Neuroimaging for Diagnosis of Dementia

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Although many clinicians consider neuroimaging studies as optional for the differential diagnosis of dementia, clinical experience suggests that they can improve diagnostic accuracy. Data are limited, however, on sensitivity, specificity, and cost-effectiveness of various neuroimaging techniques. The author reviews advantages and disadvantages of neuroimaging techniques for the differential diagnosis of dementia and describes strategies used for early detection of Alzheimer's disease, including combining positron emission tomography scanning with genetic risk assessment. Such approaches could provide a means for in vivo therapeutic monitoring of brain function during experimental antidementia treatment trials. *(J Clin Psychiatry 1998;59[suppl 11]:4–7)*

How often do geriatric psychiatrists request neuroimaging studies when evaluating patients with dementia? The frequency, no doubt, varies according to practice setting, clinician experience, availability, cost, and numerous other variables. A survey of approximately 1000 attendees (mainly psychiatrists) at a dementia symposium presented at the 1996 annual meeting of the American Psychiatric Association[1] indicated that 23% of attendees request a neuroimaging study on 10% or fewer of their dementia patients, while 34% request studies on 75% or more of patients. These survey results suggest wide variability in use of these studies; moreover, a large number of clinicians rarely recommend the techniques and a larger number recommend them quite frequently. This same survey indicated several reasons that clinicians avoid obtaining neuroimaging studies, including cost (37%), lack of usefulness (28%), uncertainty of indications (18%), and lack of availability (10%).

Clearly, considerable variation exists not only in the availability and cost of these techniques[2] but also in knowledge among clinicians regarding their utility, indications, and interpretation. Such lack of knowledge results partly from the rapid growth and technological developments in the field. What might have been the most effective technique last year may be obsolete today.

Other developments in genetics and biology offer promise of elucidating the underlying mechanisms of Alzheimer's disease, the most common progressive dementia of old age. Such understanding should lead to earlier disease detection and the development of new and effective antidementia therapies that correct the pathophysiologic processes. Neuroimaging assessments may play a prominent role in strategies for early detection of Alzheimer's disease. In this paper, we review advantages and disadvantages of available neuroimaging techniques for the differential diagnosis of dementia and describe strategies designed to detect progressive dementias early in their course, which should assist in identifying ideal candidates for novel antidementia treatments.

AVAILABLE NEUROIMAGING TECHNIQUES

Although neuroimaging techniques have considerable potential utility in the differential diagnosis of dementia, extensive data on cost-benefit or cost-effectiveness are not available. Without such data, many clinicians and experts consider neuroimaging studies as optional. For example, the 1987 consensus panel sponsored by the National Institutes of Health[3] recommended computed tomography (CT) without contrast as appropriate if the patient's history suggested a mass, focal neurologic signs, or dementia of brief duration. The panel concluded that magnetic resonance imaging (MRI) is more sensitive than CT in detecting small infarcts, mass lesions, and atrophy of brain stem and other subcortical structures. Remarkably, neuroimaging studies were considered optional for the differential diagnosis of dementia, a conclusion reached by other subsequent expert panels.[4]

The neuroimaging techniques that are currently available can be categorized as either structural or functional.

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In patients with dementia, structural imaging techniques (e.g., CT, MRI) may show atrophy, white matter changes, space-occupying lesions, and vascular disease. The presence of atrophy is usually not helpful in the diagnosis of dementia, unless it is prominent and localized (e.g., frontal atrophy in Pick's disease or temporal atrophy in primary progressive aphasia). In research imaging laboratories, however, quantitative studies of hippocampal atrophy on CT or MRI scans may be specific to Alzheimer's disease and may eventually prove useful for early detection and differential diagnosis.[5,6]

The functional imaging techniques currently available include quantitative electroencephalography (QEEG), single photon emission computed tomography (SPECT), and positron emission tomography (PET). In some patients with dementia, QEEG coherence measures show characteristic patterns. SPECT and PET often demonstrate structural changes (e.g., atrophy, space-occupying lesions) as well as provide information on neuronal function (e.g., cerebral blood flow, glucose uptake into neurons).

Functional neuroimaging often demonstrates a characteristic pattern in Alzheimer's disease of parietal and temporal deficits observed early in the disease course, while frontal abnormalities appear later. Parietal and temporal deficits and hemispheric asymmetry are extremely consistent functional patterns in Alzheimer's disease.[7] Patients with dementia and Parkinson's disease, however, demonstrate a similar functional pattern.[8] In vascular dementia, focal asymmetric cortical and subcortical deficits are observed.

Geriatric depression often has a clinical overlap with dementing illnesses, and functional imaging may be useful in the differential diagnosis. Many SPECT and PET studies show decreased brain function in depressed patients as compared with controls. For example, Lesser and coworkers[9] reported reduced orbital frontal and anterior temporal blood flow using SPECT in depressed patients aged 50 years or older. Some studies show more global deficits in geriatric depression.[10,11]

NEUROIMAGING TECHNIQUES: ADVANTAGES AND DISADVANTAGES

Computed Tomography

CT scanning has the advantages of being inexpensive and widely available. The use of intravenous contrast medium will enhance imaging of such pathology as bleeding, neoplasm, infection, and inflammation, but such agents can cause an allergic reaction. CT also does not cause claustrophobia nor expose the patient to the banging noise from MRI magnets. Many scans require only 10 minutes.[12]

Limitations of CT include its inability to distinguish gray and white matter. CT also fails to identify some forms of cerebral hemorrhage (bleeding greater than 72 hours old or from severe anemia). Other disadvantages are radiation exposure and poor visualization of the posterior fossa.[13]

Magnetic Resonance Imaging

For structural imaging, MRI has high resolution and sensitivity. Unlike CT, MRI will differentiate gray and white matter. It will also image small lacunar strokes and posterior fossa lesions and has superiority over CT in imaging subacute bleeding. Another advantage is the avoidance of radiation exposure.

A disadvantage of MRI is that patients with metallic implants are unable to undergo the procedure because the magnet may move or heat up any metal object.[14] Patients with cardiac pacemakers must also avoid the procedure since the magnet can deprogram pacemakers, causing them to misfire. Many patients will complain that they get claustrophobic or anxious during the examination, which can last up to 40 minutes in some situations.

Quantitative Electroencephalography

QEEG is inexpensive, noninvasive, and sometimes portable. Moreover, it does not expose patients to radiation. QEEG coherence measures may show patterns characteristic of some forms of dementia.[15] Disadvantages for QEEG include the artifact from eye and muscle movement. In addition, the technique provides measures that are relatively distant from the brain, making their precise physiologic meaning unclear. In many areas, expertise is not available for adequate interpretation of results.

Single Photon Emission Computed Tomography

An advantage of SPECT is its ability to confirm a diagnosis of Alzheimer's disease.[16] It also has the potential to differentiate depression and dementia. SPECT is noninvasive and causes little patient discomfort. SPECT has relatively wide availability—a radiochemistry laboratory can produce its radiotracers, making a cyclotron unnecessary.[12]

SPECT has lower spatial resolution than PET and does not identify deep structures well. SPECT uses single photon emitters, which makes determination of the source of photon emission less precise than PET, which measures two photons traveling in opposite directions.[17]

Positron Emission Tomography

PET provides information on neuronal function and can assist clinicians in confirming Alzheimer's disease when the characteristic parietal/temporal deficits are present.[7] PET images can differentiate patients with Alzheimer's disease from patients with other dementias and from cognitively intact people.[18,19] PET also can provide information on glucose metabolism, cerebral blood flow, and receptor characteristics (e.g., density, affinity). Because PET requires a cyclotron, which generates positron emitters, it

is not as widely available as other imaging techniques. It also exposes patients to a small amount of radiation.

STRATEGIES FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative condition resulting in gradual decline of memory and other cognitive functions. Clinical investigators have attempted to find a method for early detection of Alzheimer's disease for several reasons.[20] First, because any antidementia treatment is not likely to reverse existing neuronal damage but rather to slow disease progression, early detection is an important approach to identifying candidates for experimental antidementia drug trials before the dementing process causes permanent brain damage. Moreover, if the early detection measure is negative, then many people with age-related memory complaints will be reassured that their symptoms are benign. Finally, even if the early detection measure shows abnormalities, many people would like such information about their prognosis so that they might plan for their future while mental faculties are still intact.

Functional brain imaging studies such as PET are ideal for early detection strategies because they provide information on neuronal dysfunction (prior to cell death) and demonstrate, early in the disease course, the characteristic pattern of parietal and temporal deficits.[21] Recently, studies have combined this technique with information from new discoveries on genetic risk for Alzheimer's disease. A gene on chromosome 19, apolipoprotein (APOE), has been found to influence the risk of the common late-onset Alzheimer's disease. The APOE-4 allele increases risk and decreases onset age of Alzheimer's disease,[22] and the APOE-2 allele has a protective effect.[23] Alzheimer's disease susceptibility from APOE affects many races and has been confirmed worldwide.[24–26]

APOE genotyping is not recommended for people unless they already have a diagnosis of dementia, because the APOE-4 allele is neither necessary nor sufficient for a diagnosis of Alzheimer's disease.[27] It is not a cause but a risk factor. Knowledge of the presence of an APOE-4 allele in asymptomatic persons could falsely alarm them that they will eventually develop Alzheimer's, and knowledge of the absence of APOE-4 could falsely reassure them.

Because cerebral parietal hypometabolism and left-right asymmetry occur early in the course of Alzheimer's disease and the APOE-4 allele is a risk factor for familial Alzheimer's, Small and coworkers[28] investigated whether APOE-4 allele is associated with lowered brain function in nondemented relatives at risk for familial Alzheimer's. Subjects included 12 relatives with the type 4 allele, 19 relatives without the type 4 allele, and 7 patients with probable Alzheimer's disease. The 31 "at-risk" subjects had mild memory complaints, normal cognitive performance, and at least two relatives with Alzheimer's. Subjects with type 4 allele did not differ from those without type 4 allele in mean age at examination (56.4 vs. 55.5 years) nor in neuropsychological performance (mean Mini-Mental State Examination score = 28.8 vs. 29.3). Parietal metabolism was significantly lower and left-right parietal asymmetry higher in at-risk subjects with APOE-4 allele compared to those without the type 4 allele. Patients with dementia had significantly lower parietal metabolism than did at-risk subjects with the type 4 allele. These results suggest that the inheritance of APOE-4 allele is associated with reduced cerebral parietal metabolism and increased asymmetry in nondemented relatives at risk for Alzheimer's disease. Longitudinal study will determine if glucose metabolic measures provide a means to monitor experimental treatment responses during the early phases of the disorder.

Other studies using brain imaging and APOE genotyping have been conducted or are being developed. For example, Reiman and colleagues[29] also used PET to study people in their mid-50s who were homozygous for APOE-4 and found significant reductions in parietal, temporal, prefrontal, and posterior cingulate regions compared with an age-matched group without the APOE-4 allele. Other approaches include the use of a pharmacologic stress test, wherein subjects are given a short-acting anticholinergic drug (scopolamine) to attempt to temporarily exaggerate parietal metabolic deficits. Another strategy is to employ a cognitive stress test, in which people perform memory tasks during the scan.[30] Finally, use of radiolabeled small molecule probes may eventually enable disease-specific (e.g., amyloid plaques) brain imaging.[31]

Early detection strategies have implications regarding the costs of Alzheimer's disease. For example, a conventional battery of screening laboratory tests might cost $500, but result in an uncertain diagnostic outcome, which in turn could delay cholinesterase inhibitor treatment for 12 months. A patient subjected to conventional screening tests might be placed in a nursing home, which could cost $45,000, yielding a total cost for that patient of $45,500. By contrast, if a PET scan were added to the initial laboratory screening battery then evaluation costs would total $2000 (PET scan at $1500 plus laboratory screening tests at $500). However, the PET scan could demonstrate parietal hypometabolism, which could lead to immediate cholinesterase inhibitor treatment. The additional cost of such treatment would approximate $3600 for the next 12 months. If the treatment were successful, the $45,000 nursing home cost could be avoided, thus reducing total costs substantially. The above estimates are based on selective cost considerations. Comprehensive analyses that consider broader costs and outcomes from formal cost-benefit and cost-effectiveness analyses could provide useful data to assist policy makers in their decision making.[32]

CONCLUSIONS

Definitive data on the sensitivity, specificity, and cost-effectiveness of various neuroimaging techniques for the differential diagnosis of dementia are needed. Until such data are available, clinical experience suggests the utility of imaging studies in improving diagnostic accuracy and facilitating optimal treatment. Parietal and temporal deficits confirmed by functional imaging studies increase the likelihood of a diagnosis of Alzheimer's disease. Combining neuroimaging with genetic data and other strategies (e.g., mental activation during scanning, anticholinergic challenge) may improve the accuracy and utility of early detection of chronic progressive dementias such as Alzheimer's disease.

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