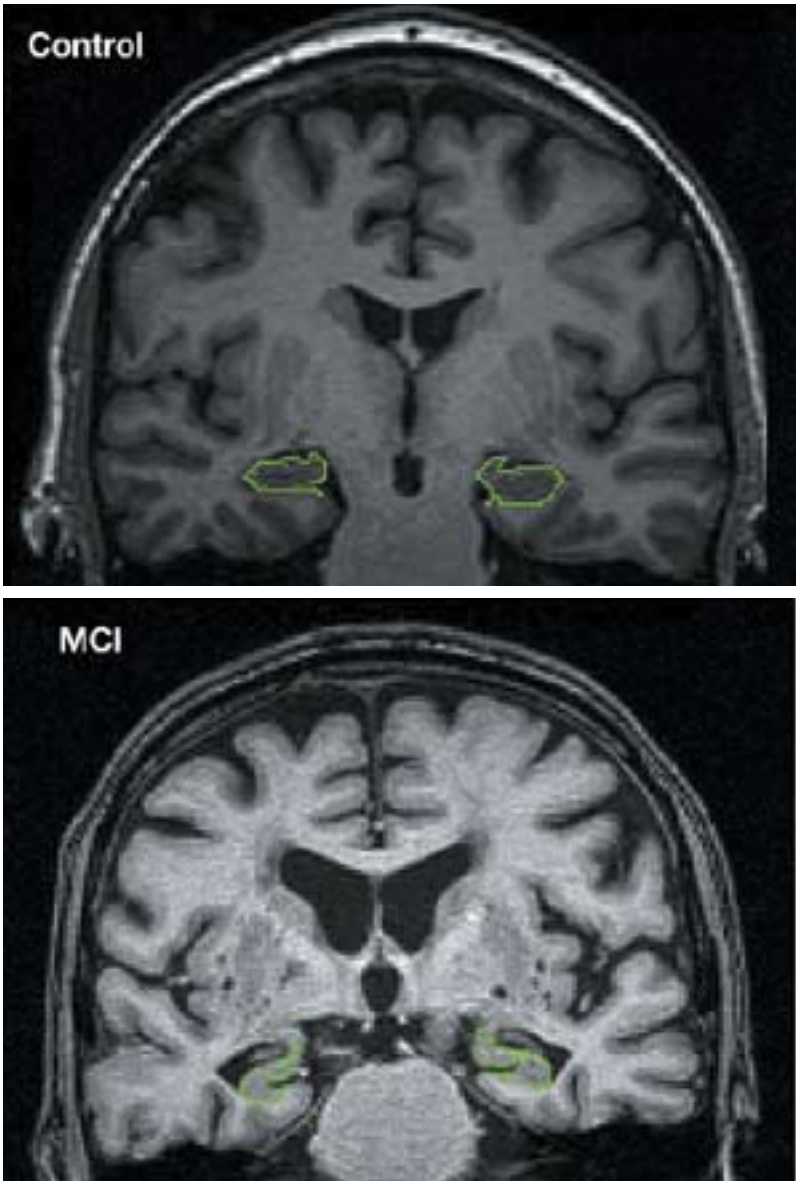
Currently, no single definitive test marks the disease. A combination of mental status exams, blood markers, cerebral spinal fluid (CSF) markers, and brain imaging studies helps to secure the diagnosis.

IMAGING'S ROLE

How Does Imaging Play a Role at the Gross Anatomic Level? What Is the Alzheimer's Disease Neuroimaging Initiative (ADNI)?

- In April 2009 results from the ADNI, published in *Radiology,* reported that semi-automated quantitative MRI can identify a brain atrophy pattern predictive of clinical mental decline. (1) The study examined 84 people with mild Alzheimer's disease (AD), 175 with mild cognitive impairment (MCI), and 139 healthy controls.
- Results showed that atrophy in the mesial and lateral temporal, isthmus cingulate, and orbitofrontal areas helps to distinguish control subjects from AD subjects, with 83% sensitivity and 93% specificity. People with MCI whose MRIs showed the AD atrophy pattern displayed significantly greater one-year clinical decline, brain loss, and progression to probable AD than those whose MRIs did not (29% of those with MCI and AD atrophy, compared to 8% with MCI without AD atrophy).
- The superior temporal gyrus showed significant atrophy in a subgroup of MCI subjects with AD atrophy. The authors hypothesize that this portends a greater risk of mental decline.

- Brain MRIs showed differential rates of temporoparietal region atrophy in prodromal AD, according to a 2008 report in *Neurology.* People who developed AD during the study showed greater atrophy in the hippocampus, entorhinal cortex, temporal pole, middle temporal gyrus, and inferior temporal gyrus compared to individuals with stable MCI. (2)
- Subjects with MCI underwent fractional anisotropy, apparent diffusion coefficient, and cortical thickness measurements, which were then compared to those of the controls. Results revealed decreased fractional anisotropy and increased apparent diffusion coefficient in white matter of the frontal, temporal, and parietal lobes in people with MCI, according to data in the *American Journal of Neuroradiology.* (3)
- Hippocampal atrophy rates add value over whole-brain volume measurements in distinguishing AD, MCI, and controls, according to a study from The Netherlands. The hippocampal atrophy rate proved especially valuable in discriminating MCI from controls. (4)
- In a study of the Mayo Clinic, gray-matter atrophy patterns correlated with neurofibrillary tangles at autopsy pathology. The authors note that this validates MRI three-dimensional atrophy patterns as surrogate indicators of AD pathology. (5)



Comparable T1-weighted coronal MRI slices perpendicular to the long axis of the hippocampus, showing a normal-sized hippocampus (top) in a control person (total hippocampal volume uncorrected for head size 3,480 mm^3 right and 3,164 mm^3 left) and a smaller hippocampus (bottom) in an MCI patient (total hippocampal volume uncorrected for head size 2,050 mm^3 right and 2,580 mm^3 left).

(Images courtesy of L. van der Pol, Alzheimer Center and Image Analysis Center, Vrije Universiteit Medical Center, Amsterdam, The Netherlands.)

- The Alzheimer's Disease Neuroimaging Initiative (ADNI) (1,6,7) began in October 2004 as a five-year collaborative effort between the National Institute on Aging, the National Institute of Bioimaging and Bioengineering, private pharmaceutical companies, the U.S. Food and Drug Administration, and several nonprofit foundations. With a $60-million budget, ADNI seeks to examine the mental status, brain structure, and brain function of 200 people with AD, 400 people with mild cognitive impairment, and 200 elderly controls. Subject recruitment involves more than 50 sites in the United States and Canada.

IMAGING & BIOMARKERS

Why Are Imaging and Biomarkers Important in AD?

Developing sensitive and specific tools to diagnose and quantify AD prior to memory loss is critical to disease prevention and monitoring therapy. Evaluating interventions need to be done in people who have not yet sustained irreparable brain-cell loss. Recent disappointing outcomes in vaccine trials, for example, underscore the need for such subjects. (8)

As noted in a recent editorial (9), markers will identify AD pathology in normal elders or those with mild symptoms; help predict future mental decline; mark progression; and stratify subjects into groups.

Large-scale, international, controlled multicenter trials performing Phase III development of imaging and CSF biomarkers include the U.S., European, Australian, and Japanese Alzheimer's Disease Neuroimaging Initiative (ADNI) and the German Dementia Network. (10)

BLOOD-BASED MARKERS

Are There any Blood-Based Alzheimer's Disease Markers?

No currently accepted blood biomarkers of sporadic AD exist. (11) Since AD can alter peripheral tissue, examination for blood constituent footprints of the disease has involved the following:

- Peripheral blood mononuclear cells are being studied for their molecular signatures of DNA, RNA, and protein (12)
- While plasma studies of Aβ are reported as inconsistent, decreased plasma Aβ42 relative to Aβ40 may increase AD risk. (10)
- Short-wavelength near-infrared spectrophotometry of blood plasma differentiated AD from normal elderly controls with 80% sensitivity and 77% specificity (11)
- Aβ42 was shown to be elevated in plasma of familial AD mutation carriers, and data suggest the levels may decrease with disease progression before overt AD occurs. (13)

CSF MARKERS

What Are the CSF Biomarkers for Alzheimer's Disease?

- As reported recently in *Nature*, "Concentrations of amyloid peptides, particularly one called amyloid-61-42, are low in the cerebrospinal fluid of patients with Alzheimer's disease compared to healthy controls because the plaques are thought to suck them out of circulation, and concentrations of tau protein and phosphorylated tau are high." (14)
- CSF Aβ42, tau, and hyperphosphorylated tau protein (p-tau) can differentiate people with mild cognitive impairment (MCI) from those with AD. They may show changes that predict future AD in currently asymptomatic people. (10)
- In the setting of very mild AD, lower CSF Aβ42, high tau or p-tau181, or high tau/Aβ42 ratios predict a more rapid onset of dementia. (15)
- A recent CSF study from The Netherlands included 177 patients with AD, examining CSF amyloid β 1-42, tau and tau phosphorylated at threonine 181 (p-tau). The authors reported different clusters of CSF biomarker levels and found them to correlate with cognition. Patients with very high CSF tau and p-tau displayed worse memory, mental speed, and executive function. (16)
- In subjects who are familial AD mutation carriers, the ratio of Aβ42 to Aβ40 was reduced in the CSF of nondemented subjects. Elevated t-tau and p-tau181 proved to be sensitive presymptomatic disease indicators. (13)
- CSF marker variability, however, proved high between and also within centers, according to a recent report. (17)

CONCLUSION

Conclusion: **While no single finding affords the diagnosis of Alzheimer's disease, the brain MRI pattern of atrophy in the mesial and lateral temporal, isthmus cingulate, and orbitofrontal areas provides 83% sensitivity and 93% specificity. In Alzheimer's, CSF amyloid is decreased, while tau is increased. Pursuit of suitable blood markers continues. ■**

Next Issue: *Our third and final article on Alzheimer's disease will review findings at PET, experimental molecular imaging, and attempts at AD treatment and prevention.*

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