HOW COULD NEUROIMAGING BE HELPFUL IN THE ASSESSMENT OF DEMENTIA IN A CLINICAL SETTING?

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Abstract- ***This study was conducted to evaluate how neuroimaging procedures (MRI, SPECT) could be used in clinical settings for diagnosis of dementia.***

Forty out of 94 patients suspected of having a diagnosis of dementia, referred to Radiology Department for consecutive neuroimaging procedures, were selected. Patients' medical records reviewed and a retrospective diagnosis was reached according to DSM-IV for Alzheimer's disease (AD) and NINDS-AINS for vascular dementia (VaD). Mann-Whitney, fisher's exact test, bivariat regression were used for analysis.

Clinical features of majority of patients were complicated with mental symptoms. Subcortical lesions were observed in both dementias but it was significantly more frequent in the VaD (P=0.000). No significant differences in the number of patients with cortical atrophy between two groups was observed. Significant agreement between SPECT and retrospective clinical diagnosis was observed (kappa=0.18, P=0.02), but no significant pattern of hypoperfusion which could predict the clinical diagnosis was observed.

This study emphasis on clinical diagnosis and the clarity of the referral process for doing neuroimaging evaluation. More sophisticated studies, either structural or functional such as volumetric measurement of medial temporal lobe, could be helpful to confirm clinicians in their diagnosis of patients with dementia.

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Key Words: ***Alzheimer's disease, vascular dementia, SPECT, MRI, brain imaging, dementia***

INTRODUCTION

Prevalence of dementia is influenced by the age of the population. It will be double in subjects over 60 for every 5 years (1) and will increase to 50% in the 90+ year old population (2). At present approximately up to 24 million people world- wide have Alzheimer's disease (AD) (3). The two most common causes of dementia are Alzheimer's disease (AD) and Vascular dementia (VaD), with frequencies of 70% and 15% to 20% of all dementias respectively (4,5). VaD is the second most common subtype of dementia in western countries (6) and may be the most common subtype of dementia in the world (7). The origin of the concept of VaD can be traced to Binswanger Syndrome, in which major vessels were proposed as was later renamed, multi-infarct dementia (MID) (8). They may appear with cortical infarctions (large and small vessel disease), sub-cortical lesions (Lacunes, Binswanger's Syndrome, White Matter Hyperintensities), hypoperfusion dementia, and hemorrhagic dementia (subdural, subarachnoid, parenchymal) (9,10). Subcortical infarctions and white matter hyperintensities (WMHIs) are mostly accompanied by cognitive impairment and dementia rather large vessel cortical infarction (11). MRI measurement of the surface area of the entorhinal cortex (ERC) is potentially useful in the early diagnosis of very mild AD (MMSE≥ 24) and may have superior diagnostic value over measurement of the hippocampus or the neocortex (12,13). Medial Temporal structures measurement by MRI with sensitivity and specificity of 85% to 90% have been promising in separating patients with AD from controls (14). Single photon emission computerized tomogram-phy (SPECT) currently has clinical utility in diagnosis of cerebrovascular disease (15,16) and Alzheimer type of dementia. In addition it has been helpful in the diagnosis and management of reversible dementias (17,18). Bilateral hypoperfusion at posterior of parietotemporal region is considered to differentiate AD from normal elderly patients (19,20) and from AD accompanied with apraxia and aphasia (21). Different patterns of hypoperfusion among demented patients could be helpful in differentiation of AD from other types of dementias (22,23), assessment of severity (24) and clinical effectivenesss of pharmacotherapy (25). SPECT findings in VaD are inconsistent. Frontal, cingulate, posterior unilateral hypoperfusion and even non-specific patterns have been reported (26,27). Neuroimaging, which is available in developed and some developing countries, can be used in everyday clinical routine procedures. Given the costs of neuroimaging, it seems that current clinical effectiveness of using neuroimaging in clinical not research setting should be carefully evaluated. The purpose of this paper is to evaluate the clinical use of SPECT and MRI in helping the diagnostic process in one of the major teaching hospitals in the US, for patients not involved in research protocols but rather on standard clinical workup of dementia.

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MATERIALS AND METHODS

Clinical information and neuroimaging reports of 94 patients who were suspected to have dementia and were referred to nuclear medicine and radiology for further evaluation during 1998 to 2000, at the University of Illinois at Chicago, Medical Center, were reviewed. Fifty two patients had both brain MRI and SPECT. They were retrospectively diagnosed with probable AD, VaD and other types of dementia (NOS) using DSM-IV (28) and NINDS-ANDS (29) diagnostic criteria respectively. According to routine practice in radiology, the subjects were scanned with a 1.5 Tesla, G.E MRI scanner obtaining axial whole brain images of the 5-mm thickness using T1, T2, Gradient, and flair images. MRI images were classified into three groups: cortical infarction, subcortical lesions (lacunes, periventricular hyperintensities, WMHIs) and cortical atrophy. SPECT was performed using a rotating triple-head gamma cammera (Picker PRISM 3000 XP, Picker International, Inc. Cleveland, OH).

Each individual slice represents approximately 0.84– 0.86 cm of thickness. The imaging scans are started after injection of 1000 mbq of 99m TC-HMPAO. SPECT reports, based on visual interpretation, were classified into eight perfusion pattern: Right, left: occipital, temporal, parietal, frontal. When the SPECT report carried a diagnosis of dementia, it was included in the data.

RESULTS

Sample description and MRI findings

A retrospective diagnosis for 52 patients was made by researchers: 24 (46.2%) patients with probable AD; 16 (30.8 %) patients with VaD; 12 (23%) patients with other dementias (NOS: frontotemporal and dementia due to general medical condition). In the 65% of cases (34 out of 52 patients) a tentative diagnosis of cognitive impairment, memory impairment, or rule out dementia, were the reasons of referral to radiology by the clinician. Ultimately, 40 patients (24 AD and 16 VaD) were included in the study. AD patients were aged 55 min to 92 max (mean= 74.8, SD= 10.04); 10 males and 14 females. VaD patients were aged 43 min to 91 max (mean=72.3, SD=13.94); 6 males and 10 females. Comparing the number of patients with subcortical lesions and cortical atrophy based on MRI in AD and VaD groups are shown in table. Mann-Whitney analysis shows that subcortical lesions (lacunes, WMHIs, Periventricular hyperintensities) in VaD patients were more frequent (No= 47, mean rank= 13.06) than AD group (No=12, mean rank = 14.06), p= 0.0005.

SPECT findings

In AD, bitemporoparietal hypoperfusion and in VaD, left temporal followed by bifrontal and biparietal were the most frequent regions with hypoperfusion (table). Significant agreement between SPECT diagnosis, according to the reports, and clinical retrospective diagnoses which were made by researchers were seen (kappa= 0.179, p= 0.02). Given the significant agreement between the both diagnoses, we tried to find if there was any specific pattern of hypoperfusion which could predict the diagnosis of AD and VaD? Bivariet logistic regression analysis was used. There was not any significant pattern of hypoperfusion to predict the diagnosis and differentiate AD from VaD, but a trend (r2= -0.12, p= 0.09) between right frontal hypoperfusion and the diagnosis of VaD group was observed. Fisher's exact test did not show any significant differences between AD and VaD for right frontal hypoperfusion.

Somatic and psychiatric symptoms

Regarding psychiatric feature, which could be seen in both kind of dementia, depressive and psychotic symptoms were the most frequent symptoms among the two groups without any significant differences (Table 1). A trend was observed for more agitation and bizarre behavior in AD group. Comparing the frequency of somatic diseases and symptoms (HTN, IHD, CHF, hyperlipidemia, diabetes, thyroid disease, B_{12} deficiency, seizure, syphilis, falling) between AD and VaD showed that although vascular disease were observed in AD, but HTN, seizure and falling were significantly more frequent in VAD group (Fisher's exact test, P. value less than 0.05).

DISCUSSION

Judging the utility of neuroimaging in the routine clinical assessment of dementia continues to be controversial. We are not discussing in this paper the utility of neuroimaging in the reversible types of dementias like hypothyroidism, but rather helping the clinicians in the differential diagnosis between AD and VaD or to confirm the clinical diagnosis of dementia. From a clinical point of view, many times because of complication with psychiatric symptoms and somatic disease, the diagnosis of dementia is a difficult task. Comparing to cortical infarctions, subcortical lesions are more frequently accompanied by cognitive impairment and dementia (30-32). Our study showed that AD patients had subcortical lesions even though they were four times more in VaD than AD groups (Table 1).

Table 1. Frequency of patients with psychiatric symptoms, somatic disease, cortical regions with hypoperfusion and subcortical lesions.

	AD		VaD		
	No. of patients	**%**	**No. of patients**	**%**	P. value**
Psychiatric symptoms					
MDD	**11**	**45.81**	**3**	**1.8**	ns
Depressive symptoms	**10**	**40.1**	**3**	**1.8**	ns
Anxiety	**10**	**40.1**	**4**	**25**	ns
Agitation	**11**	**45.8**	**6**	**37.5**	0.1
Aggression	**4**	**16.6**	**4**	**25**	ns
Hallucinations	**7**	**29**	**2**	**12.5**	ns
Delusions	**6**	**25**	**2**	**12.5**	ns
Bizarre behavior	**7**	**29**	**4**	**25**	0.1
Disorientation	**4**	**16.6**	**1**	**6.2**	Ns
Somatic disease					
HTN	**9**	**37.5**	**11**	**68.7**	0.01
IHD	**5**	**20.8**	**-**	**-**	ns
CHF	**2**	**8.3**	**5**	**31.2**	0.07
Hyperlipidemia	**5**	**20.8**	**2**	**12.5**	ns
Diabetes	**3**	**12.5**	**3**	**18.7**	ns
Thyroid disease	**1**	**4.1**	**2**	**12.5**	ns
B_{12} deficiency	**3**	**12.5**	**0**	**0**	ns
Seizure	**0**	**0**	**3**	**18.7**	0.05
Syphilis	**2**	**8.3**	**0**	**0**	ns
Fall	**1**	**4.1**	**4**	**25**	0.04
SPECT					
Occipital					
Rt	**2**	**8.3**	**-**	**-**	
Lt	**2**	**20.8**	**-**	**-**	ns
Both	**3**	**41.6**	**-**	**-**	
Temporal					
Rt	**2**	**8.3**	**3**	**18.7**	
Lt	**5**	**20.8**	**6**	**37.5**	ns
Both	**10**	**41.6**	**4**	**25**	
Parietal					
Rt	**2**	**8.3**	**1**	**6.2**	
Lt	**8**	**33.3**	**5**	**31.2**	ns
Both	**11**	**45.8**	**5**	**31.2**	
Frontal					
Rt	**2**	**8.3**	**5**	**31.2**	
Lt	**2**	**8.3**	**2**	**12.5**	ns
Both	**8**	**33.3**	**5**	**31.2**	
MRI					
PVHIs	**3**	**12.5**	**8**	**50**	0.01
PONs	**2**	**8.3**	**1**	**6.3**	ns
WMHIs	**1**	**4.2**	**7**	**43.8**	0.004
B.G	**2**	**8.3**	**5**	**31.3**	0.007
Thalamus	**-**	**-**	**5**	**31.3**	0.007
I.C	**1**	**4.2**	**2**	**12.5**	ns
GCA**	13	54.2	9	56.2	ns

++ Fisher's exact test

** Chi square: value=0.01, df=1.

Ns: not significant; PVHIs: Paraventricular hyperintensities; WMHIs: White matter hyperintensities; BG: Basal ganglia; IC: Internal capsul; GCA: General cortical atrophy.

This is compatible with previous studies (32-34) which showed subcortical lesions exist in AD, VaD, Lewy Body Dementia, healthy elderly population and non-demented mentally ill patients (35,36). Observing subcortical lesions may lead clinicians to overdiagnose VaD. An Autopsy study showed that near to 30% of patients with clinical mixed dementia had only AD (37). Cortical and ventricular atrophy is another neuropathological feature which can be seen in radiologic descriptive reports. In this study, 50% of AD and 56% of VaD patients, according to their reports, had general cortical atrophy, without a significant difference between them, which is concordant with the study of Schelton et al., (2000) (34). Although AD and VaD may be clinically distinct, analysis of neuroradiological data revealed considerable overlap between them for the presence of subcortical lesions and cortical atrophy. Given the above mentioned findings, traditional descriptive report of brain MRI including cortical atrophy, subcortical lacunes, leukoariosis and PVHIs may not increase the accuracy of differential diagnosis between AD and VaD. Volumetric studies of brain MRI have produced more valuable data. Hippocampus and middle temporal lobe volume have significant inverse correlation with delay memory (38) which has predictive value with high degree of accuracy (89%) for diagnosis of probable AD (39). A longitudinal study (40) revealed that hippocampal atrophy in healthy elderly population can predict the AD. Several studies confirmed that AD patients can be separated from normal healthy group using volumetric measurement of ERC, Hippocampal cortex (41,42) and Corpus Callusom (36,43). Biparietotemporal hypoperfusion pattern is a consistent feature of SPECT in AD patients (20,24,25,44). According to the SPECT reports of studied subjects, the hypoperfusion patterns of 50% of patients were convincing enough that it led the SPECT readers to write a probable diagnosis as a final conclusion. The results showed signifcant agreement between retrospective clinical diagnosis and SPECT diagnosis. Even the accuracy of neuroimaging procdures, their effectiveness in diagnosis of dementia is not remarkable more than clinical criteria such as NINCDS-ADRDA (45) for diagnosis of dementia, therefore it can not be relied completely or suitable substitution for prior clinical judgement. Our study showed that cognitive impairment of majority of patients was complicated with psychiatric symptoms and some somatic diseases (table), which have distorted the clinical features of dementia. It may happen that some primary psychiatric patients are presented with cognitively impaired features, which are to be ruled out. In these cases, routine reporting of neuroimaging may show subcortical lesions or cortical atrophy which may not render to differentiate AD, VaD, pseudodementia, or primary psychiatric disorders. MRI, in volumetric measurement, and SPECT, in combination, can add to the differential diagnosis especially for the patients whose clinical features are complicated with mental disorders. In conclusion two major issues would need to be addressed if neuroimaging is going to be used as a routine procedure in the clinical workup of patients with dementia. Given the high rate of demented patients complicated with psychiatric symptoms or mental disorders with cognitively impaired presentation, the clinician should reach a probable clinical diagnosis of dementia before referring the patient for the neuroimaging. Referrals like memory impairment, or rule out dementia, as were observed in our study which compromised more than 65% of cases, were not helpful to the radiologist in allowing them to tailor specific radiological procedure techniques. Clinicians should mention a clear expectation when referring to neuroimaging services especially if the main question is to confirm the dementia diagnosis. Second, the neuroimaging reports need to be more specific. The presence of cortical atrophy, subcortical ischemic or hyperin-tensity changes, do not help the clinicians in the clinical diagnostic process. Volumetric study of medial temporal lobe should be included in the report when diagnosis of dementia is required.

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