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Dementia

Five New Things

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While much neuroscientific research remains focused on finding better treatments for Alzheimer disease (AD), important work is contributing to progress in understanding related aspects of AD, and other dementias as well. This review considers 5 areas in which recent developments have informed clinical practice in the dementias. The topics were selected because they frequently arise in discussions with colleagues and patients, and concern practical issues in dementia diagnosis and prevention that require attention while the search for more effective treatments continues.

CSF DIAGNOSIS OF AD A major goal of current research in AD is the discovery of biomarkers that can identify patients at an early stage and facilitate treatment at a time when it can be most effective. One of the categories of biomarkers involves neuroimaging, and medial temporal atrophy on magnetic resonance imaging (MRI), reduced glucose metabolism in temporoparietal cortices on positron emission tomography (PET) scans, and imaging of brain amyloid using PET with an agent such as Pittsburgh compound B have attracted attention. The other important biomarker category is biochemical testing, the most highly touted of which is a profile in the

cerebrospinal fluid (CSF) of low β -amyloid protein 1–42 ($A\beta$ 1–42), high total tau protein (T-tau), and elevated phosphorylated tau protein 181 (P-tau).

In a much-discussed recent report examining CSF diagnosis of AD and other conditions, DeMeyer and colleagues¹ found that this profile was present in 90% of patients with probable AD, 72% of those with mild cognitive impairment (MCI), and 36% of normal subjects. Additional analyses showed that 64 of 68 autopsy-confirmed AD cases had the profile (94% sensitivity), and that in a cohort of 57 MCI cases followed for up to 5 years, the profile had 100% sensitivity in predicting progression to AD.¹

In light of this and other studies, support for using the CSF AD test in clinical practice has been mounting. In an editorial accompanying the article by DeMeyer et al., Herskovits and Growdon² “. . . strongly recommend CSF analyses of $A\beta$ 1–42, T-tau, and P-tau in circumstances where having a definitive diagnosis of AD is important for counseling patients. . . .” Neurologists are thus faced with how to accommodate these new findings. It is clear that CSF amyloid and tau measurements do not stand alone as a diagnostic test for AD, since low CSF amyloid and high tau can both be found in other conditions.² The question is whether to use the CSF profile as an adjunct to the widely accepted practice of conducting a thorough history and examination, and obtaining brain imaging, laboratory tests for reversible dementia, and neuropsychological testing.

The CSF profile represents important research in understanding the early phases of AD and may lead to the identification of highly accurate biomarkers, but its utility in diagnosis is uncertain. Enthusiasm for the test should be tempered by observations that reported sensitivities range between 75% and 100% and specificities between 65% and 90%,² and that threshold diagnostic levels of the 3 CSF markers in AD have varied across studies.³ The necessary lumbar

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Neurology® Clinical Practice 2011;76 (Suppl 2):S26–S30

“The CSF profile represents important research in understanding the early phases of AD and may lead to the identification of highly accurate biomarkers, but its utility in diagnosis is uncertain”

puncture, while arguably justifiable,² involves certain well-known risks and discomfort, as well as the cost of the procedure and the biochemical testing itself. Even if the procedure goes well in most cases, the occasional difficult spinal tap requiring fluoroscopic guidance will give neurologists pause. Moreover, research on peripheral biomarkers may soon reveal that a simple blood test is adequate for AD diagnosis.⁴ Most importantly, the unavailability of effective treatment to modify the biology of the disease calls into question why a promising but not foolproof CSF test should be used in an attempt to gain more confidence about the diagnosis.

Counseling patients is indeed a vital function of the neurologist, in the dementias or any other clinical setting. This service can be offered to people with memory concerns, however, using proper application of available diagnostic methods. Even if a person with memory complaints but normal cognition has a CSF profile consistent with AD, neurologists would not make a clinical diagnosis unless and until cognitive impairment becomes evident. The CSF profile may find a place in the everyday diagnosis of AD, but at present its role remains unclear.

FRONTOTEMPORAL DEMENTIA RARELY CONSIDERED BY RADIOLOGISTS In another disease that can be diagnostically challenging, frontotemporal lobar dementia (FTLD), an instructive retrospective clinical study found that radiologists seldom consider the patterns of frontal and temporal lobe atrophy on MRI scans that suggest the various subtypes of this disease. Suárez and colleagues⁵ reviewed radiologists' MRI reports in 40 patients with clinically diagnosed behavioral variant frontotemporal dementia (bvFTD), and noted that FTD or Pick disease was considered in only 4 patients (10%). When neuroradiologists were shown the same scans, recognition of the focal atrophy was far better, as the bvFTD pattern was identified with nearly 100% specificity and approximately 60% sensitivity.

These data highlight a common occurrence in dementia, memory, and neurobehavior clinics: the radiologic reporting of nonspecific cerebral atrophy on

neuroimaging when there is clearly a suspicious pattern of focal volume loss that assists in diagnosis. This observation is not surprising given that many neuroimaging scans are read by general radiologists who may lack neuroradiologic expertise, and neuroradiologists are indeed more able to recognize focal atrophy and its potential significance. In any case, however, one practical implication of this study is for the neurologist to be sure to review the scan personally. As Suárez and colleagues⁵ point out, diagnostic accuracy improves when the clinical history is known, and a diagnostic conundrum may be readily resolved by the availability of this information. If possible, a discussion with the general radiologist about the clinical history may also clarify the situation and help avoid this problem.

Structural brain imaging remains a cornerstone of dementia diagnosis, particularly as technological improvements in MRI enhance our ability to see the brain and its component structures in ever greater detail. Not only do these scans identify mass lesions, stroke, white matter disease, hydrocephalus, and many other lesions, the patterns of atrophy—frontotemporal, hippocampal, or in other regions—can add relevant data to the clinical assessment. A scan of the brain is typically obtained to exclude reversible structural lesions in the evaluation of dementia, but the astute neurologist can glean still more information by careful study of regional atrophy patterns that may be the key to accurate diagnosis.

MIDLIFE OBESITY AND DEMENTIA A common observation in recent years has been the association of midlife obesity with a risk of dementia in later life.^{6,7} Such an association is not surprising if one considers vascular dementia, but the risk of AD has also been reported to be higher in people with midlife obesity.⁷ Consistent with both of these associations are data showing that both white matter hyperintensities (WMH) and decreased hippocampal volume have been associated with central obesity.⁸

In this context, a recent report by DeBette and colleagues⁹ adds new information. In a large cohort of healthy middle-aged adults from the Framingham Offspring Study, these authors found that visceral fat was associated with lower brain volume, but notably, there was no association between central obesity and volume of WMH, temporal horn volume (reflecting hippocampal volume), and the number of brain infarcts. Although the subjects in this study did not have dementia, the results suggest that increased body mass and visceral fat may lead to cognitive decline and dementia through accelerated atrophy of the entire brain. The authors speculate that the effects of inflammation, diabetes, and

insulin resistance, or adipose tissue-derived hormones, may be at work.⁹

Another investigation has disclosed associations between obesity and damage in more specific brain regions. Studies with magnetic resonance spectroscopy (MRS) have found higher midlife body mass index to be associated with lower *N*-acetylaspartate (NAA) and choline (Ch) concentrations in the frontal white matter, suggesting axonal and myelin injury.¹⁰ The frontal lobes are known to be highly susceptible to aging effects, and these MRS abnormalities may reflect accelerated aging specifically within white matter tracts.¹⁰ Central obesity in midlife may thus predispose to AD by hastening brain aging in vulnerable areas before dementia begins.¹⁰

Identification of brain abnormalities in association with midlife obesity^{9,10} does not, of course, tell us that obesity in middle age causes dementia or AD, that normal body weight can prevent these problems, or that obesity leads to brain neuropathology. Such studies simply point out associations that invite further investigation. Still, the somewhat unexpected links between midlife obesity and changes in the brain suggest a number of research ideas that may illuminate brain pathophysiology and help guide lifestyle choices in our patients. It seems prudent, for example, to counsel middle-aged patients without dementia that achieving normal body weight may help maintain normal cognition as well as confer other well-established benefits.

PROGRESS IN UNDERSTANDING WHITE MATTER DEMENTIA The dementias are most often considered to derive from cortical dysfunction, and in some cases subcortical gray matter damage can be implicated, but less well-appreciated is the potential of white matter disorders to produce dementia. The concept of white matter dementia has been proposed to signify a specific dementia syndrome that can be ascribed to the burden of cerebral white matter involvement from a wide range of neuropathologic states.¹¹ Whereas neurologists know that diseases such as multiple sclerosis (MS) and leukodystrophies can cause dementia,¹¹ a more common—and less clear—scenario arises when the evaluation of older people with cognitive decline discloses WMH on MRI. A common interpretation is that these changes are related to small vessel narrowing and white mat-

ter ischemia, but their relevance to cognition remains incompletely understood.

A recent systematic review and meta-analysis of 46 longitudinal studies concluded that MRI WMH predict an increased risk of dementia,¹² and consistent with evidence from study of other white matter disorders,¹¹ executive function and processing speed were the domains most implicated as cognition declined.¹² As could be expected, WMH were associated with incident vascular dementia, and prior work has shown that in patients with MCI, vascular subcortical hyperintensities predict conversion to vascular dementia with prominent executive dysfunction.¹³ Importantly, however, WMH were also associated with the risk of AD, reflecting either an interaction of vascular and AD pathology, or the presence of white matter changes (from amyloid angiopathy or wallerian degeneration) related to AD cortical pathology.¹² These data thus support the idea of white matter dementia as a sequel of vascular white matter changes on MRI, but also raise the possibility that WMH somehow predispose to AD. While the potential interactions of WMH and AD raise intriguing research possibilities, examining the specific cognitive effects of white matter dysfunction on cognition in the absence of WMH allows more focused analysis of the role of white matter in cognition.

One clinical model that allows study of white matter and cognitive loss before MRI lesions appear is systemic lupus erythematosus (SLE). Whereas cognitive impairment is frequent at any stage of SLE and in part relates to WMH,¹¹ more subtle white matter changes can be studied early in the disease before WMH develop. In patients with SLE without overt neuropsychiatric (NP) dysfunction, what has been called non-NPSLE, white matter that appears normal may harbor subtle microstructural changes that are demonstrable with MRS.¹⁴ In preliminary studies of patients without NPSLE, higher Ch in frontal lobe white matter, implying inflammation and demyelination, was associated with executive and attentional dysfunction, while no association of cognitive dysfunction with total brain or gray matter volume was found.¹⁴ Thus, while these patients do not have dementia, their early cognitive deficits may be predictive of the more severe cognitive dysfunction that will in some cases result in white matter dementia. As in AD, finding the earliest manifestations of cognitive impairment is important in SLE and other disorders where white matter may be primarily affected.

The frequent presence of white matter lesions on MRI in older people will continue to challenge neurologists, but advances in understanding the neurobehavioral significance of white matter shed light on this issue. In clinical practice, it remains important to

Dementia: Five New Things

- CSF diagnosis of Alzheimer disease is still unclear.
- Frontotemporal dementia: Read the scan yourself.
- Midlife obesity is associated with dementia.
- White matter MRI hyperintensities predispose to vascular dementia and AD.
- No firm association of a modifiable risk factor with either cognitive decline or AD has been established.

determine the etiology of white matter lesions— ischemic, demyelinative, inflammatory, and so on—and to appreciate that even white matter that appears normal on conventional MRI may be damaged at the microstructural level and contribute to cognitive loss.

GIVING ADVICE FOR DEMENTIA PREVENTION

One of the questions most frequently asked of neurologists who care for patients with dementia is about how to prevent the problem from developing. As the number of reversible dementias is small and prospects for effective treatment of AD remain limited, physicians and patients alike naturally ask what can be done to prevent cognitive decline leading to dementia, whether AD or another variety. The model of prevention, after all, has been effective in other areas of medicine, such as with management of hypertension and smoking cessation to reduce the risk of cardiovascular disease. Much investigation has in fact been conducted on a variety of behavioral, lifestyle, and pharmaceutical interventions that are hoped to maintain cognitive function in later life.

An expert panel convened by the National Institutes of Health met in April 2010 to consider these questions, and concluded that no firm association of a modifiable risk factor with either cognitive decline or AD could be established.¹⁵ This report was based on an extensive literature review including a formal evidence report from the Clinical Practice Institute of Duke University commissioned by the Agency for Healthcare Research and Quality.¹⁶ Evidence did not support the use of any pharmaceutical agents or dietary supplements to prevent cognitive decline or AD. Areas that were considered to offer potential leads were cognitive training, physical exercise, and nutritional patterns such as a Mediterranean diet or diets high in vegetables or ω -3 fatty acids.^{15,16}

What, then, is the neurologist to do? Is there anything to offer people who seek a possible way to ward off the scourge of late-life dementia? As tempting as it is to revert to nihilism regarding irreversible dementia, there is ample reason to maintain hope that preventive measures may turn out to be salutary. While data are not yet adequate to permit robust recommendations, no responsible physician would disparage the potential benefits of ordinary health maintenance practices such as regular exercise, cognitive engagement, achieving normal body weight, and a diet with generous portions of vegetables and fish. There are other health benefits—and likely psychological advantages—from such advice, and indeed, one or more of these measures may in fact be found effective for dementia prevention. Neurologists can join other physicians in recommending a healthy lifestyle

that will likely benefit general well-being, and perhaps in some manner act to prevent or forestall dementia. At the same time, we can assure patients that while the research on this question is proceeding, living the best possible life without the burden of undue anxiety about dementia or AD is a goal to be earnestly sought.

DISCLOSURE

Dr. Filley has received funding for travel and speaker honoraria from the American Academy of Neurology, the International Neuropsychological Society, the American Neuropsychiatric Association, and Weill Medical College-Cornell University; receives publishing royalties for *Neurobehavioral Anatomy* (University Press of Colorado, 2nd ed., 2001) and *The Behavioral Neurology of White Matter* (Oxford University Press, 2001); has received/receives research support from the University of Colorado Alzheimer's Disease and Cognition Center, the Alzheimer's Association, and the NIH/NIAMS; and has given expert legal testimony. Dr. Anderson receives research support from AGA Medical Corporation, the NIH, and the Alzheimer's Association; served on the editorial board of *Applied Neurology*; and has served as a consultant in medico-legal cases. His spouse has received speaker honoraria from Creighton University and publishing honoraria from McGraw-Hill for a book chapter; serves on the speakers' bureaus of Merck Serono, Sanofi Pasteur, and Novartis; and has received research support from Novartis and the NIH.

Received October 4, 2010. Accepted in final form December 16, 2010.

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Neurology 2011;76;S26-S30

DOI 10.1212/WNL.0b013e31820c35e1

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