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Imaging the Brain in Dementia: Expensive and Futile?

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It is estimated that by the year 2030, 17% to 20% of the US population, or approximately 50 million people, will be older than 65 years of age (1). Dementia affects between 1% and 6% of people over the age of 65 and 10% to 20% of people over the age of 80 (2). Evans et al (3) reported that the community prevalence of dementia for persons over the age of 85 may be as high as 47%, although most studies have reported lower figures.

Eight times that number of persons also suffer from milder forms of cognitive deterioration (4). Thus, in the next 35 years, 15 to 20 million elderly people will exhibit mild to severe cognitive deterioration. This represents an enormous unfolding human and socioeconomic burden. Imaging such a large number of people, which exceeds the population of many of the world's countries, is a daunting task for radiologists to contemplate.

Background

Cross-sectional imaging in dementing disorders is used to rule out so-called treatable causes of dementia and to identify conditions that may be associated with dementia, such as multiple strokes (multi-infarct dementia). Treatable causes include chronic subdural hematoma, normal pressure hydrocephalus (NPH), and strategically located tumors or metastatic disease. The practice of defensive medicine rather than the hope of a cure or palliation dictates many of these decisions. Initial enthusiasm for breakthroughs, such as the emergence of the concept of NPH, has often led to disappointing outcomes.

Current Status of Imaging in Dementia

Radiologists have at their disposal the use of a growing high-tech armamentarium, including cross-sectional imaging, such as computed tomography (CT) (5–7) and magnetic resonance (MR) imaging (8), functional studies, such as positron emission tomography (PET) (9) and single-photon emission CT (SPECT) (10), and new functional MR techniques, including perfusion echo-planar scanning and MR spectroscopy (11, 12).

Slowly but remarkably, owing to much painstaking effort over many years in many laboratories and to the use of neuropathologic radiologic correlations, radiologic markers for dementing diseases and consequently predictors of subsequent decline are being identified. In the brave new radiologic world that is emerging we can identify those who are at risk for Alzheimer dementia (13). This group would most likely benefit from treatments currently under Food and Drug Administration investigation to arrest the progression of disease, and from the use of recently approved cholinesterase inhibitors, which have proved effective as memory enhancers.

Improved diagnostic techniques, especially the multiplanar capabilities of MR imaging and the ability to quantify cerebrospinal fluid flow, have also improved our proficiency at diagnosing NPH (14, 15) so that shunting procedures can be used with greater likelihood of success. Imaging markers have also been identified for subcortical microvascular encephalopathy (Binswanger encephalopathy), multisystem atrophies and olivopontocerebellar degeneration, Parkinson disease, Creutzfeldt-Jakob disease, and Pick disease.

The future seems promising and bright. What, then, is the downside?

Controversies

One of the most compelling arguments against routine studies in dementia is the low yield of the procedures. In many cases, cross-sectional studies produce equivocal findings that overlap with those in healthy subjects. Although this fulfills the "rule out other pathology" use of the study, it does little to help rule in the pathology in question without additional specialized studies. Ultimately, the cost per patient increases markedly in an era of ever-increasing constraints on the cost of medicine.

The issue, therefore, is reduced to the question, How much is society willing to spend? Based on the above-mentioned estimate of 20 million cognitively impaired present and future patients, the cost of a single MR study for every patient would be between $10 and $20 billion or $350 to $700 million a year over the next 35 years, a not insignificant amount, especially in a time of shrinking health dollars. Third-party carriers, eager to cut costs, may approve only CT for dementia or may reimburse an MR study at CT scan rates (notably Medicare), thereby seriously constraining the radiologic workup. PET scanning and functional MR imaging for the workup of dementia are not reimbursed and may not be for the foreseeable future. As new treatment strategies become available, these fiscal constraints may result in the application of sometimes risky medications or procedures on the basis of limited imaging studies.

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The next argument against routine imaging is based on the belief that the workup of dementia is essentially futile because no effective treatments are available or the beneficial effects of treatment are short lived. Therefore, the trillion-dollar health industry would best spend its resource dollars on conditions for which treatments may benefit the patient.

To counter these concerns, several points can be made. 1) First of all, the ruling out of other disease that may mimic degenerative brain disease remains an important indication for imaging. Of particular interest is the identification of patients with NPH who may be helped by shunting procedures (see below). 2) The cost of these tests must be weighed against the human cost of not helping those who could be helped and of depriving others of treatment in the future. In addition, the actual dollar costs of long-term custodial care for persons who might otherwise be helped and who are deprived of treatment must also be estimated. The cost of such care could be potentially enormous, and more than offset the cost of radiologic imaging. 3) An important indication for imaging today is the diagnosis of conditions that previously were not able to be diagnosed, thereby permitting the institution of treatment and the monitoring of disease progression. Thus, as markers for Alzheimer disease are being identified (13, 5), the potential effectiveness of drug therapy can be monitored. As mentioned above, memory enhancers are already available, and drugs to arrest disease progression are being investigated. 4) An important indication that we may lose sight of is based on the fact that imaging patients with dementia provides ongoing experience that builds on that already available. Thus, it is not only hypothesis testing done in a controlled, funded paradigm that adds to our knowledge of a pathologic condition but the day-to-day clinical scanning that, little by little, contributes to our fund of information. As examples, the advances made in the diagnosis of NPH, various brain conditions associated with cerebral atrophy, and microvascular diseases of the brain would be inconceivable in the absence of clinical scanning.

In vivo studies that clinical scans provide can be thought of as the only resource we have for investigating the pathology of early Alzheimer disease and its progression over time. In this regard, because most Alzheimer disease patients survive until the late stages of the illness, when the disease diffusely involves the brain, early alterations of brain anatomy cannot be defined at postmortem examination. Similarly, the findings in the few postmortem examinations we have of patients with early Alzheimer disease cannot determine the future evolution of changes in that group. Therefore, by definition, the longitudinal changes that occur in Alzheimer disease and in patients at risk for Alzheimer disease can only be defined by means of in vivo imaging.

Thus, clinical scanning is a prerequisite that provides the background and the database from which hypotheses are generated to be tested using the scientific method. To underscore this point, a brief review follows of the evolution of imaging findings in three often interrelated conditions: Alzheimer disease, NPH, and microvascular disease. Without the imaging experience of the last several years, our understanding of these conditions would still be fixed at the level it was in the 1970s.

Alzheimer Disease

The most common dementing disorder of the elderly is Alzheimer disease, which, therefore, is the most common cause of cerebral atrophy in the elderly (6). A majority of early CT studies showed that Alzheimer disease is associated with ventricular enlargement as well as cortical atrophy (7, 16), which exceeds the atrophy seen as part of normal aging. However, correlations were weak and there was significant overlap with healthy subjects so that the clinical utility of a CT scan at any given time for the evaluation of generalized atrophy was and is of limited value. Larger differences were shown when comparing patients and healthy subjects over time. In the era of MR imaging, more specific and sensitive measures of cerebral atrophy have been developed. For example, using image processing to quantify gray and white structures, Rusinek et al (17) reported that cerebral atrophy of Alzheimer disease was due to loss of gray matter, especially of the temporal and parietal lobes.

In the next step, attention was directed to the temporal lobes (18, 5), as the concept of Alzheimer disease as a hippocampal dementia was put forward (19, 20). In 1986, LeMay (18) reported that, using CT, perceptual ratings of temporal lobe atrophy were 89% accurate in distinguishing Alzheimer disease patients from healthy control subjects. George et al (5) found comparable accuracies and also reported specificity of more than 95%. Thus, a new role for imaging emerged: the identification of healthy subjects, which was more accurate than the identification of demented patients. Such a distinction is important for the identification of "pseudodementia," a treatable psychological condition caused by depression. We now know that an elderly patient with no brain atrophy is extremely unlikely to be harboring Alzheimer disease.

Longitudinal studies of Alzheimer disease have shown increasing atrophy of the temporal lobes progressing to generalized cerebral atrophy. As noted above, healthy persons with temporal lobe atrophy are at some risk for decline to dementia (13). MR studies that quantify hippocampal volume (8, 21) have been highly accurate in the identification of Alzheimer disease. Furthermore, in healthy subjects, loss of hippocampal volume as measured on MR images is associated with decreased memory performance and is a risk factor for accelerated cognitive decline (22).

PET metabolic studies using fludeoxyglucose F 18 and SPECT perfusion studies with Tc-HMPAO have shown diffuse metabolic and perfusion deficits in patients with Alzheimer disease, with the most severe changes involving the temporal and parietal lobes. Smith et al (23) found large progressive deficits in glucose metabolism of the temporal lobes when studying patients with Alzheimer disease over time. New studies applying MR spectroscopy have shown abnormalities in phosphorus-31 spectra (11) as well as metabolite changes in proton spectra with dec-

rements in *N*-acetylaspartate/creatine ratios and increases in *myo*-inositol in patients with Alzheimer disease (12).

The above brief review exemplifies how, through relentless efforts on the part of the research community, the secrets of Alzheimer disease have slowly begun to unravel. Another qualified success story is that of NPH. Described by Hakim and Adams in 1965 (24), this idiopathic form of communicating hydrocephalus is characterized by ventricular enlargement (which may be severe to very severe), relatively small sulci, and gait and motor deficits, which may be marked. The motor deficits tend to improve, often dramatically, after shunting. Cognitive deficits are typically mild and may improve to a mild degree after shunting. Severe dementia will not improve to a useful degree after shunting, and may portend underlying Alzheimer disease (15).

The initial report of NPH was met with enthusiasm; however, early successes were followed by unsuccessful shunting procedures, leading eventually to disenchantment with the concept of NPH and its treatment. Cross-sectional imaging, however, and trials of cerebrospinal fluid drainage have shown greater reliability in helping to identify shunt candidates, so that most NPH patients who undergo shunting procedures can be expected to improve. In challenging cases, cerebrospinal fluid flow quantification (14) and PET or SPECT studies may provide important additional data on which to base clinical management. Today, NPH patients who are likely to respond to shunting, although still a small group, are routinely identified and are typically helped by the procedure.

Microvascular Disease

A qualified success story can also be told about the ubiquitous microvascular disease of white matter (25–28). The "unidentified bright objects" of old have now been identified as patches of demyelination caused by hypertension-type microvascular disease. These patients exhibit motor deficits but minimal or no cognitive deficits. However, the motor deficits include decreased reaction time, as shown on simulated driving tests (28), and an increased rate of falls (29). Both these observations, which have obvious and serious medical implications, have come through clinical scanning as well as organized research.

Subcortical infarcts are now identified with greater accuracy, and acute infarcts can be distinguished from chronic microvascular disease and chronic infarcts with the use of diffusion MR imaging (30). Because of the relatively modest deficits associated with microvascular disease, the term *Binswanger disease* should be reserved for severe cases, in which there is motor impairment and associated infarcts (27), or should best be avoided (31). We have learned about the clinical significance and the correlates of microvascular disease through research as well as through day-to-day clinical scanning.

Summary

The verdict is obvious. There is really no choice but to image a patient with dementia to rule in the most likely diagnosis, to rule out unsuspected disease, and to continue to advance our understanding of the disease processes and their longitudinal progression. Although the cost is substantial, the potential benefits justify the expenditure. As new treatments and treatment strategies become available, the cost to the patient and to society of not scanning dementia will far surpass the cost of scanning. Those researchers and clinicians who doggedly pressed on during years of painstakingly slow progress are finally being vindicated.

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