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Posterior Parietal Hypoperfusion in Differentiation of Alzheimer's Disease, Fronto-temporal Dementia and Vascular Cognitive Impairment

SEDAGHAT FERESHTEH[1], GOTZAMANI-PSARRAKOU ANNA[1], DEDOUSI ELENI[1], BALOYANNIS IOANNIS[2], PSARRAKOS KYRIAKOS[3], SIOUNDAS ANASTASIOS[3], RAKHSHANI ALIASGHAR[1], DIMITRIADIS S. ATHANASIOS[4], BALOYANNIS J. STAVROS[2]

[1]Department of Nuclear Medicine, [2]1th Department of Neurology, [3]Department of Medical Physics, [4]Department of Radiology AHEPA University Hospital, S. Kiriakidi 1, 54636 Thessaloniki-Greece

Abstract: Single photon emission computed tomography (SPECT) brain imaging adds diagnostic information in dementia. In this study we evaluate the role of bilateral posterior parietal hypoperfusion (BPPH) finding in (SPECT) with ^{99m}Tc-HMPAO, in the early diagnosing of AD and the differentiation of AD from fronto-temporal dementia (FTD) and vascular cognitive impairment (VCI). In this study 106 subjects, are included with a main complaint of memory impairment or for a check-up of their cognitive state. Each patient was injected with 555 MBq ^{99m}Tc-HMPAO(Ceretec-Amersham). Semiquantitative rCBF analysis was done. The patients were followed up every 3 months which was our gold standard of diagnosis. 25 healthy subjects that were among the patients are included in the study as our control group.
Our patients based on clinical diagnosis and SPECT were differentiated as following:
1-AD group fulfilled NINCDS-ADRDA criteria (36 patients, 13 men, 23 women), which was consisted of two subgroups:(a) Strongly suggestive of AD (SSAD): included 32 patients with a bilateral posterior parietal and medial temporal hypoperfusion with or without reduction at frontal region. 30 of them showed to be AD. (b) Suggestive of AD (SAD): included 4 patients with a bilateral posterior parietal and unilateral medial temporal hypoperfusion which showed to suffer from AD. (2) FTD group: consisted of 7 patients, 3 male and 4 female fulfilled Neary criteria, with a bilateral prefrontal, medial and lateral temporal perfusion reduction in SPECT. 3-VCI group with two subgroups of: (a) Strongly suggestive of vascular cognitive impairment (SSVCI): contained 11 patients, 7 male and 4 female fulfilled NINCDS-AIREN criteria with focal or multifocal infarct defects in SPET. 4 of them had focal large infarcts seen in CT images too. 7 patients had multinfarct dementia (MID). (b) Suggestive of vascular cognitive impairment (SVCI): included 28 patients who had definitely abnormal blood flow pattern but not clearly categorized as mentioned in groups above. 24 of these patients were diagnosed as having vascular dementia.
We observed that posterior parietal (PP) was the specific region affected in the early stage of AD and could help us in differentiating AD from other dementias.
SPECT, with the perfusion patterns that mentioned had the specificity of 97% in the diagnosis of AD. 25% of the patients with AD were in mild stage of the disease. Also the specificity of 100% and 86% for diagnosing FTD and VCI were obtained respectively.
We conclude that bilateral posterior parietal hypoperfusion may play a crucial role in early diagnosing of AD and differentiating it from frontotemporal and vascular cognitive impairment.

Key words: Posterior parietal hypoperfusion, SPECT, Alzheimer's disease, fronto-temporal dementia, vascular cognitive impairment

1 Introduction:

The increased social awareness of cognitive disturbances brings patients for medical observation in earlier stages of the dementing disorder [1]. Single photon emission tomography (SPECT) was developed in the 1960s by Kuhl and Edwards and have been used to study cerebral function [2-4].

Numerous studies confirm the value of functional brain imaging as a potentially cost effective mean of establishing an earlier diagnosis of AD [5].

The aim of this prospective study is to evaluate the role of posterior parietal hypoperfusion in SPECT with ^{99m}Tc-HMPAO in the classification of dementia in patients referred to us with a chief complaint of short term memory impairment.

2 Patients and methods:

106 subjects, 39 men and 67 women (53-84 years old), are included in this study from patients who were referred to the first memory clinic of AHEPA University Hospital of Thessaloniki for three years, with a chief complaint of short term memory impairment and a mini mental state examination (MMSE) of ≤ 30.The patients were considered to have severe, moderate and mild dementia with a MMSE of 0-12, 12-20 and 20-30 respectively. The Short performance test, Syndrom-Kurz Test (SKT) was done in most the patients with a MMSE of 20 and higher (mild stage). CT scan and SPECT were performed as routine examinations for investigation of dementia in our patients. Magnetic resonance imaging (MRI) was also performed in every patient indicated. Among these 91 patients, were included 25 healthy subjects (9male, 16 female, age range 53-76 years) with a MMSE of 29-30 and SKT of 1-3 and normal laboratory examination, who were referred in the study as the healthy control group. SPECT brain imaging was undertaken 45 min after the IV injection of 555 MBq (15mci) ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime, Ceretec-Amersham) in a quiet and bright room in the Department of Nuclear Medicine of AHEPA hospital with patient's eyes opened. Each patient had an IV line at least 15 minutes before the injection of the agent.

Images were acquired using a single headed ADAC gamma camera equipped with a low energy high resolution (LEHR) collimator. The patient was in a supine position with his head stabled with a special belt. The total acquisition consisted of 120 projections acquired for 20 seconds into a 128×128 acquisition matrix; the magnification factor of 2.19 gave a pixel size of 2.2 mm. The images were processed on a Sun Pegasys computer and were reconstructed with Butterworth filter back projection. Slices were generated parallel to the orbitomeatal line.

The attenuation correction and reorientation were done on reconstructed brain images. The images were visually evaluated and then the region of interest (ROI) with the size of 4×4 pixels was used to measure the mean count, accounting for blood flow (rCBF) in the following regions: right and left prefrontal cortex (RPF, LPF)(Broadmann areas BA 9-12), frontal (BA 4,6,8) (RF,LF), anterior parietal(BA 1-3,5) (RAP,LAP), posterior parietal (BA 7,39)(including: precuneus, angular gyrus, inferior parietal lobule and superior parietal lobule) (RPP, LPP), medial and lateral temporal (RTm, RTl, LTm, LTl), occipital (RO, LO), and cerebellum (CER). The above regions were determined based on the references 6 and 7 [6,7]. Based on visually evaluation, if needed, the ROI was done in every other region of the brain too. The coronal slices were used to study the temporal lobes. Semiquantitative rCBF analysis using cortex to cerebellum ratio was done. In the presence of cerebellar defects, the patient was omitted from our calculation study. The control group was used to set the mean and SD of the semiquantitative analysis for each brain region. A reduction more than two folds of the standard deviation (SD) for a region in the normal group, was considered as significant reduction. Three-dimensional surface-rendered images derived from transverse cross sectional data of the brain was obtained to determine the distribution of surface cortical defects and the connectivity of defects seen in tomographic slices. The patients were followed up every 3 months at the memory clinic. Since biopsy or autopsy was not performed in any cases, the follow-up of patients was our gold standard of diagnosis.

3 Results:

Our patients based on SPECT and clinical diagnosis (NINCDS-ADRDA criteria for AD) were classified as follows:

1- AD group (36 patients, 13 men and 23 women) which was consisted of two subgroups:

(a) Strongly suggestive of AD (SSAD): included 32 patients with a bilateral posterior parietal and medial temporal hypoperfusion with or without reduction at any other region. 31 of them showed to be AD based on follow-up and one of them proved to suffer from collagen vascular disease. 7 of these patients were in the mild stage of the disease.

(b) Suggestive of AD (SAD): included 4 patients with a bilateral posterior parietal and unilateral medial temporal hypoperfusion which plead in favor of AD (Diagram 1).

2- Frontotemporal dementia (FTD): consisted of 7 patients, 3 male and 4 female fulfilled Neary criteria with a bilateral prefrontal and medial and lateral temporal perfusion reduction (Fig 1).

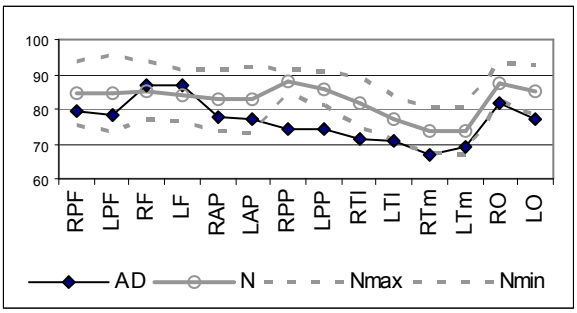

Diagram 1: Average rCBF ratio in different regions of the brain in AD and normal group. Significant hypoperfusion is observed at right and left posterior parietal regions in AD. Medial temporal regions don't show significant decrease. Nmax: maximum ratio in normal group, Nmin: minimum ratio in normal group. PF: prefrontal, F: frontal, AP: anterior parietal, PP: posterior parietal, Tm: medial temporal, Tl: lateral temporal, O: occipital

3- VCI group which was consisted of two subgroups:

(a) Strongly suggestive of vascular cognitive impairment (SSVCI): contained 11 patients, 7 male and 4 female fulfilled NINCDS-AIREN criteria with focal or multifocal infarct defects in SPET. 4 of them had focal large infarcts seen in CT images too. 7 patients had multinfarct dementia (MID).

(b) Suggestive of vascular cognitive impairment (SVCI): included 28 patients with a potential of vascular etiology capable of producing cognitive impairment, who had definitely abnormal blood flow pattern in SPECT but not clearly categorized as mentioned in groups above. Since 24 of these patients were clinically and after follow-up diagnosed as having vascular cognitive impairment, this group is realized as suggestive of VCI. One patient showed to have Lewy body dementia (LBD), 2 had both hypothyroidism and B_{12} deficiency and one of them suffered from depression.

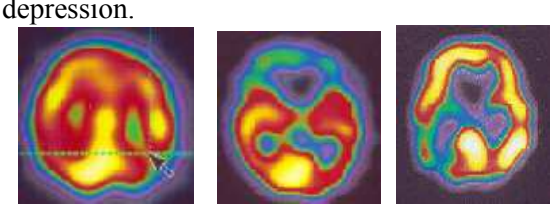

Figure 1: Transverse slices of a patient with senile AD in moderate stage, patient with FTD and a patient with SSVCI.

The prevalence of AD and VCI by MMSE score group are demonstrated in diagram 2. 70% of the patients with VCI referred to us were in the mild stage, versus 25% of the patients with AD.

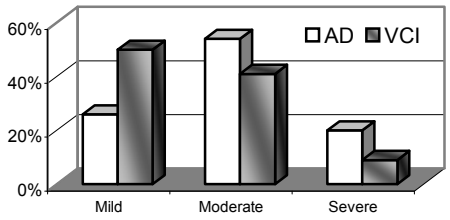

Diagram 2:The prevalence of AD and VCI / VaD by MMSE score group. Most the patients with VCI who were referred to us were in mild stage versus AD patients who were referred in moderate stage of the disease.

4 Discussion:

Hypoperfusion in the posterior temporoparietal regions are recognized in AD [8-13]. Based on our results, posterior parietal region (BA 7,39), a region that consists of precuneus, angular gyrus, inferior parietal lobule and superior parietal lobule, was the specific region which was affected in the early stage of AD and could facilitate the differential diagnosis of AD from other types of dementia. The posterior parietal cortex was the region that showed a significant decrease in comparison with the normal group (Diagram 1). In a early stage of AD, even before a clinical diagnosis of probable AD is possible, decreases of rCBF and glucose metabolism in the posterior cingulate gyri and precunei have been reported using PET [14,15] and SPECT [16,17]. The region containing the posterior cingulate gyrus and precuneus is known to be important in memory [18]. The precuneus [19] possibly receives inputs from the parahippocampal gyrus, especially the entorhinal cortex, and also from the subiculum and presubiculum. Therefore this region is likely to be opposed to "disconnection" due to pathology affecting the medial temporal lobe. The neuronal circuit described by Papez may be important in memory. Therefore lesions of the cingulum and retrosplenial cortex may cause memory disfunction by disrupting this pathway [20]. A PET study showed activation in the precuneus during episodic memory retrieval tasks [18].

Kemp P. et al (2003), visually analyzing, reported significant greater posterior cortical association area involvement in patients with presenile AD and significantly greater medial temporal hypoperfusion in patients with senile AD [21] and this finding was reported by other authors using PET and SPECT [22-24].

The medial temporal region was the most sensitive site that was affected in all kinds of dementia without showing a significant decrease in rCBF in AD, comparing with our normal group and the other groups of dementia. So this region had less specificity in classifying dementia (Diagram 3). Ibanez et al (1998) reported no significant decrease in glucose metabolism in the medial temporal structures of AD patients [25]. A study which used a triple headed gamma camera and MRI, reported that medial temporal structures shows functional reductions to a lesser degree than does atrophy in very mild to moderate AD [26]. In our subjects with mild to moderate AD, there were no significant temporal atrophy in their MR images but they showed reduction of the medial temporal blood flow in SPECT.

We believe that the group comparisons provide limited information due to heterogeneity of the disease, as already pointed out by Versijpt J. et al (2001) and Waldemar (1995) [27,28].

The determination of the normal baseline state of the brain is not an easy procedure since many brain functions and mental processes affect the activity of the brain and because of the existence of individual variations [29-31]. In this study SPECT with the perfusion pattern mentioned, had respectively the sensitivity and the specificity of 100% and 97% for diagnosing of AD, the sensitivity and specificity of

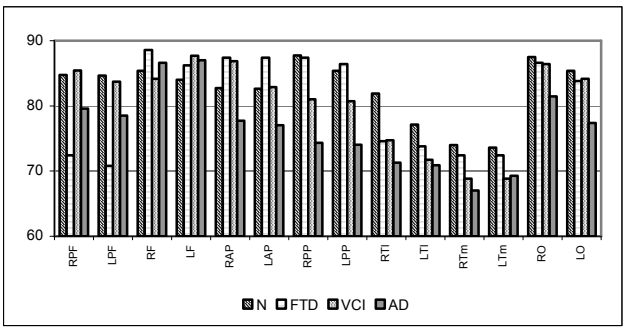

Diagram 3:The average rate of blood flow in different regions of the brain. This diagram compares the AD ratios with normal group and other groups of dementias. Medial temporal region doesn't show a significant hypoperfusion in AD versus the posterior parietal region.

100% for diagnosing of FTD and the specificity of 86% for the diagnosis of VCI.
Further studies are needed for more valuable diagnostic criteria of VCI.

In conclusion we suggest that SPECT and bilateral posterior parietal blood perfusion reduction may have a crucial role (a) in diagnosing of AD at the early stage of it, (b) in confirming the clinical diagnosis, (c) in differentiating AD from FTD and VCI and (d) in following-up of the patients.

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