IV. 5. Regional Glucose Hypometabolism in Brain of Patients with Dementia with Lewy Bodies and Alzheimer's disease

Okamura N., Arai H., Higuchi M., Tashiro M., Maruyama M., Matsui T., Hu X. S., Itoh M.* and Sasaki H.

Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine
Division of Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University*

Introduction

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder that is characterized by a progressive cognitive decline and the presence of numerous Lewy bodies (LB) in the cortical and subcortical brain regions. In 1996, the consortium on dementia with Lewy bodies (CDLB) proposed clinical and pathological criteria of DLB\(^1\). However, some groups indicated a relatively poor sensitivity of the CDLB criteria to accurately detect DLB\(^2\)\(^-\)\(^3\). It is clinically important to discriminate DLB patient from AD patients because the patients with DLB often exhibit life-threatening neuroleptic adverse effects\(^4\). Therefore, the objective diagnostic aid for the antemortem diagnosis of DLB is desperately needed. In this article, we report functional neuroimaging features of one autopsy-confirmed case of DLB. Furthermore, we describe the characteristic features of cerebral glucose metabolism in a larger sample of DLB.

Case Report

Patient had been well until 55 years old when depression developed with prominent headache, anxiety and loss of interest. At age 58, she became progressively disorientated and had memory deficits. She also developed difficulty with performing fine movements such as using chopsticks and buttoning her clothing. On neurological examination performed at age 59, she was emotionless and hypophonic, lost her facial expression, was slowed down and shuffled on walking with reduced arm swing. Cog-wheel rigidity was present at both wrists and elbows. Bilateral hand tremor was noted as well. She drew a clock poorly, and she scored 12 out of 30 on Mini-Mental State Examination (MMSE). Deep tendon reflexes were normally active. Brain CT and MRI revealed diffuse cortical atrophy, while 7-8 Hz slow background activity was noted on EEG. At age 60, PET scans were performed using \(^{[18}F\)2-fluoro-deoxy-D-glucose (FDG) and \(^{[18}F\)-6-fluorodopa (FDOPA). On FDG-PET images showing widespread cortical hypometabolism, the occipital metabolic deficit was
particularly noticeable. The glucose metabolic ratio in the visual association cortex (normalized by the radioactivity in cerebellar vermis) was 0.78, which was lower than an average value (1.02) in AD patients. FDOPA-PET image revealed low dopamine uptake rate of FDOPA, representing a reduction in the number of nigrostriatal dopaminergic neurons at the presynaptic sites. The rate of influx (K_i) in the striatum, calculated by the graphical analysis, was 0.0062 min⁻¹, that was lower than the average values in AD (0.0110) and aged normal subjects (0.0116). Levo-dopa with carbidopa produced a transient improvement in the motor features of parkinsonism, while cognitive impairment continued to deteriorate with a persistent visual hallucination and delusion that was unrelated to the levo-dopa therapy. At age 63, she became wheelchair bound and had a difficulty in verbal communication. At age 64, she was unable to feed herself because of progressive dysphasia, and died of aspiration pneumonia and congestive heart failure 9 years after the onset of the disease. Postmortem brain examination revealed numerous LBs and LB-neurites that were immunoreactive to anti-
α-synuclein and anti-ubiquitin antibodies as well as abundant senile plaques and neurofibrillary changes. Hence, final pathological diagnosis was made as "DLB plus AD". In addition to such well-documented hallmarks, there was an extensive spongiform change and gliosis throughout the white matter. The most extensive white matter change was observed in the occipital region. An extensive gliosis also was present in the white matter with relative sparing of the gray matter.

Subjects and methods

Eleven patients with probable AD, seven patients with probable DBL and ten age-matched normal subjects were examined. All of the patients and the normal subjects were evaluated by medical and neurological examinations as well as by MRI to exclude other causes of dementia. The diagnosis of "probable AD" was established by the NINCDS-ADRDA criteria. We followed CDLB criteria for the diagnosis of probable and definite DLB. Normal subjects were all volunteers without any confirmed neuropsychiatric or major medical illnesses. The severity of dementia was assessed by Mini-Mental State Examination (MMSE) was 18.8±3.3 points (range 12-24 points) in the AD group and 16.1±7.1 points (range 6-24 points) in the DLB group.

Measurement of cerebral glucose metabolism with PET and FDG was performed using a PET scanner (SET2400W, Shimadzu Inc., Japan). Subjects were scanned in a quiet and dimly-lit room with their eyes open after at least 4 hours of food restriction. Following a ⁶⁸Ge/Ga transmission scan of 7 min duration, an emission scan was performed which lasted 60 min after intravenous injection of FDG. Arterial blood was sampled from the radial artery during the scan, and an input function was obtained by measuring plasma radioactivity. The cerebral metabolic rate of glucose (CMRglu) was calculated using the autoradiographic method by Hutchins et al.
Volume of interest (VOI) with an area of 1 cm² was drawn on individual MR images that were matched to the PET images by a linear spatial transformation. Multiple VOIs were placed to cover the whole target anatomical structure, and were transferred to the PET images. CMRglu was then calculated for cortical and subcortical structures. The whole brain CMRglu was defined as an average over both gray and white matter structures. Among many brain structures included in the VOI analysis, the absolute glucose metabolism in the cerebellar vermis was most preserved in AD and DLB. Therefore, normalized CMRglu values or metabolic ratios were calculated using the cerebellar vermis as a reference region. The metabolic ratio was estimated in VOIs including the lateral frontal cortex (Brodmann’s area [BA] 8, 9, 10, 44, 45, 46 and 47), lateral temporal cortex (BA 21, 22, 37 and 38), medial temporal cortex (BA27, 28, 34 and 35), lateral parietal cortex (BA39 and 40), posterior parietal cortex (BA 5 and 7), anterior (BA 24 and 32) and posterior (BA 23 and 31) cingulate cortices, and primary (BA 17) and association (BA 18 and 19) visual cortices. Averaged values of right and left hemispheric VOIs were used for statistical analysis. Statistical analysis was performed by analysis of variance (ANOVA).

Results

Absolute CMRglu values in the whole brain of each group were as follows; the AD group: 3.66±1.26 mg/100g/min, the DLB group: 3.59±0.54 mg/100g/min, and the aged normal group: 7.52±1.20 mg/100g/min. Statistically, the whole brain CMRglu was significantly lower (p<0.0001) in the AD and DLB groups compared to that in the normal group. The results demonstrate a significant difference in the metabolic ratio between the AD and normal group in the posterior parietal cortex (p<0.0001), the posterior cingulate cortex (p<0.0001), the lateral parietal cortex (p<0.001) and the medial and lateral temporal cortices (p<0.01). The metabolic ratio was relatively preserved in the frontal and occipital cortices. When comparing metabolic ratios between the DLB and normal groups, the metabolic decline in the DLB group was evident virtually throughout the entire cortical region extending from the frontal to occipital cortex. Notably, the reduction in the metabolic ratio in the DLB group compared to the AD group was most pronounced in the visual association cortex (Figure 1) (For further details, see Ref 5).

Discussion

Our results indicated that occipital hypometabolism is the feature of DLB that discriminate it from AD. Previous functional imaging studies in DLB showed a characteristic pattern of regional glucose hypometabolism and hypoperfusion in the primary visual cortex and occipital association cortex in addition to the patterns of abnormal metabolism found in AD⁸⁻⁹. Our results are comparable to the finding of these previous reports. In our study population using a metabolic ratio of 0.92 in the visual association
cortex as a cut-off, DLB could be distinguished from AD with a sensitivity of 86% and a specificity of 91%\(^3\). Therefore, these findings suggest that PET measures of glucose metabolism may help in enhancing the clinical diagnosis of DLB particularly in the early stages of the disease. In our examination, the patient described in the case report showed the lowest value of metabolic ratio in the visual association cortex among DLB patients. In addition, there was a severe spongiform change and gliosis mainly in the occipital cortex at postmortem examination in this patient. These findings suggest a possibility that the white matter spongiform pathology is likely to be a pathological substrate for a characteristic pattern of glucose hypometabolism in DLB, although there is only limited information in the pathological basis of the spongiform change.

References


Fig. 1 Glucose metabolic ratio in the visual association cortex in dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and age-matched normal control (Aged Normal). An arrow indicates the metabolic ratio of the autopsy confirmed case with DLB.