【著者】
| 著者   | 重信 克浩、上田 正敏、戸井 佳、山口 修、松井 詠、金村 孝、山田 俊三 |

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IV. 9. Decreased Cerebral Glucose Metabolism Associated with Mental Deterioration in Dementia of the Vascular Type

Meguro K., Ueda M., Doi C.*, Yamaguchi T., Matsui H., Kinomura S. and Yamada K.*

Department of Radiology and Nuclear Medicine, Research Institute for Tuberculosis and Cancer, Tohoku University
Department of Psychology, School of Literature, Tohoku University*

Summary

Cerebral glucose metabolism of twelve patients with senile dementia of the vascular type (VD) and six age-matched normal subjects was examined with Positron Emission Tomography. VD patients had significantly lower glucose metabolism than normal subjects in all the grey matter regions measured, and the former were also characterized by more individuality in metabolic pattern. Five age-matched pre-dementia were added to the twelve dementia patients and these seventeen patients were examined for intelligence quotient (IQ). A positive correlation between IQ and glucose metabolism was found, not only for the entire grey matter but also for brain regions such as the bilateral anterior frontal regions, the temporal regions, the temporo-parieto-occipital regions and the cerebellum.

Key words: Senile dementia - Vascular dementia - Intelligence quotient - Glucose metabolism - Positron emission tomography

Introduction

Senile dementia is a clinical syndrome which is caused by various diseases, senile dementia of the Alzheimer type (SDAT) and the vascular type (VD) being typical.1) Positron Emission Tomography (PET) and the F-18 deoxyglucose (FDG) method have been used to investigate glucose metabolism of brains of SDAT patients.2-6) The following findings have been noted: glucose metabolism in the bilateral temporo-parieto-occipital regions decreases;7-9) decreased glucose metabolism in the right hemisphere and left hemisphere are associated with deteriorated visuo-spatial and verbal function as shown by Wechsler Adult Intelligence Scale (WAIS), respectively.10-13)
However, studies on VD are surprisingly few,\textsuperscript{14}) probably because, unlike Japanese, Westerners suffer more from SDAT than from VD.

Therefore, we studied the glucose metabolism of the brain of VD patients using the FDG method and PET and investigated the relationship between glucose metabolism and intelligence.

**Subjects and Methods-1**

1. Subjects

First, 6 normal aged people and 12 VD patients were studied. Regarding the normal group, which consisted of 4 males and 2 females, ages ranged from 68 to 79 with a mean age of 71. As to the VD group, which consisted of 7 males and 5 females, ages ranged from 67 to 81 with a mean age of 73. Regarding mean age, no statistical difference was noted.

The 6 normal aged people had no mental deterioration or cognitive impairment based on clinical observation and had no history of stroke. Results of standard neurological examinations and X-ray CT were normal. The other 12 patients were diagnosed as VD based on DSM-III-R (American Psychiatric Association, 1987), clinical course, Hachinski\textsuperscript{15}) and Rosen\textsuperscript{16}) ischemic scores and X-ray CT findings. They were hospitalized because of mental deterioration and decreased daily activity. All were within three years of onset and showed moderate severity of dementia. Eight patients had a history of stroke within 3 years prior to onset, and 6 of them suffered slight hemiparesis. X-ray CT of all the patients showed lacunar infarctions, and revealed limited low density areas in the cortices of 2 patients. The clinical characteristics of the subjects are shown in Table 1. Informed consent was received from normal aged people and from the families of dementia patients.

2. Measurement of cerebral metabolic rate for glucose
(CMRGluc.)

The FDG technique was used to measure cerebral glucose metabolism. Calculation was performed without transmission scan\textsuperscript{17,18}) because such patients cannot tolerate lengthy examination. Two scans were done 40 to 60 min. after 2 to 6 mCi FDG injection. One scan consisted of 7 slices, each slice being 7 mm in thickness. One scan was done 30 mm above the orbitomeatal line(OM+30 mm) and the other, OM+77 mm. The type of tomography used was PT931-04 (CTI inc. U.S.A.), which has a resolution of 7 and 8 mm (FWHM) in the trans-axial and axial planes, respectively.
The subjects were positioned spine on the scanner bed with their eyes converted with patches. A Japanese popular music was played to stimulate the subjects. Head movements were monitored using a video sensor with an alarm system and corrected manually.

Regional values of CMRGluc. were obtained from the printout of matrix data. To avoid subjective region of interest (ROI) selection, the printout data of OM+50, +60, +70 mm were divided into 12 pie-shaped sections. A 2.9 cm² ROI in each section was chosen which contained the maximum value. Therefore, these regions corresponded to those of the grey matter. Also, ROIs of the white matter and the Wernicke area were chosen anatomically using X-ray CT film and PET images. Brain regions measured are shown in Figure 1. The average value of the entire grey matter CMRGluc. was calculated and corrected by brain atrophy. The values were divided by brain volume index, showing the volume percentage of the brain to that of cranial cavity.¹⁹,²⁰

Statistical analyses were performed using dual scaling and Student's t test: the former was used to find the relationship between the patterns of regional CMRGluc. and dementia; the latter was performed to detect the difference between average CMRGluc. of dementia and that of normal aged people.

Subjects and methods -2

1. Subjects

Secondly, 5 patients with pre-dementia were added to the original group of 12 dementia patients, and these 17 patients were studied. Pre-dementia was indicated by clinical observations and information from family members. Such patients were characterized by slight disorientation as to time and space, as well as slight cognitive impairment. However, they did not meet the criteria of dementia by DSM-III-R and hospitalization was not deemed necessary. Of these 5 patients, there were 2 males and 3 females (age-matched) with ages ranging from 67 to 79, the mean age being 72.

2. Measurement of glucose metabolism and intelligence quotient (IQ)

The CMRGluc. of these patients was examined by the same method described above. Intelligence quotients (IQ) of the 17 patients were evaluated by a battery of neuropsychological tests, namely, the WAIS and the Tanaka-Bienet Test. The WAIS used was a simplified version designed for the elderly including performance and verbal subtests. Tanaka-Binet Test is a modified version for Japanese from the original Binet-Simon Test²¹, being a method by which mental age is evaluated and IQ was calculated from the ratio of mental age to chronological age.
Results

1. Dual scaling of regional CMRGluC. of 12 VD patients and 6 normal subjects is noted in Figure 2. Closed circles and open circles indicated VD patients and normal subjects, respectively, and triangles represent brain regions. In this figure, the closer the symbols, the closer the relationship (i.e., subject to subject, subject to brain region, and brain region to brain region relationships.) Figure 2 shows that there was a range of individual differences among the dementia patients, from the subject who had a close relationship with the left temporal region and basal ganglia to the subject who showed a close correlation with the bilateral frontal regions, inferior temporal regions and the cerebellum.

2. Regional CMRGluC. values of the normal subjects are shown in Table 2 and Figure 3. High values are noted in the upper frontal regions, anterior frontal regions, parietal regions, primary auditory regions and visual regions. Regional CMRGluC. values of the VD patients are noted in Table 2 and Figure 4. Compared with those of the normal subjects, all the average values of the entire grey matter CMRGluC. and the IQ measured by the Tanaka-Binet Test (Figure 5). The IQ as shown by WAIS was not evaluated because the scores of most of the patients fell below the limit of the test. As far as the regional CMRGluC. values were concerned, positive correlations were noted bilaterally for the anterior frontal regions, temporal regions, temporo-parieto-occipital regions and the cerebellum (Figure 6).

Discussion

As far as methodology was concerned, we used the calculation method without transmission scan for measuring glucose metabolism\(^{17,18}\) because dementia patients cannot tolerate lengthy examination. The reason why the CMRGluC. of the subjects was studied not in resting state but in auditory activated states was that the psychologically activated studies had been found to be result in reduced intraindividual variability.\(^{22}\)

We found that there was an individuality of CMRGluC. in VD patients: some patients showed decreased CMRGluC. in the temporo-parieto-occipital regions (Figure 8) compared with those of normal subjects (Figure 7); others also had decreases in the frontal regions (Figure 9). Previous studies on SDAT have shown a more marked and sharp bilateral decrease in the temporo-parieto-occipital regions and/or the frontal lobes.\(^{23,24}\) Our study on SDAT patients also indicated the same tendency (data not shown), although the decrease in VD patients was not so sharp. This was probably because the brain of VD patients had several to multiple infarcted areas causing to more complicated and heterogeneous glucose metabolism. However, we felt that the bilateral temporo-parieto-occipital regions and the frontal lobes were important not only in SDAT patients but also VD patients.
As for mental function, the WAIS, which is commonly used to evaluate the mental function of dementia patients, could not be used to quantitate the cognitive function in these patients, and thus, the IQ's of most patients were not evaluated. WAIS scores did not show a significant correlation with glucose metabolism. This lack of correlation was true not only with the total scores for whole brain metabolism, but also with the verbal subscores for the left hemisphere and with the performance subscores for the right hemisphere. However, we were able to evaluate the mental function of the patients with the Tanaka-Binet Test, which measured IQ as the ratio of mental age to chronological age. There was a significant correlation between IQ and glucose metabolism, not only the entire grey matter CMRGluc, but also regional CMRGluc, bilaterally in the anterior frontal regions, the temporal regions, the tempo-parieto-occipital regions and the cerebellum.

We postulate two explanations for the phenomena, i.e., the focal theory and the global theory. According to the former, the brain regions such as the anterior frontal regions or the tempo-parieto-occipital regions are considered to be critical for the mental function in VD patients as well as in the onset of dementia. According to the latter, metabolism of the entire grey matter is important probably because the brain of VD patients has a compensatory mechanism under conditions of multiple infarctions which cause glucose metabolism heterogeneity and results in great individuality. That the anterior frontal regions, the temporal regions, the tempo-parieto-occipital regions were correlated with IQ is explainable by the local theory; the results for the cerebellum might be explainable by the global theory. Nevertheless, the relatively small size of the sample in this study needs to be substantially expanded before either theory can be considered definitive, or both theories can be said to be true. And also, the intercorrelation of regional CMRGluc., which was noted in SDAT patients,

Acknowledgement

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References

8) Friedland RP., Budinger TF., Koss E et al., Neurosci. lett. 64 (1985) 235.
21) Termann LM., An explanation and a complete guide for the use of the standard revision and extension of the Binet-Simon scale.
Table 1. Clinical characteristics of the study population: VD patients and normal subjects as outlined in Subjects and Methods-1, and VD patients and pre-dementia patients as outlined in Subjects and method-2.

<table>
<thead>
<tr>
<th>Subjects</th>
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<tr>
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<td>Sex</td>
</tr>
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<td>M</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>M</td>
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<td>3</td>
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<td>F</td>
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<td>5</td>
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Dementia patients

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<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Sex</th>
<th>IQ (Tanaka-Binet)</th>
<th>Onset</th>
<th>Stroke</th>
<th>CT findings</th>
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<td>81</td>
<td>F</td>
<td>33</td>
<td>2y</td>
<td>2y</td>
<td>lacunar+MCA infarction</td>
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<tr>
<td>5</td>
<td>71</td>
<td>F</td>
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<td>1y</td>
<td>1y</td>
<td>lacunar+MCA infarction</td>
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<tr>
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<tr>
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<td>F</td>
<td>24</td>
<td>3y</td>
<td>No</td>
<td>lacunar</td>
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</table>

Onset: 1y(year) and stroke: 2y (years) of dementia patient (#6) indicate that he had a stroke 2 years ago and have demented for 1 years.
MCA: middle cerebral artery.
Table 2. Regional CMRGluc. values of 6 normal subjects and 12 VD patients
All the regions except for the white matter of VD patients showed significantly lower values compared with those of normal subjects (p<0.01).
CMRGluc. = Cerebral Metabolic Rate for Glucose

<table>
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<tr>
<th>Brain regions</th>
<th>Normal subjects (N=6)</th>
<th>Dementia patients (N=12)</th>
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<tr>
<td></td>
<td>CMRGluc. (mg/100ml/min) (mean ± S.D.)</td>
<td>CMRGluc. (mg/100ml/min) (mean ± S.D.)</td>
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<tr>
<td>UFF (R)</td>
<td>6.18±1.38</td>
<td>9.61±1.93</td>
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<td>(L)</td>
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<td>9.07±1.73</td>
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<td>AF (R)</td>
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<td>4.78±1.48</td>
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<td>IF (R)</td>
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<td>7.05±1.56</td>
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<tr>
<td>(L)</td>
<td>4.62±1.37</td>
<td>7.16±1.52</td>
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<td>P (R)</td>
<td>5.27±1.25</td>
<td>9.28±1.76</td>
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<td>(L)</td>
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<td>H (R)</td>
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<td>9.94±1.73</td>
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<td>9.32±1.42</td>
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<tr>
<td>W</td>
<td>5.20±1.14</td>
<td>8.42±0.64</td>
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<td>TPO (R)</td>
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<tr>
<td>(L)</td>
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<td>BG (R)</td>
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<td>CE (R)</td>
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<td>FO (R)</td>
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<td>ABG</td>
<td>4.50±0.98</td>
<td>7.57±1.07</td>
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</table>

UFF : upper frontal  IT : inferior temporal
AF : anterior frontal  O : occipital
IF : inferior frontal  V : visual
P : parietal  BG: basal ganglia
H : heschl  CE: cerebellum
         (primary auditory)
W : Wernicke
FO : formen centrum semiovale (white matter)
TPO : temporo-parieto-occipital
Fig. 1. Brain regions measured in this study

Fig. 2. Dual scaling of regional CMRGluc. of 12 VD patients and age-matched normal subjects. Closed circles and open circles indicate VD patients and normal subjects, respectively, and triangles represent brain regions. The closer the symbols, the closer the relationship (i.e., subject to subject, subject to brain region, and brain region to brain region relationships.)

CMRGluc. = Cerebral Metabolic Rate for Glucose
UPF: upper frontal IT: inferior temporal
AF: anterior frontal O: occipital
IF: inferior frontal V: visual
P: parietal BG: basal ganglia
H: Heschl CE: cerebellum
W: Wernicke FO: foramen centrum semiovale
TPO: temporo-parieto-occipital

○ Normal
● Vascular Dementia
△ Brain Region (R:Right, L:Left)
Fig. 3. Regional CMRGluc. of the normal subjects
From left to right brain regions are represented as follows:
the right upper frontal region, the left upper frontal region,
the right anterior frontal region, the left anterior frontal region,
and so on. Mean values of regional CMRGluc. are figured.
CMRGluc. = Cerebral Metabolic Rate for Glucose
UFF : upper frontal    IT : inferior temporal
AF : anterior frontal  O : occipital
IF : inferior frontal  V : visual
P : parietal          BG: basal ganglia
H : heschl            CE: cerebellum
       (primary auditory)
W : Wemicke
FO : foramen centrum semiovale (white matter)
TPO : temporo-parieto-occipital

Fig. 4. Regional CMRGluc. of the VD patients
From left to right, the right upper frontal region,
the left upper frontal region, the right anterior frontal
region, the left anterior frontal region, and so on.
Mean values of regional CMRGluc. are figured.
CMRGluc. = Cerebral Metabolic Rate for Glucose
Fig. 5. Relationship between the entire grey matter CMRGluc. and IQ
A positive correlation between the average values of the entire grey matter CMRGluc. and the IQ measured by Tanaka-Binet Test.

Fig. 6. Correlation coefficients between regional CMRGluc. and IQ
Positive correlations were noted between the IQ and the regional CMRGluc. in the bilateral anterior frontal regions, the temporal regions, the temporo-parieto-occipital regions and the cerebellum. Double underlining of correlation coefficients of regions indicates significance. IQ were measured by the Tanaka-Binet Test.
Fig. 7. PET images of a normal subject.

Fig. 8. PET images of a VD patient showing decreased CMRGlu. in bilateral temporo-parieto-occipital regions.
Fig. 9. PET images of a VD patient showing decreased CMRGluc. in the frontal regions.