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Clinical, molecular imaging and biomarker concordance in the diagnosis of Alzheimer's disease and vascular dementia

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RESEARCH

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ABSTRACT

Background

The CSF and plasma biomarkers may help clinicians in differentiating between Alzheimer and Vascular dementia. Apart from biopsy, FDG PET, MRI Brain and clinical examination gives a reliable diagnosis of AD and VaD.

Aims

To evaluate the correlation of molecular imaging (FDG PET brain) with CSF Alzheimer profile and Plasma hemostatic biomarkers in Mild Cognitive Impairment (MCI), Alzheimer's disease (AD) and Vascular dementia (VaD).

Methods

Neuropsychological assessment, MRI brain, FDG-PET brain, CSF biomarkers of AD (Aβ42 and total tau) and plasma hemostatic biomarkers (Fibrinogen and D dimer) were done for evaluation.

Results

FDG PET Brain, plasma fibrinogen and D dimer were done in 68 patients. CSF biomarkers were done in 46 patients. Clinical-PET discordance was found in 7 patients. One patient of MCI-VaSC had a normal PET study with elevated haemostatic biomarkers. Those with clinical diagnosis of Alzheimer's disease either had normal hemostatic biomarkers and supporting Alzheimer profile CSF biomarkers where they were done. The discordant vascular group had elevated plasma hemostatic biomarker with normal CSF profile. Even those who were reported as FTD in PET imaging had Alzheimer profile and normal hemostatic factors.

Conclusion

FDG PET brain findings were concordant with the CSF biomarkers (CSF Aβ42, Total tau and Tau/Aβ42 ratio) in Alzheimer's disease and Haemostatic biomarkers (Plasma Fibrinogen and D dimer) in vascular dementia. In clinical and molecular imaging discordance, biomarkers help in making a reliable diagnosis which favours the clinical assessment.

Key Words

Dementia, FDG PET, Alzheimer's disease, vascular dementia, biomarkers

What this study adds:

1. What is known about this subject?

FDG PET (Fluorodeoxyglucose Positron Emission Tomography) is a downstream marker in pathogenesis of dementia. The concordance of PET, biomarkers and clinical diagnosis in dementia is still controversial.

2. What new information is offered in this study?
FDG PET brain findings were concordant with the CSF biomarkers in Alzheimer's disease and Haemostatic biomarkers in vascular dementia.

3. What are the implications for research, policy, or practice?
In clinical and molecular imaging discordance, biomarkers help in making a reliable diagnosis which favours the clinical assessment.

Background

The two most common type of dementia are Alzheimer's disease (AD) and vascular dementia (VaD). Differentiating between them is a common dilemma in memory clinics. Apart from biopsy, FDG PET, MRI Brain and clinical examination gives a reliable diagnosis of AD and VaD. When there is discordance between molecular imaging (FDG PET) and clinical diagnosis, biomarkers may be helpful. In this study we analysed the concordance of dementia diagnosis using molecular imaging (FDG PET) and fluid (CSF and plasma) biomarkers.

Method

The study population was recruited from the outpatient services of Postgraduate Institute of Medical Education and Research, Chandigarh. According to the diagnostic criteria (Dubois criteria for AD, DSM IV Criteria for VaD, National Institute on Aging- Alzheimer's Association (NIA-AA) criteria for MCI) the patients were divided into various subgroups: Mild cognitive impairment-Alzheimer's disease (MCI-AD), Mild cognitive impairment-Vascular (MCI-VaSC), Alzheimer's disease (AD), Vascular Dementia (VaD). The Alzheimer patients were classified based on the MMSE scores into mild (MMSE 21–26), moderate (MMSE 11–20) and severe AD (MMSE ≤10). Involvement of activities of daily living was used to distinguish between MCI and Mild dementia. The institutional ethics committee approved the study. All patients/caregivers provided informed consent.

The evaluation of the study population included clinical history, medical and neurological examination, laboratory investigation(Complete blood count, Electrolytes, Renal function tests, Liver function tests, HIV, VDRL, Vitamin B12, TFT, Anti-TPO), neuroimaging {MRI Brain and Fluorodeoxyglucose Positron Emission Tomography (FDG PET)} and neuropsychological evaluation.

PET/CT imaging was performed using a Discovery LS (GE) PET scanner. Patients were fasting for at least 4 hours and blood glucose level <200mg/dl was ensured. Acquisition was initiated 45 minutes after intravenous administration of 10mCi (370MBq) of FDG. Reconstruction of data was done using iterative method (OSEM-Ordered subset expectation maximization method) and images were read in transaxial, coronal and saggital views. The scans were evaluated qualitatively and visual analysis was used for the interpretation of the scans.

The radiation burden to the persons due to the proposed study was minimal and well within the limits prescribed by atomic energy regulatory board (AERB) and there was no known harmful radiation effect from such procedures.

Visual reading
All images from each subject were scaled to his/her own global maximal voxel value. The relative intensity between various cortical and subcortical regions was focused on rather than absolute values of any particular region to achieve uniformity. Each image was interpreted by an expert PET physician blinded to the clinical data.

FDG-PET scans in patients were classified into four categories:

1. High likelihood for AD (HLAD)
   Hypometabolism in parieto-temporal (symmetrical or asymmetrical), including posterior cingulate and precuneal cortices, with or without frontal hypometabolism (symmetrical or asymmetrical) and preserved metabolism in sensorimotor and visual cortices, both basal ganglia, thalami, and cerebellar cortices
2. Intermediate likelihood for AD (ILAD)
   Hypometabolism in any isolated region pertaining to the above mentioned Alzheimer's territory
3. Vascular Dementia (VaD)
   Regional cortical hypometabolism corresponding to a vascular territory with corresponding signal changes on MRI.
4. Frontotemporal dementia (FTD)
   Hypometabolism in both frontal and anterior temporal cortices
5. Mixed dementia
   Hypometabolism in Parieto-temporal region and ischaemic cortical and subcortical signal changes on MRI.

Neuropsychological assessment included MMSE, Alzheimer's Disease Assessment Scale (Cognitive), PGI (Postgraduate Institute) Memory scale, Verbal fluency – Controlled oral word test (phonemic) & Animal Names test

(categorical), Quality of life – AD, ADCS (Alzheimer's Disease Cooperative Study)- Activities of Daily Living Inventory and Hamilton depression rating scale.

Lumbar punctures were performed using a 22 gauge spinal needle without any blood contamination and 5ml CSF was collected in polypropylene tubes, centrifuged and was analyzed for cell count, total protein, glucose, VDRL, ADA, Aβ42 and total tau (T-tau). CSF total tau and Aβ42 were determined quantitatively using a commercial sandwich enzyme linked immunosorbent assay (Invitrogen ELISA kits). ELISA analyses were performed according to the manufacturers' protocols. Baseline venous blood samples were taken after overnight fast. The plasma biomarkers assessed were Fibrinogen and D dimer.

Analyses were done at Experimental Pharmacology laboratory, PGIMER, Chandigarh, by operators who were blinded to all clinical information.

Statistical analysis

Non-parametric test (Kruskal Wallis test with multiple comparisons) and Mann Whitney U test were used for continuous ranked data. Chi square (Fisher's Exact test) was used to analyze categorical variables. Data was analyzed using SPSS version 22 statistical software.

Results

Sixty eight patients who agreed to undergo either FDG PET or CSF analysis were included in the study. Of the 68 patients, FDG PET was done in all while only 48 patients gave consent for performing Lumbar puncture. CSF biomarker analysis was done in these 48 patients.

Eleven patients were diagnosed with MCI, of which 7 were MCI-AD and 4 were MCI-VaSC. We had 27 patients with Alzheimer's dementia (Mild AD- 7, Mod AD -15, Severe AD-5) and 8 patients with vascular dementia. The Alzheimer pathology group (MCI-AD and AD) had 34 patients while Vascular group (MCI VaSC & VaD) consisted of 12 patients. The baseline characteristics are depicted in supplementary appendix Table e1.

FDG PET Brain was done in 68 patients. In most of the patients' clinical diagnosis of MCI/AD/VaD were concordant with FDG PET brain (Table 1, Figure 1). There was discordance in 7 patients. Of these seven patients, three (Frontotemporal dementia-2, Mixed Dementia-1) had both CSF and plasma biomarkers. Four patients had only plasma biomarkers done. One patient of MCI-VaSC had a normal PET study. His CSF biomarkers were not done but plasma fibrinogen and d dimer were elevated. Two patients with Moderate AD and one patient with mild AD were reported as FTD. In two patients in whom FTD was reported, CSF profile was typical of Alzheimer's disease (Reduced CSF Aβ42, Increased Total tau and Tau/Aβ42 ratio). Among these two, one patients with had raised fibrinogen and d-dimer while other patient had normal values. The third patient with PET finding as FTD also had normal plasma fibrinogen and d dimer but CSF was not done. One patient with Moderate AD and two patients with vascular dementia were reported as mixed dementia. Of the two patients who were clinically diagnosed as vascular dementia, one patient had normal CSF biomarkers and raised fibrinogen and d-dimer. The other patient had raised fibrinogen and d dimer, while CSF was not done in this patient. The other patient with clinical diagnosis of Moderate AD had normal plasma fibrinogen and d dimer, but CSF was not done.

All those patients who were having Alzheimer type (AD and MCI-AD) and Vascular type (VaD and MCI-VaSC) based on FDG PET were assessed for CSF and plasma biomarkers. We found that CSF Aβ42 Amyloid, Total-tau and Tau/Amyloid ratio were significantly different among the two groups (Table 2). Hence CSF biomarkers and FDG PET were concordant in differentiating between Alzheimer and Vascular group. The plasma biomarkers fibrinogen and d dimer were significantly different in vascular group than Alzheimer group (Table 2).

Discussion

Molecular Imaging with FDG PET (Fluorodeoxyglucose Positron Emission Tomography) indirectly measures neuronal activity by assessing cerebral glucose metabolism. It is a downstream marker of neuronal injury in the amyloid cascade hypothesis of Alzheimer's disease (AD). FDG-PET studies have shown hypometabolism in temporoparietal and posterior cingulate cortices in Mild Cognitive Impairment (MCI) who progress rapidly to dementia especially AD.[1,2] In Alzheimer's disease, FDG-PET brain shows a specific topographic pattern of decreased glucose uptake in a lateral temporal-parietal and posterior cingulate, precuneus distribution.[4] In cognitively normal elderly individuals also, correlations are seen between decreased FDG-PET uptake and both low CSF Aβ and increased CSF tau.[5] Thus FDG-PET uptake is a valid indicator of the synaptic dysfunction associated with neurodegeneration in AD.

In Vascular Dementia (VaD), there is more diffuse pattern of hypometabolism not just involving the association cortex but also the primary cortices, basal ganglia, thalamus, and

cerebellum[3] with the frontal lobe and more particularly the anterior cingulate and superior prefrontal gyri predominantly hypometabolic. More than 90 per cent concordance have been reported between visual evaluation of FDG-PET scans and clinical diagnosis of the dementia type.[6]

We used automatic software programmed to do 3-D Stereotactic Surface Projection (SSP) to evaluate the areas of hypometabolism. However, this program was not used to quantify the severity of hypometabolism and calculating z score, due to lack of validation data on cut off values for our population. Statistical Parametrical Mapping (SPM) and SSP are computing methods which can add objective parameters to assessment of FDG brain PET studies[7-11] and are especially useful for the earlier disease stages when only subtle metabolic abnormalities may be present. In those cases where discordance was there, the PET findings were unlikely to change as the changes were significant and not subtle. Our objective was to find the utility of biomarkers in routine clinical practice during clinico-imaging discordance.

In our study we analysed the concordance of biomarkers with FDG PET Brain findings. CSF Aβ42 Amyloid, Total-tau and Tau/Amyloid ratio were significantly different among Alzheimer and Vascular group. Hence CSF biomarkers and FDG PET were concordant in differentiating between Alzheimer and Vascular group. The plasma biomarkers, plasma fibrinogen and d dimer were significantly different in vascular group than Alzheimer group.

The concordances of CSF biomarkers (CSF Aβ42 Amyloid, Total-tau and Tau/Amyloid ratio) with autopsy proven AD cases are already established. There have been conflicting reports on plasma fibrinogen and d dimer in case of vascular dementia. In our study since the sample size of vascular dementia was small, definitive conclusion cannot be made.
In most of the patients, clinical assessment and imaging (MRI and FDG PET) are concordant. But the role of biomarkers comes in discordant cases. In our study among patients with discordant PET findings, the clinical diagnosis was more likely. The two patients whose PET brain was reported as FTD had Alzheimer profile of CSF biomarkers and clinically also they were diagnosed as Mild AD. These two patients probably represented the frontal variant of AD. The one patient who was clinically diagnosed as Vascular dementia and PET reported as mixed dementia had normal CSF biomarker profile with raised fibrinogen and d-dimer which suggests that the predominant pathology is Vascular dementia.

The major limitation of our study was the lack of pathological confirmation of the diagnosis. But in routine clinical practice of dementias, biopsy is not used for confirmation of diagnosis especially if the suspected diagnosis is a degenerative dementia. But a pathological diagnosis would have bolstered our results.

Only biopsy can conclusively decide the definite diagnosis, but short of that the biomarkers can certainly help us in making a reliable diagnosis. Thus our study has shown the importance of a detailed clinical assessment including neuropsychological evaluation. Wherever discordance occurs, biomarkers can reliably help in achieving the diagnosis.

Conclusion

FDG PET brain findings were concordant with the CSF biomarkers (CSF Aβ42, Total tau and Tau/Aβ42 ratio) in Alzheimer's disease and Haemostatic biomarkers (Plasma Fibrinogen and D dimer) in vascular dementia. In clinical and molecular imaging discordance, biomarkers help in making a reliable diagnosis which favours the clinical assessment.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

Institute ethics committee, Postgraduate Institute of medical education and research.

Table 1: FDGPET Brain diagnosis in MCI, Alzheimer and Vascular Groups

PET	Diagnosis						Total
	MCI AD	MCI VaSC	MILD AD	MOD AD	SEV AD	VaD	
Normal	0	1	0	0	0	0	1
HLAD	4	0	4	16	9	0	33
ILAD	5	0	3	4	0	0	12
VAD	2	4	0	1	0	9	16
FTD	0	0	2	1	0	0	3
MD	0	0	0	1	0	2	3
Total	11	5	9	23	9	11	**68**

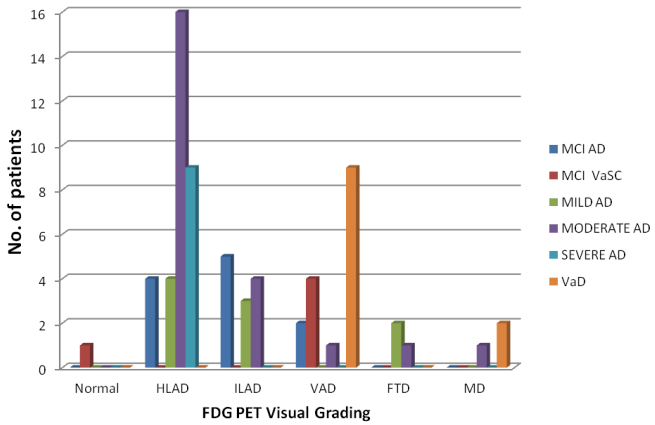
MCIAD- Mild Cognitive Impairment-Alzheimer disease type, MCI-VaSC- Mild Cognitive Impairment-Vascular dementia type, AD- Alzheimer's disease, VaD- Vascular Dementia, HLAD- High Likelihood of Alzheimer's disease, ILAD- Intermediate Likelihood of Alzheimer's disease, VAD- Vascular Dementia, FTD- Frontotemporal dementia, MD- Mixed dementia.

Table 2: Biomarkers in Alzheimer and Vascular Groups based on FDGPET diagnosis

Biomarker	Diagnosis based on FDG PET Brain		P value
	Alzheimer(N=45)	Vascular(N=16)	
$A\beta_{42}$ Amyloid No. (Median pg/ml)	29(296.12)	14(761.54)	0.000
Amyloid IQR	158.41-296.12	501.48-933.53	
Total Tau (No. of patients) (Median pg/ml)	29(298.84)	14(258.38)	0.000
Total Tau IQR	281.50-316.19	171.68-273.56	
Tau/Amyloid ratio (No. of patients) (Median)	29(0.93)	14(0.33)	0.000
Tau/Amyloid IQR	0.65-1.85	0.20-0.55	
Fibrinogen (No. of patients) (Median g/L)	45(3.5)	16(4.31)	0.000
Fibrinogen IQR	2.85-3.90	3.54-6.08	
Ddimer (No. of patients) (Median mg/L)	45 (0.40)	16(0.80)	0.004
Ddimer IQR	0.30-0.62	0.49-1.28	

AD- Alzheimer's disease, VaD- Vascular Dementia, IQR-Interquartile Range

Figure 1: Dementia diagnosis using FDG PET Brain



Supplemental Appendix Table e1: Baseline characteristics

	MCIAD	MCI VaSC	AD	VaD
No. of patients	11	5	41	11
Median age (yrs)	65	60	67	60
Inter-Quartile range	60-74	51.5-61.5	61.5-73.5	55-71
Male (No.)	9	4	24	10
Education (No. of patients) Illiterate	1	1	8	1
School (No. of patients)	5	3	27	9
College (No. of patients)	5	1	6	1
HTN (No. of patients)	8	4	10	10
DM (No. of patients)	4	1	8	5
CAD (No. of patients)	1	2	4	1
DYSLIPIDEMIA[a] (No. of patients)	2	4	4	8
Median duration of disease (months)	12	24	24	12
MMSE (Median)	25	25	18	17

Abbreviations: AD=Alzheimer' disease, CAD=coronary artery disease, DM=diabetes mellitus, HTN=hypertension, MCI AD=mild cognitive impairment- alzheimers disease, MCI VaSC=mild cognitive impairment- vascular, MMSE=mini mental state examination

[a]Diagnosed according to NCEP guidelines