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Neuroimaging in the Clinical Diagnosis of Dementia: Observations from a Memory Disorders Clinic

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Abstract

OBJECTIVES—To determine how often neuroimaging confirms, clarifies, or contradicts initial diagnoses of late life cognitive disorders.

DESIGN—Retrospective case review.

SETTING—An outpatient clinic specializing in memory disorders.

PARTICIPANTS—193 consecutively referred, cognitively impaired patients.

MEASUREMENTS—Diagnoses using research criteria were developed for each patient at the first visit, and ranged from cognitive impairment without dementia to dementias of single, complex, or indeterminate etiology. Structural (non-contrast MRI) and perfusion (Tc-99m ECD SPECT) images were categorized together as normal, suggestive of specific diseases, or abnormal/not diagnostic.

RESULTS—When a single neurodegenerative disease was suspected clinically (n=94) imaging confirmed the diagnosis in 50, contradicted the diagnosis in 32, and was abnormal/not diagnostic in 12. When more than one neurodegenerative etiology was clinically suspected (n=21) imaging assigned a single diagnosis in 13 and only cerebrovascular disease in 1, and was abnormal/not diagnostic in 7. In dementia NOS (n=33), imaging suggested a specific etiology in 23 and was abnormal/not diagnostic in 10. Abnormal/not diagnostic images were more common in cognitive disorder NOS (n=25) than in other clinical groups (68% vs. 22%, $\chi^2 = 22.8$ $p < 0.001$).

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Initial clinical assessment was performed by SMD and SB, radiologic assessment by VM, SP and DHL, retrospective chart review by PRB, SMD, and SB, and all authors contributed to manuscript preparation and review. Initial clinical assessment was performed by SMD and SB, radiologic assessment by VM, SP and DHL, retrospective chart review by PRB, SMD, and SB, and all authors contributed to manuscript preparation and review.

Design conceptualization by PRB, SMD, SB, and DL; clinical chart review by PRB, SMD and SB; neuroimaging review by PRB, SMD, VM, SP and DHL; and all authors contributed to and reviewed the final the manuscript.

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Neuroimaging indicators of cerebrovascular disease were common (60% prevalence) but not predicted by the presence of vascular risk factors alone.

CONCLUSION—Overall, neuroimaging confirmed, clarified, or contradicted the initial clinical diagnosis in >80% of patients while < 20% had abnormal/not diagnostic patterns. Imaging suggested a complex dementia etiology in 21% of cases clinically thought to be caused by a single process, while 46% of complex clinical differential diagnoses appeared to reflect a single causal pattern. Further work is needed to determine whether refinement of clinical diagnoses by specialized neuroimaging improves clinical decision-making and patient outcomes.

Keywords

dementia; differential diagnosis; SPECT; MRI; cognitive disorders; neuroimaging

INTRODUCTION

Population aging brings a growing need for clinical assessment and management of older persons with cognitive impairment and dementia[1]. Although it is generally agreed that the initial evaluation of patients with cognitive changes should include a detailed clinical history, physical exam, selected laboratory studies, and some neuroimaging, which components are essential and who should perform them continues to be debated. [2, 3] Both primary care providers and specialists (neurologists, geriatric psychiatrists, and geriatricians) have the skills to elicit a detailed history and conduct a physical exam that may suggest specific dementia diagnosis. [4] However, a complete dementia evaluation is time-consuming and difficult to complete in many primary care settings. [5, 6] Specialized neuroimaging approaches have developed in response to the diagnostic challenge of dementias. For example, functional imaging with SPECT [7] or PET [8] can differentiate AD from frontotemporal dementia (FTD), [9-11] but there is strong interest in exploring the value of these modalities in evaluation of dementias more generally. [12] In this study we sought to determine if a combination of MRI and SPECT imaging could add to a comprehensive, office-based diagnostic assessment via confirming, clarifying or contradicting the initial clinical diagnosis.

Functional imaging studies using metabolic (F-18 fluorodeoxyglucose (FDG)-PET) and perfusion (Technetium-99m (99mTc) ECD or other SPECT) tracers have demonstrated patterns of change that can be considered characteristic of specific dementing diseases. For instance, reductions in metabolism and perfusion of the posterior cingulate and temporoparietal association cortex are typical of Alzheimer's disease (AD) and may allow early identification of AD in a subgroup of patients with mild cognitive impairment. [7, 8, 13] Although the spatial and contrast resolution of FDG-PET is typically better than most applications of SPECT, [14] use of SPECT will continue to be relevant because of its wider availability and lower cost relative to PET. [15] Normalized registration and visualization techniques such as 3-dimensional stereotactic surface projection (3D-SSP, freely available for download), can transform novice raters into experts [16] and is more sensitive and specific for diagnosing AD than standard visualization, [17] for which inter-rater reliability is moderate at best. [18] There are few prospective studies that assess the ability of neuroimaging to distinguish different etiologies during the initial evaluation of persons presenting with cognitive difficulties (but see [17]); most have retrospectively examined highly selected patients or diagnostic groups in restrictive research environments and may not apply to less selected clinical populations. Partly for this reason, many health care plans consider functional imaging ‘experimental’ and deny coverage as part of a standard dementia workup.

We sought to determine whether an imaging protocol, developed in collaboration with neuroradiologists and nuclear medicine specialists, contributed to clinical understanding of heterogeneous, unselected patients presenting to a memory disorders clinic. To answer this question, we compared radiologic interpretation of our combined MRI and SPECT protocols with criterion-based clinical diagnoses made during the initial office assessment.

METHODS

Subjects, setting, and study design

One hundred ninety three consecutive patients seen over a 2 year period in the Memory Disorders Clinic at the University of Washington Medical Center (UWMC) were studied using the combined imaging protocol. The UWMC Memory Disorders Clinic is a specialty clinic serving a five state region, accepting referrals from primary care providers, neurologists, psychiatrists, and other clinicians for evaluation and management of persons with a suspected cognitive disorder. The initial clinical assessment and diagnostic classification are guided by the National Alzheimer's Coordinating Center (NACC) uniform data set (UDS) protocol. This includes clinical interviews with the patient and a knowledgeable informant, review of medical and neurological status, an abbreviated cognitive assessment, usually including at least a Mini Mental State Exam (MMSE) [19] and a Mini-Cog [20, 21], a simplified 12-item mood and behavioral inventory adapted from the Neuropsychiatric Inventory [22], a functional activities assessment [23], pertinent laboratory evaluations, and additional tests based on clinical indicators (e.g., sleep studies, pulmonary or cardiac function tests). The data on which this report is based include the initial clinical assessments and the subsequent neuroimaging reports, categorized as described below. The protocol, approved by the UWMC IRB, allowed review of all cases without individual informed consent by patients or proxies.

Clinical categorization

Clinical diagnoses were confirmed to fulfill criteria NACC UDS coding guidebook and DSM-IV TR criteria by two fellowship trained and board certified psychiatrists (PRB and SMD). Inter-rater reliability for categorization was >90% (n=20 cases) and if a single rater was unsure of a diagnosis or raters disagreed, discrepancies were resolved by consensus conference with both raters and the clinic director, a senior clinician fellowship trained and board certified in geriatric psychiatry and with extensive experience in dementia evaluation and management (SB). For analytic purposes diagnoses were classified into 8 categories: 1) mild cognitive impairment (MCI), 2) cognitive disorder not otherwise specified (cognitive disorder NOS), 3) probable Alzheimer's disease (AD), 4) probable vascular dementia (VaD), 5) all other single etiology dementias (other) including frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and dementia related to medical disease, 6) mixed cerebrovascular/neurodegenerative pattern, 7) multiple, specific neurodegenerative etiologies which included combinations of AD, FTD, DLB and medical causes (see results) and 8) dementia NOS, when dementia criteria were fulfilled but the clinical presentation was atypical and the contribution of medical illness unclear. Of note, “VaD” is used herein as a clinical diagnosis in contrast to “CVD” which denotes cerebrovascular pathology observed on MRI/SPECT imaging.

Neuroimaging and neuroradiologic classification

Most (>80%) of subjects underwent non-contrast MRI using a dementia-specific protocol. If recent, high quality, reviewable MRIs were available (<20% of subjects) the MRI was not repeated at our institution. The MRI dementia protocol included sagittal and axial T1 images; axial T2, FLAIR, and diffusion weighted images; and coronal 3D FSPGR images. MRIs were evaluated for micro- and macrovascular disease (3-point Fazekas scale: mild,

moderate or severe[24]) and morphological abnormalities (e.g. lobar atrophy and ventricular enlargement). Herein, CVD includes multiple etiologies including microvascular ischemic disease, lacunes and lesions consistent with cerebral amyloid angiopathy. [25] All patients underwent SPECT using Tc-99m ethyl cysteine dimer (ECD) or hexamethylpropyleneamine oxime (HMPAO) in accordance with the Society for Nuclear Medicine guidelines. [26] Statistical parametric mapping was performed using 3D-SSP (Neurostat, University of Washington, Seattle WA USA, http://128.95.65.28/~Download/). [27] Image interpreters had access to the standard SPECT reconstructions and 3D-SSP as well as MRI reports/images such that atrophy and/or cerebrovascular disease could be qualitatively accounted for while interpreting the SPECT images thus necessitating lumping the utility MRI and SPECT reads together rather than considering these two imaging modalities individually. Images were reviewed by two (or more) nuclear medicine physicians including one certified in nuclear medicine by the American Board of Nuclear Medicine (DHL). Detailed reports were later reviewed (by PRB and SMD) and categorized as 1) normal for age, 2) reflecting a single neurodegenerative disease (AD, FTD or DLB), 3) consistent with CVD alone, 4) consistent with multiple neurodegenerative processes, 5) mixed degenerative/CVD or 6) abnormal but not diagnostic. This last category includes (for example) imaging consistent with alcoholic brain disease or chronic depression; for which sensitivities and specificities remain unknown. In agreement with current understanding and practice, [28] MRI interpretation alone was not used to make a specific dementia diagnosis. If cortical strokes, multiple lacunes, or severe subcortical white matter disease were present, cerebrovascular disease was considered to be an etiology for dementia.

RESULTS

Subject characteristics

193 consecutive patients were clinically evaluated prior to neuroimaging and retrospectively classified into 3 general disease categories: a) cognitive impairment, not demented (CIND 21%, n=40, which included MCI and cognitive disorder NOS), b) dementia, single etiology (29%, n=57, which included AD, VaD or other causes) and c) dementia, complex etiology (50%, n=96, which included mixed cerebrovascular (CVD)/degenerative, multiple degenerative or dementia NOS). The CIND group was slightly younger than the demented groups (70.9 vs. 74.4, t-test $p < 0.05$) and performed better on both the MMSE and the Mini-Cog (27 vs. 22 and 3.6 vs. 1.6, respectively, both t-test $p < 0.001$). When corrected for multiple comparisons neither age nor cognitive test scores differed between individual dementia diagnosis (not shown but see Table 2).

Relationship between clinical and radiographic diagnoses

Overall, neuroimaging suggested a specific clinical diagnosis in 72% of cases while in 26% of cases an abnormal/not diagnostic pattern was noted (Table 3). Only 4 subjects (2%, ages 69,71, 76 and 82) were felt to have entirely normal scans. The proportion of abnormal/not diagnostic scans was similar across all 7 diagnostic categories (38 of 171 cases, 22%) except cognitive disorder NOS (17 of 25 cases ($\chi^2 = 22.8$ $p < 0.001$).

Results from the selected individual dementia groups are worthy of note. In clinical AD (n=43) 23 cases had confirmatory imaging while in 14 patients had patterns suggestive of other diagnoses and 6 had abnormal/not diagnostic patterns. When mixed vascular/degenerative processes were suspected (n=42) 20 demonstrated a mixed pattern on imaging, 9 showed CVD alone, 7 a single degenerative process and 5 abnormal/not diagnostic results. When multiple degenerative processes were clinically suggested (n=21), the differential diagnosis was narrowed in 10 cases, a mixed vascular/degenerative pattern was seen in 4, only a single case was consistent with co-occurring degenerative diseases and 6 were

abnormal/not diagnostic. Finally, in dementia NOS (n=33) 23 of cases were given a specific radiologic diagnosis while in 10 the pattern was abnormal/not diagnostic.

Relationship between vascular risk factors, clinical vascular dementia (VaD), and cerebrovascualar disease (CVD)

In cases where VaD was not clinically suspected (e.g., CIND, single etiologies other than VaD and complex etiologies other than mixed vascular/degenerative disease, n=146) imaging demonstrated vascular changes alone in 15 patients or in combination with a neurodegenerative pattern in 19 (Table 3). As predicted, when VaD was clinically suspected, either alone or in combination with a neurodegenerative etiology (n=47) CVD alone was found in 11 patients, and CVD in combination with neurodegenerative disease was found in 22 patients, a significantly greater proportion than when VaD was not suspected (70% suspected vs. 23% not-suspected; $\chi^2 = 34.5$ $p < 0.001$). To determine if vascular risk factors and/or known systemic vascular disease predicted imaging indicators of CVD we stratified subjects into 4 groups: those with no vascular risk factors or vascular disease, those with vascular risk factors (diabetes, hypertension, hyperlipidemia, or a history of smoking) but no known vascular disease, those with known vascular disease (cardiac, carotid, or peripheral) and those with suspected VaD by clinical symptoms and signs. Overall, neuroimaging revealed no radiographic evidence of significant CVD in 40%, mild CVD in 31% and moderate to severe CVD in 29% (Table 4). There was no significant difference between persons with and without vascular risk factors in the prevalence or severity of CVD ($\chi^2 = 0.4$ $p > 0.8$). By contrast, both known vascular disease and suspected VaD were associated with neuroimaging CVD (86% if vascular disease was present or VaD was suspected on clinical grounds vs. 40% in others; $\chi^2 = 40$ $p < 0.001$). In addition, subjects with suspected VaD had more severe CVD than in those with vascular disease alone (65% severe in suspected VaD vs. 36% severe in vascular disease; $\chi^2 = 5$ $p < 0.05$).

DISCUSSION

This study compares the initial office-based differential diagnostic assessment of cognitive disorders to the radiologic assessment provided by a combination of structural MRI and SPECT perfusion imaging. If neuroimaging fails to provide either new or clinically relevant information, its benefits relative to costs should be questioned. Overall, in 39% of all dementias (single or complex etiology) the diagnosis was confirmed, in 18% the differential was narrowed (e.g. CVD or degenerative cause judged absent), in 24% a new diagnosis was suggested (either CVD or degenerative cause) and in 19% imaging was abnormal/not diagnostic. Thus in >80% of clinically diagnosed dementia cases neuroimaging provided useful information, confirming, clarifying, or contradicting the initial clinical diagnosis. This suggests that functional neuroimaging, at least as applied in the ‘expert’ setting of a memory disorders clinic, reduces ambiguity in the clinical diagnosis, raises alternative diagnostic possibilities, and should be considered an important part of the dementia evaluation. Conceptually similar studies evaluating CT alone [29] or CT accompanied by a detailed neurocognitive assessment [30] have reported, respectively, that CT influenced ~12% of dementia diagnostic assessments, and that the number of persons needed to assess via CT and neurocognitive testing to change one clinical diagnosis was 9.

In agreement with current Medicare rules authorizing PET imaging to distinguish AD from FTD, [9] we found that 17 of 20 such cases meeting criteria for both diagnoses were classifiable with SPECT imaging (11 FTD, 6 AD), while only one was felt to represent a mixed neurodegenerative process (prominent frontal hypoperfusion with AD like SPECT pattern) and only two were abnormal/not diagnostic. In MCI (n=15), only a single case had imaging considered “normal for age” while 6 appeared AD-like, supporting the ability of SPECT to detect early disease [7] but also illustrating the heterogeneity of MCI as noted by

both prognostic clinical [31] and neuroimaging [32] studies. Finally, we found CVD in 60% of individuals, half mild and half moderate-to-severe. [24] The presence of vascular risk factors did not specifically predict the presence or severity of CVD: 25% and 15% of those with or without vascular risk factors had radiographic findings consistent with mild or moderate-to-severe CVD, respectively.

It would be reasonable to query whether imaging has specific utility in diagnosing the etiology of mild cognitive disorders in clinically ambiguous presentations that do not meet diagnostic criteria for dementia. [12] Such cases would be classified as Cognitive disorder NOS, defined by the DSM-IV TR as cognitive impairments believed to result from a medical condition that is not better classified by the many other DSM-IV TR categories. [33] Factors that contributed to our use of this diagnosis included unclear time of onset, atypical (e.g. fluctuating) course, and unusual presentations (e.g. substantial memory complaint without observable memory deficit; functional deficits in no clear pattern). In only 8 of 25 cases of cognitive disorder NOS did neuroimaging suggest a specific etiology.

Although we were not able to assess how neuroimaging affected clinical decision making and patient outcomes in this study, confirming or clarifying the dementia diagnosis can and should influence patient care and treatment and management decisions. First, the identification of CVD is important. In individuals without known vascular disease (as occurred in 40% of such subjects in this study), clinicians should be alerted to several specific issues. One is the need for close review of modifiable vascular risk factors and efforts to assure adequate treatment for known conditions associated with CVD (e.g., hypertension, diabetes, and hyperlipidemia). Another is knowledge of cerebral risks that may result from age-related loss of vascular compliance and/or overtreatment of medical conditions associated with vascular disease (e.g. hypotension, and hypoglycemia). Finally, it focuses attention on the possibility of non-ischemic cerebrovascular pathology, such as amyloid angiopathy, which carries an important risk of intraparenchymal hemorrhage and appears indistinguishable on MRI from microvascular ischemic disease. [25, 34]

A second way that well-interpreted neuroimaging studies can contribute to patient care relates to directing follow up, treatment choices, and overall patient management. In AD, imaging confirmation of the diagnosis (found in 24% of our sample) can bring to a conclusion what is often for the patient and family a frustrating, multi-year process of repeated evaluations by several different specialists, in the search for an explanation for cognitive changes. Once the diagnosis is established, a comprehensive care and management plan for the patient and family can be initiated with confidence. On the other hand, when neither the clinical nor the radiographic findings point to a specific diagnosis for an observed cognitive change, a low-intensity “watch and wait” approach would be most appropriate. Further, the kinds of problems that should be anticipated, and what treatments or management interventions are likely to help, differ across neurodegenerative disorders such as AD, DLB, and FTD. Distinguishing between them is therefore clinically important.

There are several limitations to this study. Dementia remains a clinical diagnosis; we did not attempt to determine a “true” diagnosis by tracking longitudinal course and examining post-mortem neuropathology. Furthermore, we did not assess change in diagnosis as an indicator of the value of imaging, because neither the radiological interpretations nor the clinical follow-up visits were blinded, a potential source of bias. Likewise, we did not assess how imaging affected the plan of care, as such outcomes require a true prospective design. Future studies should be designed to answer these questions. Finally, we could not compare the utility of MRI to SPECT, or formally determine what SPECT added to MRI alone. Although MRI by itself can do more than rule out surgical lesions [35, 36] its clinical usefulness in differentiating AD from normal aging remains to be established [37] and current

recommendations do not encourage its use for achieving a differential diagnosis of dementias. [28] Thus, the clinical MRI evaluators were not specifically instructed to make a "best guess" as to diagnosis, in contrast with SPECT evaluators, who, at our institution, are asked to attempt to differentiate dementing illnesses. Future work should include parallel MRI and SPECT evaluations with formal instructions regarding classification (i.e., instructing MRI readers to specifically attempt to distinguish regional patterns of atrophy and to suggest an etiology).

Memory disorder clinics such as ours offer expert assessment of cognitive disorders. However, the key components of an office assessment of patients with cognitive decline are well within the scope of general medical practice, and MRI and SPECT are widely available and accessible to informed providers. In our experience neuroimaging was useful even if it only confirmed a suspected diagnosis. "Seeing" the disease process increased both our diagnostic confidence and our ability to explain cognitive symptoms to patients and families. Visual images seem to have special resonance for patients and families[38], grounding clinical symptoms in observable brain changes.

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Table 1

SPECT Criteria for Radiologic Interpretation

Radiologic interpretation	SPECT*
AD	Reduced perfusion in the lateral parietotemporal and posterior cingulate with sensorimotor preservation
FTD	Reduced perfusion in the prefrontal and temporal regions
DLB	Reduced perfusion in the occipital and parietotemporal regions
CVD	Asymmetric cortical, subcortical, cerebellar or watershed deficits

* see Silverman, J Nucl Med (2004) for review

Abbreviations: AD = Alzheimer's disease; FTD = frontotemporal dementia; DLB = dementia with Lewy bodies; CVD = cerebrovascular disease

Table 2

Clinical Diagnoses in 193 consecutive patients

Clinical diagnosis	N (%)	Age (±SD)	MMSE (±SD)	Mini-Cog (±SD)
CIND				
MCI	15 (8)	77 (4)	27 (2)	2.9 (2)
Cognitive disorder NOS	25 (13)	68 (11)	27 (3)	4.2 (1)
Dementia, single etiology				
AD	43 (22)	74 (10)	21 (6)	1.2 (1)
VaD	5 (2)	80 (7)	24 (5)	2.3 (2)
Other*	9 (5)	69 (14)	24 (4)	1.3 (1)
Dementia, complex etiology				
Mixed vascular/degenerative†	42 (22)	78 (7)	22 (5)	1.6 (1)
Multiple degenerative‡	21 (11)	72 (10)	20 (7)	2.3 (2)
Dementia NOS	33 (27)	72 (11)	23 (4)	1.7 (2)
Totals	193 (100)	73 (10)	23 (5)	2.0 (2)

*5 FTD, 3 DLB and 1 dementia secondary to general medical disease.

†2 MCI, 32 AD, 1 FTD and 7 multiple degenerative

‡14 AD+FTD, 3 AD+DLB, 2 FTD +DLB and 2 AD + general medical disease.

Abbreviations: CIND = cognitive impairment, no dementia; MCI = mild cognitive impairment; NOS = not otherwise specified; AD = Alzheimer's disease; VaD = vascular dementia.

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Table 3

Clinical Diagnosis versus Radiologic Interpretation*

Clinical diagnosis	Radiologic interpretation							
	Normal for age	Single pattern				Complex pattern		
		AD pattern	FTD pattern	DLB pattern	CVD alone	Mixed ND	Mixed CVD/ND	Abnormal, not diagnostic
CIND								
MCI (n=15)	1	6	1		2		1	4
Cognitive disorder NOS (n=25)	2	2			3		1	17
Dementia, single etiology								
AD (n=43)		23	1		3	2	8	6
VaD (n=5)					2		2	1
Other (n=9)			6	2				1
Dementia, complex etiology[b]								
Mixed vascular/degenerative (n=42)	1	6	1		9		20	5
Multiple degenerative (n=21)		2	6	1	1	1	4	6
Dementia NOS (n=33)		7	4		6	1	5	10
Totals (n=193)	4 (2%)	46 (24%)	19 (10%)	3 (2%)	26 (13%)	4 (2%)	41 (21%)	50 (26%)

*SPECT and MRI images were read in tandem by expert neuroradiologists. Numbers represent actual cases with (%) provided for column totals.

Abbreviations: see Tables 1 & 2; ND = neurodegenerative disease.

Table 4

Vascular Risk factors, vascular disease, vascular dementia and radiologic findings of cerebrovascular disease

		Radiographic interpretation*		
	N	**No significant CVD**	**Mild CVD**	**Moderate-severe CVD**
No vascular risk factors	40	60% (24)	28% (11)	12% (5)
Vascular risk factors	68	60% (41)	24% (16)	16% (11)
Known vascular disease	27	18% (5)	52% (14)	30% (8)
CVD suspected as sole or contributory etiology	58	12% (7)	31% (18)	57% (33)
Totals	193	40%	30.5%	29.5%

Abbreviations: CVD = cerebrovascular disease

* "No significant CVD" included periventricular capping and/or patchy deep white matter hypertensities (Fazekas Grade 1[24]) and/or 1-2 lacunes; "mild CVD" included moderate hyperintensities (Fazekas Grade 2) and/or <2 lacunes "moderate- severe CVD" included substantial, confluent hyperintensities (Fazekas Grade 3) and/or significant macrovascular disease.