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Cerebral blood flow and metabolic abnormalities in Alzheimer's disease

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In this review I summarize observations of PET and SPECT studies about cerebral blood flow and metabolic abnormalities in Alzheimer's disease. In very early AD flow or metabolism reduces first in the posterior cingulate gyrus and precuneus. This reduction may arise from functional deafferentation caused by primary neural degeneration in the remote area of the entorhinal cortex that is the first to be pathologically affected in AD. Then medial temporal structures and parietotemporal association cortex show flow or metabolic reduction as disease processes. The reason why flow or metabolism in medial temporal structures shows delay in starting to reduce in spite of the earliest pathological affection remains to be elucidated. It is likely that anterior cingulate gyrus is functionally involved, since attention is the first non-memory domain to be affected, before deficits in language and visuospatial functions. However few reports have described involvement in the anterior cingulate gyrus. Relationship between cerebral blood flow or metabolism and apolipoprotein E genotype has been investigated. Especially, the *APOE* ε4 allele has been reported to increase risk and to lower onset age as a function of the inherited dose of the ε4 allele. Reduction of flow or metabolism in the posterior cingulate gyrus and precuneus has been reported even in presymptomatic nondemented subjects who were cognitively normal and had at least a single ε4 allele. On the contrary the relation of ε4 allele to the progression rate of AD has been controversial from neuroimaging approaches. PET and SPECT imaging has become to be quite useful for assessing therapeutical effects of newly introduced treatment for AD. Recent investigations observed significant regional flow increase after donepezil hydrochloride treatment. Most of these observations have been made by applying computer assisted analysis of three-dimensional stereotactic surface projection or statistical parametric mapping instead of a conventional regions of interest technique.

Key words: Alzheimer's disease, SPECT, PET, regional cerebral blood flow, regional cerebral metabolic rate for glucose

INTRODUCTION

FOR ALMOST TWO DECADES, PET and SPECT have been used to investigate functional alteration of the brain in patients with Alzheimer's disease (AD). Recent advances of instruments enabled us to investigate functional alteration in fine structures of not only cortical but also subcortical areas with high spatial resolution. Moreover development of computer assisted analysis using three-dimensional stereotactic surface projection (3D-SSP)[1–3] or statistical parametric mapping (SPM)[4] afforded objective and more reliable assessment of functional abnormalities by means of stereotactic coordinates than visual interpretation of raw tomographic images. This stereotactic approach is voxel by voxel analysis in the stereotactic space to avoid subjectivity and to adopt the principle of data-driven analysis. Although alternative approach by a regions of interest (ROI) technique has gained general acceptance, it is limited by the fact that the selection of sample depends on the observer's *a priori* choice and hypothesis, and

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leaves large areas of the brain unexplored. Recent medications like cholinesterase inhibitors; e.g., tacrine hydrochloride, donepezil, and rivastigmine tartrate has turned out to be able to delay the progression of AD.[5] This fact makes present studies on AD go toward earlier diagnosis and longitudinal investigation to assess therapeutical effects. This review article summarizes cerebral blood flow and metabolic abnormalities in AD.

FUNCTIONALLY AFFECTED AREAS IN AD

Cerebral association cortex

Many researchers have demonstrated metabolic and blood flow reductions in the parieto-temporal association cortex.[6–21] This finding has been widely recognized as a diagnostic pattern for AD. Metabolic abnormality in parietal association cortex is the best discriminator of patients with probable AD from normal subjects.[22] The parieto-temporal involvement is bilateral, although asymmetry in the degree of flow or metabolic reduction is recognized.[7,12,13,20,23–25] While frontal association cortex is reduced in certain cases, often in advanced disease.[11,13,21,26] Several investigators have addressed longitudinal changes of functional alteration in AD.[13,27–30] It has been reported consistently that the posterior association cortex is the first cortical region to be affected in AD. This deficit then spreads to the frontal lobes as the disease progresses with persisting asymmetry.

Medial temporal areas

Most previous pathological and morphological studies suggest that structures within the medial temporal structures, amygdala, hippocampal formation, entorhinal cortex, and parahippocampal and fusiform gyri, are the first to be affected in AD with histological changes, including amyloid deposits and neurofibrillary changes.[31–37] This pattern is in keeping with the first neuropsychological deficit in AD being episodic memory loss.[38,39] The reduced rCBF in the medial temporal structures demonstrated by PET[40] or by a recent high-resolution SPECT system is consistent with these pathological findings.[41–43] Our longitudinal study[44] also observed significant flow reductions in the medial temporal area on the left side when the mean score of mini-mental state examination (MMSE) was 22.3. The possibility cannot be excluded that this decrease may be related to a partial volume effect from focal atrophy. However our cross-sectional study[45] on both anatomical and functional measurements in the same individuals using MRI and SPECT would explain that the rCBF reduction in the hippocampus is not solely due to a partial volume effect in AD. Early AD patients showed much less decline (12.4% on the average) in rCBF than that (22.2%) in volume in the hippocampus compared with normal control, while advanced AD patients showed almost equal decline in rCBF (25.9%) and in volume (29.3%). This much greater difference in rCBF than in volume between early and advanced AD patients would be attributed not to a mere partial volume effect but to disease process.

Our longitudinal study[44] did not observe significant decrease in hippocampal blood flow in very early AD patients with the MMSE score of above 24, either. In mild-to-moderate AD patients, Ishii et al.[46,47] demonstrated PET findings of significant reduction of oxygen metabolism in medial temporal structures without flow decrease. They suggested the presence of luxury perfusion in the medial temporal structures of AD patients. Elevation of lactate in experimentally injured hippocampi of rat[48] might support the presence of luxury perfusion. These results suggest the possibility that the lactic acidosis introduces the relative increase of rCBF in atrophic hippocampi in early AD patients.

Posterior cingulate gyrus and precuneus

In a very early stage of AD, even before clinical diagnosis of probable AD is possible, decrease of regional cerebral blood flow as well as glucose metabolism in the posterior cingulate gyrus and precuneus has been reported using PET[49,50] or SPECT.[44,51] 3D-SSP and SPM methods have made these observations. We could hardly distinguish slight decrease of flow or metabolism in this area in patients with early AD by visual inspection, since metabolic activity or flow in the posterior cingulate gyrus is as high as primary visual cortex in normal individuals at rest.[50] Reduced PET measures of glucose metabolism in AD remain even after accounting for partial volume effects; thus, it is more than just an artifact resulting from increased cerebral fluid space.[52]

The observation that metabolic reduction in this area predicts cognitive decline in presymptomatic persons indicates that the pathophysiologic process begins well before even mild or questionable dementia is recognized clinically.[53,54] PET measures of glucose hypometabolism reflect decreased synaptic activity due either to loss or dysfunction of synapses,[55] and regional metabolic deficits observed on PET may reflect projections from dysfunctional neurons in other brain lesions. In non-human primates, lesions of entorhinal cortex that is the first to be affected in AD[35] cause significant and long-lasting metabolic decline in a small set of remote brain regions, especially in the inferior parietal, posterior temporal, posterior cingulate and associative occipital cortices, and posterior hippocampal regions.[56] These results suggest that flow or metabolic reduction in the posterior cingulate gyrus and precuneus indicates the earliest functional changes in AD as a remote effect. According to our longitudinal SPECT study,[44] flow decrease in the posterior cingulate gyrus and precuneus became ambiguous as disease processed. This may be due to more stability of flow in this area than that of other cortical areas as disease process.

The area of the posterior cingulate gyrus and precuneus

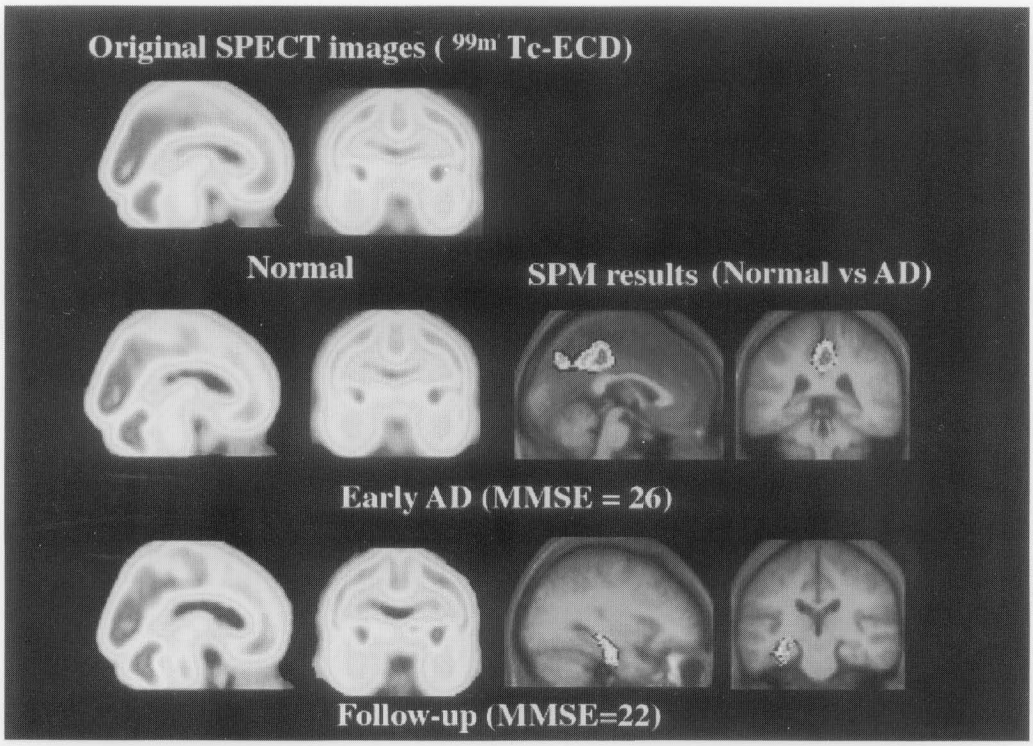

Fig. 1 Group comparison between patients with early Alzheimer's disease and age-matched normal subjects using statistical parametric mapping (SPM). At the baseline study when mini-mental state examination (MMSE) score was 26 on the average, SPM showed significant flow decrease in the posterior cingulate gyrus and precuneus in AD patients. At the follow-up study 15 months later when MMSE score was 22 on the average, significant flow decrease shifted to the left hippocampus and parahippocampal gyrus. It is difficult to detect regional flow decrease on original SPECT images by visual interpretation.

is known to be important in memory.[57] A PET study revealed activation of the retrosplenial area of the cingulate cortex during the episodic memory encoding task.[58] Clinical evidence of existence of brain tumor[59] or arteriovenous malformation[60] in the retrosplenial cingulate cortex supports the importance of this area in memory function. The retrosplenial cortex receives input from the subiculum and projects to the anterior thalamus, thus providing and alternative route between the hippocampus and thalamus. Medial temporal structures involved in memory receive anterior thalamic input directly via the cingulate bundle and indirectly through a relay in the retrosplenial cortex.[60] This thalamocortical portion of Papez' circuit[61] may be important in memory, and that lesions of the cingulum and retrosplenial cortex may cause memory dysfunction by disrupting this pathway.

The PET study also showed activation in the precuneus during the episodic memory retrieval task but not in the control or the semantic memory tasks.[57] Little is known concerning either the functions or connectivity of the precuneus. Anatomical evidence indicates prefrontal, temporal, occipital and thalamic connections to the precuneus.

Anterior cingulate gyrus

Current evidence suggests that after an initial amnesic stage in Alzheimer's disease, attention is the first non-memory domain to be affected, before deficits in language and visuospatial functions.[62] This is consistent with the possibility that difficulties with activities of daily living, which occur in even mildly demented patients, may be related to attentional deficits.

Following involvment of the medial temporal structures, neuropathological changes of neurofibrillary tangles spread to the basal forebrain and anterior cingulate before encroaching of the neocortical association areas.[33] Decreased rCBF in the anterior cingulate gyrus has been reported in subjects with questionable AD at baseline SPECT who converted to AD on follow-up.[51] Among AD patients it appears that divided attention is particularly vulnerable while sustained attention is relatively preserved in the early stage.[62,63] Divided attention activates the anterior cingulate gyrus though sustained attention does not.[64,65] This tendency may be peculiar to older adults comparing with younger adults.[66]

Functionally preserved areas in AD

The primary motor, sensory, and visual cortices are typi-

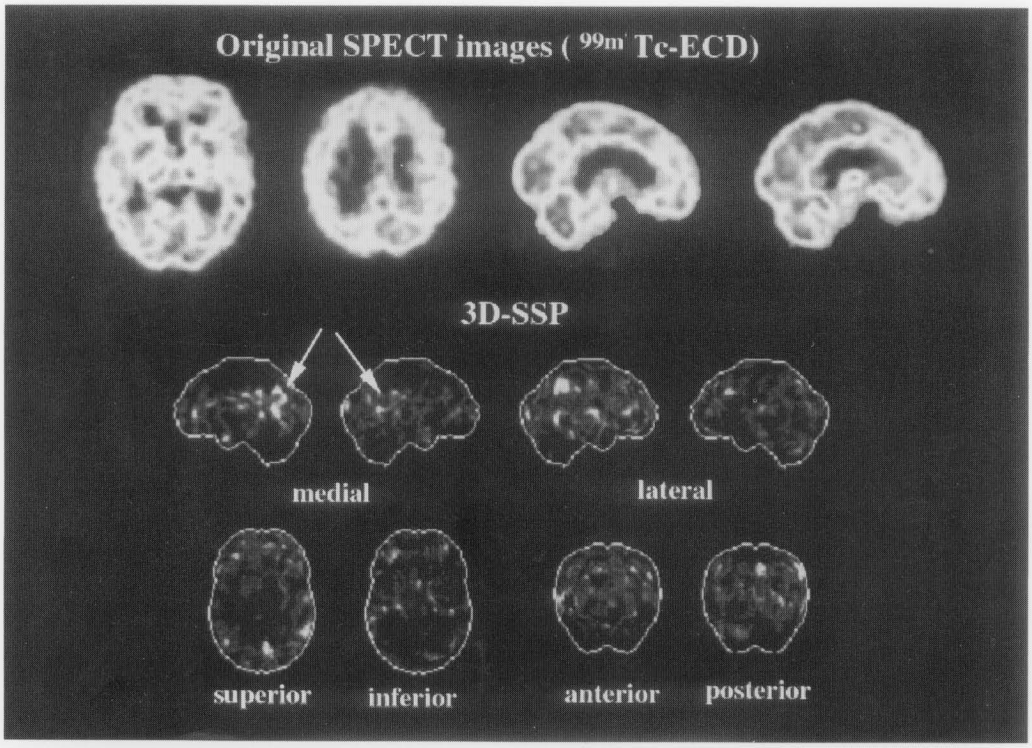

Fig. 2 Detection of significant flow decrease in the posterior cingulate gyrus and precuneus (arrows) in a patient with early Alzheimer's disease compared with normal database using three-dimensional stereotactic surface projection (3D-SSP) method. Visual interpretation of original SPECT images can not point out any flow decrease.

cally spared until the very severe stages of the disease, and the subcortical structures such as thalamus also remain relatively affected.[18,20,21,44,67] The stereotactic PET and SPECT analysis revealed the strong invulnerability of pons.[44,68] Cerebellar blood flow are relatively preserved in mild to moderate AD, but significantly reduced in advanced AD with distinct atrophy.[69]

Relationship between cerebral blood flow/metabolism and apolipoprotein E genotype

Apolipoprotein E (*APOE*) is located on the arm of human chromosome 19 within an apolipoprotein gene family and has 3 common alleles, designated $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$.[70] These genetic variations result in amino acid substitutions at positions 112 and 158 of the protein. Minor variations and different genotypes have a major effect on the risk and onset of AD.[71] Especially, the *APOE* $\varepsilon 4$ allele has been reported to increase risk and to lower onset age as a function of the inherited dose of the $\varepsilon 4$ allele.[71] These findings have been also confirmed in Japanese studies.[72] A lot of studies on *APOE* have given a sidelight on its function, neurofibrillary tangle formation, amyloid plaque deposition or clearance, cholesterol transport, oxidation, and so on.[73–75]

Reduction of flow or metabolism in the posterior cingulate gyri and precunei has been reported even in presymptomatic nondemented subjects who were cognitively normal and had at least a single $\varepsilon 4$ allele.[53,54,76] The relation of $\varepsilon 4$ allele to the progression rate of AD has been controversial from the standpoint of both neuropsychological and neuroimaging approaches. Lehtovirta et al.[30] reported a three-year longitudinal study in which the homozygous $\varepsilon 4$ allele patients with AD had lower cerebral perfusion at the baseline in the parietal and occipital cortices and at the follow-up in the temporal, parietal, and occipital cortices than patients with AD with one or no $\varepsilon 4$ alleles. This result agreed with the report that $\varepsilon 4$ homozygosity is associated with a faster rate of cognitive decline.[77] By contrast, many investigators suggested that the presence of the $\varepsilon 4$ allele does not affect clinical progression in AD patients.[78–80] Slooter et al.[80] reported no significant difference in cognitive function and severity of dementia for AD patients with and without $\varepsilon 4$ allele. Cross-sectional PET studies demonstrated no distinct patterns of cerebral metabolic rate for glucose (rCMRGlu) in AD patients as a function of genotype.[81,82] On the other hand, some investigators presented longer disease duration in $\varepsilon 4$ carriers than in non-carriers and suggested that $\varepsilon 4$ is associated with a less aggressive form of AD.[83–85]

In subjects in nondemented relatives at risk for AD, Small et al. found that carrying the $\varepsilon 4$ allele was associated with significantly lower parietal rCMRGlu and greater parietal asymmetry.[53] However, in patients with AD, van Dyck et al. found that the no-carrying the $\varepsilon 4$ allele

subjects had significantly greater rCMRGlu asymmetry in superior parietal and superior temporal regions.[84] They did not make reference to consistent difference in left and right sides. Asymmetry in rCMRGlu may take place in the medial temporal structures in relation to *APOE* genotype. MRI studies demonstrated that smaller hippocampal volumes in ε4 carriers than in non-carriers especially on the right side.[86,87]

Lehtovirta et al.[30,88] reported that the ε4 carriers showed more decrease in occipital rCBF in time-course changes than non-carriers. This phenomenon might be ascribed to the greater cholinergic depletion in the ε4 carriers reflecting an earlier hypoperfusion in the areas where cholinergic innervation is more sparse.[88] Presence of diffuse Lewy body might also have to do with this phenomenon. The ε4 allele is reported to be highly related to diffuse Lewy body disease[89] that shows hypometabolism in occipital lobes.[90]

Effects of cholinesterase inhibitor on cerebral blood flow/metabolism

Pharmacological, biochemical, and functional imaging observations implicate a cholinergic defect underlying many behavioral abnormalities in AD.[91] Donepezil hydrochloride is a piperidine-based acetylcholinesterase inhibitor that is clinically used for the symptomatic treatment of mild to moderate AD.[92,93] Donepezil has been shown to significantly improve cognition and to maintain global function compared with placebo, and also to be well tolerated.[93] The results of 24-week studies have indicated that the well-established benefits of donepezil on cognition may extend to improvement of the ability to perform complex activities of daily living.[92] Although donepezil has been approved in many countries for the treatment of patients with mild to moderate AD, its effect on cerebral blood flow or metabolism has not been fully investigated yet.

In a longitudinal study using ^{99m}Tc-HMPAO SPECT with SPM analysis, Warren et al.[94] found a significant flow increase in occipital lobes after donepezil treatment in a AD patient with visual form. The presence of lower lateral orbital frontal and dorsolateral frontal perfusion suggested good response to donepezil and was significantly related to behaviors of irritability, disinhibition, and eupholia.[95] Staff et al.[96] also observed the most significant increase in frontal lobes as well as overall slight increase in global cerebral blood flow after donepezil treatment in AD patients.

CONCLUSION

PET and SPECT imaging for the assessment of cerebral blood flow and metabolism will play still more important roles in diagnosing early AD, staging of AD, and assessing therapeutical indication and its effects. Recently developed tracers for a PET study[97–99] have directly measured inhibition of cholinesterase by donepezil treatment.[100] Development of a SPECT tracer for routine clinical use would expect this direct measurement.

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