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Past Glory and Future Promise: Maximizing and Improving Understanding of Atrophy Patterns in the Diagnosis of Degenerative Dementias

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In this issue of the *AJNR*, Hanyu and colleagues (page ?) present an elegant quantitative study that compares the thickness of the substantia innominata in patients with Alzheimer's disease (AD) to that in elderly non-AD subjects with dementia and elderly non-AD subjects without dementia. This work follows the seminal investigation of Whitehouse et al (1) that reported findings of diminished concentration of cholinergic neurons in the nucleus basalis of Meynert within the region of the ventral globus pallidus (the substantia innominata) in AD patients. These subcortical cholinergic neurons supply the cortex with most of its acetylcholine. It is remarkable and surprising that more than 20 years have passed between the time that novel work linked this area to AD and the completion of a quantitative imaging study in which the size of this region in the presence of AD has been determined. Hanyu and colleagues report a statistically significant loss of tissue in AD patients compared with that in age-matched control subjects without dementia but note no difference in this region between AD patients and control subjects with dementia. Additionally, the authors show that the performance on a cognitive task, the Mini-Mental-State Examination, strongly correlates with the severity of atrophy in the substantia innominata in AD patients but not in the cohort of non-AD subjects with dementia. Therefore, this fine study adds to our evolving knowledge regarding the structural brain changes that occur in AD but fails as a novel diagnostic test for AD or for other dementias.

Understanding of dementia has matured markedly since the early 1980s when the first quantitative imaging studies of AD were performed (2). In particular, understanding of the molecular underpinnings of AD and the other major non-AD dementias including frontotemporal dementia, dementia with Lewy bodies, Jakob-Creutzfeldt disease, progressive supranuclear palsy, and corticobasal degeneration continues to advance at a rapid rate. Importantly, unraveling molecular mechanisms associated with dementia is leading to potential new treatments that offer far more promise, yet far more potential toxicity, than that of current treatments for AD (vitamin E and anticholinesterase compounds). Immunization against amyloid (Aβ42) as a therapy for AD (3) and the planned treatment trial with the antimalarial compound quinacrine for Jakob-Creutzfeldt disease (4) represent two such examples of high-risk but potentially high-impact therapies. These studies and others yet to follow will place even greater pressure on internists, neurologists, psychiatrists, and radiologists to make better diagnoses in their patient populations so that individuals are not wrongly subjected to potentially toxic therapies, but the individuals who will truly benefit are.

In the clinic, neuroimaging still remains a cornerstone for diagnosis. AD and the other degenerative dementias progress in an orderly and predictable manner, all showing somewhat distinctive regional patterns of neuronal dysfunction and degeneration (5). The diagnostic utility of this regional vulnerability has been extensively studied with structural, spectroscopic, and functional neuroimaging. Another fruitful approach has been to correlate patterns of atrophy with cognitive or behavioral performance in order to infer the function of these brain regions or to stage the illness (6). Hanyu et al's investigation exemplifies such strategies by exploring the value of substantia innominata atrophy as a diagnostic marker and a staging measure for AD. The use of substantia innominata atrophy as a treatment marker is one potential application of this investigation and not yet explored by the authors.

With the appearance of CT in the late 1970s, various investigators started to compare AD patients with cognitively normal control subjects with simple measures of brain atrophy (2). In more recent years, this approach was pursued vigorously in AD by focusing on measures of medial temporal atrophy, particularly atrophy in the hippocampus. Qualitative and quantitative neuroimaging techniques show that this region is significantly smaller in AD patients compared with that in control subjects. Similarly, patients with mild cognitive impairment, often a precursor to AD, show greater atrophy in the hippocampal complex than do control subjects (7). Proton spectroscopy depicts loss of the neuronal marker *N*-acetylaspartate

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in the hippocampal complex in AD compared with that in cognitively normal control subjects (8). Functional imaging, particularly single-photon emission CT (SPECT) and positron emission tomography (PET), has been applied to the diagnosis of AD and to the differential diagnosis of dementia. With SPECT and PET, the cortex is where the most dramatic differences have been found between AD patients and healthy control subjects (9, 10). Recent work suggests that abnormal activation patterns on functional MR images may help to separate AD patients from healthy control subjects (11). Not surprisingly, all of these techniques have their advocates, but clinical overlap between these methodologies is significant and abnormalities in structure, neurochemistry, and metabolism tend to develop in parallel. Indeed, even after decades of study it is still difficult to say which of these techniques is the most powerful diagnostic tool.

Additionally, structural, spectroscopic, and functional imaging have been used to differentiate patients with other degenerative disorders, particularly frontotemporal dementia from AD and normal aging (12). Anterior frontal atrophy or temporal atrophy or both, neuronal loss, and hypometabolism remain the key features of frontotemporal dementia (13). With corticobasal ganglionic degeneration, these changes are localized to the posterior parietal regions or frontal regions or both, whereas with PSP the midbrain and frontal lobes represent the major sites of atrophy (14). For all of the neurodegenerative conditions, predicting neuropathology on the basis of atrophy, neurochemistry, or function alone is still fraught with error because of overlap between all of these disorders.

Despite these caveats, as a clinician who has benefited from both MR imaging and SPECT to help with the differential diagnosis of dementia I suspect that the visual estimation of patterns of atrophy or hypometabolism are greatly underestimated as diagnostic tools in most clinical settings. In our own clinics at the University of California at San Francisco, we routinely consider the atrophy patterns found on MR images to help differentiate patients with AD, frontotemporal dementia, dementia with Lewy bodies, corticobasal ganglionic degeneration, and progressive supranuclear palsy. Similarly, in my clinics at University of California at Los Angeles, the cortical pattern of perfusion seen with SPECT served as an important guide for diagnosis. Neuroradiologists need to learn these patterns in order to be maximally supportive to their clinical colleagues.

For dementia diagnosis, the specificity and sensitivity of neuroimaging methods need to be improved. In the next decade, it will be important for these techniques to move beyond atrophy and imaging approaches that can capture differences between the dementias that truly reflect pathologic abnormalities of the brain. For example, in a patient with dementia caused by vascular disease, MR imaging evidence of lesions from multiple strokes is highly supportive of the diagnosis of multi-infarct dementia (15). MR imaging evidence of stroke is highly predictive of neuropathologic sequelae, although in such patients it is not possible to know whether AD is also present (16). A technique that allowed imaging of the neuropathologic substrate of AD, brain amyloid, would allow in vivo diagnosis (17). Similarly, the basal ganglia and cortical necroses that are evident on diffusion-weighted images are highly characteristic of Jakob-Creutzfeldt disease and are not seen in other degenerative dementias (18, 19).

In summary, a clearer picture of the neuroimaging correlates of dementia has emerged over the past two decades. Patterns of atrophy remain at the center of our diagnostic armamentarium and allow the differentiation of most patients with degenerative or vascular dementias. As better therapies emerge for all of these disorders, earlier and more precise diagnoses will be required. Neuroimaging should continue to meet these diagnostic challenges.

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