福岡大医紀（*Med. Bull. Fukuoka Univ.*）：36(4), 215–222, 2009

Longitudinal Morphometric MRI Study of Alzheimer's Disease

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Abstract：A longitudinal morphometric MRI study of Alzheimer's disease (AD) was conducted to determine the relationship between the progression of the symptoms and the progression of the brain atrophy. The Voxel-based Specific Regional Analysis System for Alzheimer's Disease (VSRAD), developed by Matsuda et al. was used as a method of morphometry to perform the statistical MR image analysis. Thirty-eight patients of AD patients were investigated with VSRAD. These patients were divided into two groups according to the progression of symptoms based on a clinical evaluation. One group was the progress group (20 patients), while the other group was the stable group (18 patients) for comparison. The relationship was investigated between the speed of the symptomatic progression and the change in each VSRAD indicator. Consequently, the entorhinal Z-score and the entorhinal atrophy rate showed a correlation with the speed of the symptomatic progression. The increase of the entorhinal Z-score in the follow-up was larger in the progress group than that in the stable group (0.65/1.28 years in the progress group and 0.05/1.26 years in the stable group.). These results suggest that a rapid symptomatic progression in an AD patient accompanies the rapid progression of atrophy in the entorhinal cortex.

Key words：**Alzheimer's Disease, MRI, Morphometry, Entorhinal cortex, Parahippocampal Gyrus**

Introduction

Alzheimer's disease (AD) is a disease in which dementia is caused by Alzheimer-type pathology that leads to diffuse cerebral atrophy. The pathological change begins in the medial temporal lobe, especially from the entorhinal cortex, which is a part of the parahippocampal gyrus.[1] Matsuda and others[2)3)] demonstrated that the entorhinal cortex is the part where atrophy starts in the early stage of AD, using a statistical image analysis with voxel-based morphometry of MRI. In addition, a computer software program was developed which automatically measures the volume of the entorhinal cortex of patients with AD and compares it with that of healthy control subjects.[4)5)] In this software program, the deviation from the average of the healthy control subjects is shown as a Z-score based on the standard deviation.

This software program, known as the Voxel-based Specific Regional Analysis System for Alzheimer disease (VSRAD), has become popular in Japan and it is now often used in the early diagnosis of AD.

It is common to perform MRI examinations regu-

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larly (every year) during the clinical follow-up of AD. However, at an interval of around one year, it is difficult to find a change indicating progression of atrophy by visual inspection. This study measured the change of Z-score was measured more than twice with VSRAD at intervals and the relationship between the change of VSRAD indicators and the symptomatic progression was evaluated. A longitudinal study of AD was conducted with VSRAD to examine the actual relationship between the progression of atrophy in the entorhinal cortex and the symptomatic progression of AD. The clinical usefulness of VSRAD in the clinical follow-up of AD is discussed based on these results.

Subjects and Methods

This study retrospectively investigated those patients diagnosed to have AD whose brains were examined by MRI more than twice among those examined at the Department of Psychiatry at Fukuoka University Hospital from December 2004 to April 2008. The clinical diagnosis was done according to the diagnostic criteria of probable AD by NINCDS-ADRDA.[6] The study protocol was approved by the Independent Ethics Committee/Institution Review Board of Fukuoka University Hospital.

MR images were obtained with a 1.5-T Achieva Nova Dual and a 1.0-T Gyroscan NT Intera MR imager (Philips Medical Systems, Best, the Netherlands). Three dimensional (3D) volumetric T1-weighted sagittal acquisition was used for the analysis in all of the patients.

A T1-weighted field echo sequence at 25/5/30/1 (TR/TE/flip angle/excitation) was obtained on the 1.5-T system and a 3D turbo-field echo sequence at 11/5/25/800/1 (TR/TE/flip angle/TI/excitation) was performed on the 1.0-T system. Two hundred and forty overcontiguous slices with 0.75 mm thickness were acquired for both 3D sequences with a sagittal orientation and 256×256 matrix over a 240×240 mm field of view, covering the entire brain. The images of the subjects' brains were taken by either of these two types of machines.

The 3D images were inspected by radiologists, which were used for the VSRAD analysis. The patients with images with artifacts, including body motions, were excluded from the study. The patients with an apparent cerebral infarction with a diameter more than 10 mm were also excluded. In addition, the images were verified in the stage of the gray matter separation in VSRAD analysis, to exclude any patients with a separation error. A statistical image analysis for each subject was performed by VSRAD. The following four indicators including the Z-score were calculated.

1. The Z-score (entorhinal Z-score : the degree (severity) of atrophy in the entorhinal cortex, the average value of the Z-score in the voxels in which the Z-score is a positive (plus) value)
2. The ratio of the atrophy area in the whole brain (% ; whole brain atrophy rate : The ratio of the voxels which exceeds Z-score 2.0)
3. The ratio of the atrophy area in the entorhinal cortex (% ; entorhinal atrophy rate : The ratio of the voxels that exceeds the Z-score 2.0.)
4. The ratio of entorhinal atrophy rate to whole brain atrophy rate (entorhinal/whole brain atrophy ratio ; The atrophy in the whole brain is qualified as 1.)

In addition, the change of each VSRAD indicator between at the initial examination and the follow-up was calculated.

Next, the subjects were divided into two groups by the clinical evaluation according to the 7 grade score used in Clinician's Interview-Based Impression of Change plus-Japan (CIBIC plus-J),[7] in which the clinical impression of change is scored as very much improved, much improved, minimally improved, no change, minimal worsening, moderate worsening or marked worsening. One group included the patients who were scored as minimal worsening, moderate worsening or marked worsening (the progress group). The other group included the patients who were scored as very much improved, much improved, minimally improved or no change (the stable group). The clinical evaluation includes the Mini-Mental State Examination (MMSE)[8] and Clinical Dementia Rating (CDR).[9] However, a comprehensive evaluation was conducted by the primary physician, who was a psychiatrist, to judge whether each patient had symptomatically progressed or stable. All pa-

tients were followed up and evaluated by the one primary physician. The physician evaluated the change of the social adaptability and the problem solving ability of a patient, based on the information obtained from each patient's family members for the comprehensive final evaluation. In other words, if the primary physician evaluated a patient's symptom to be worsening in his comprehensive evaluation, the patient was included in the progress group even if the MMSE and CDR scores did not show worsening. A comparison was made between the four indicators in VSRAD at the first examination (the initial examination) and the second examination (after the follow-up), as well as a comparison between the two groups. The SPSS-16.0J software package for Windows was used for the statistical analysis. Two tailed paired *t*-test was used to compare the VSRAD indicators before the follow-up with those after the follow-up in each two group, while the two tailed non-paired *t*-test was used to compare the indicators between the two groups. These two tests determined whether there was any significant difference between the groups.

Results

1 The comparison of the VSRAD indicators between before and after the follow-up in the total study population

The subjects included 38 patients who met the diagnostic criteria of probable AD based on NINCDR-ADRDA (14 cases of male and 24 cases of female patients). The follow-up period was 1.27±0.44 years on average.

The average age at the initial examination (± the standard deviation) was 73.84±9.18 (minimum 54 to m maximum 86) years old. The average score of MMSE (±the standard deviation) was 21.87±4.73 (minimum 12 to maximum 30). The CDR score showed that 33 cases had CDR1 and 5 cases had CDR2. Twenty-nine patients were treated with Donepezil, and 9 were treated without Donepezil.

The average score of the MMSE after the follow-up was 20.08±6.12 (minimum 4 to maximum 29). Thirty-three cases had CDR1 and 5 cases had CDR2. Statistically, the average score of MMSE fell significantly after the follow-up. There was no change between before and after the follow-up in the CDR score.

Intera Achieva 1.5 Tesla by Philips Electronics was used 26 times for the MRI machine examination (at the initial examination:10 times, after the follow-up : 16 times) and Gyroscan NT Intera 1.0 Tesla was used 50 times(at the initial examination: 28 times, after the follow-up : 22 times).

Table 1 shows the changes of each VSRAD indicator between before and after the follow-up for all subjects. Consequently, the entorhinal Z-score increased after the follow-up. The ratio of the atrophy area in the whole brain (whole brain atrophy rate)and the ratio of the atrophy area in the entorhinal cortex (entorhinal atrophy rate) also increased after the follow-up. Regarding the ratio of entorhinal atrophy rate to whole brain atrophy rate (entorhinal/whole brain atrophy ratio), no significant change was found between the findings obtained before and after the follow-up.

2 The comparison of the VSRAD indicators between the progress and the stable group

A progression of the symptoms was recognized in the cases of 20 patients out of 38, and these were

Table 1 The comparison of the VSRAD indicators between before and after the follow-up in the whole subjects

	at the initial examination	after the follow-up	p value
entorhinal Z-score	2.10±1.38	2.46±1.58	0.001**
whole brain atrophy rate (%)	7.65±4.12	9.25±5.04	0.015*
entorhinal atrophy rate (%)	43.11±33.40	51.43±35.51	0.005*
entorhinal/whole brain atrophy ratio	5.84±4.85	6.60±6.50	0.377 n.s.

Data are the mean±SD
* : $p<0.05$
** : $p<0.005$

defined as the progress group. The remaining 18 cases with the stable symptoms were defined as the stable group. Table 2 shows the comparison of age, sex, follow-up period, MMSE score and CDR score between the two groups.

The average age was 71.50±9.43 in the progress group (20 cases), with 8 male and 12 female cases. The follow-up period was 1.28±0.45 years. Fifteen patients were treated with Donepezil, and 5 were treated without Donepezil. The MMSE score was 21.30±5.07 at the initial examination, and 17.20±6.50 after the follow-up. Sixteen patients showed CDR1, while 4 patients showed CDR2 at the initial examination as well as after the follow-up.

The average age in the stable group was 76.44±8.38 years with 6 male and 12 female patients. The follow-up period was 1.26±0.44 years. As for the treatment, 14 patients were treated with Donepezil, and 4 patients were treated without Donepezil. The MMSE score was 22.50±4.40 at the initial examination, and 23.27±3.71 after the follow-up. Seventeen patients showed CDR1, while 1 patient showed CDR2 at the initial examination as well as after the follow-up.

The mean age was about 5 years younger in the progress group than in the stable group. Statistically, however, there was no significant difference in the average age between the two groups ($p=0.098$). No statistically significant difference was recognized between the two groups with regard to the sex, the follow-up period, treatment (with Donepezil or not), the MMSE score and the CDR score at the initial examination. A significant difference was observed in the MMSE score after the follow-up between the two groups.

Table 2 The comparison between the two groups; the progress and the stable group: the comparison of age, sex, follow-up period, MMSE score and CDR score

	the progress group	the stable group
age at the initial examination (years old)	71.5±9.4	76.4±8.4
men : women	8 : 12	6 : 12
follow-up period (years)	1.28±0.45	1.26±0.44
MMSE score at the initial examination	21.3±5.1	22.5±4.4
MMSE score after the follow-up	17.2±6.5	23.3±3.7**
CDR score at the initial examination	16 : 4[a]	17 : 1[a]
CDR score after the follow-up	16 : 4[a]	17 : 1[a]
Treatment	15 : 5[b]	14 : 4[b]

Data are the mean±SD
[a] : number of patients with CDR1 : number of patients with CDR2
[b] : number of patients treated with Donepezil : number of patients treated without Donepezil

Table 3 The comparison of the VSRAD indicators between before and after the follow-up in the progress group and the stable group

	progress group (20 cases)			stable group (18 cases)		
	1st	2nd	p value	1st	2nd	p value
entorhinal Z-score	2.49±1.64	3.13±1.80	<0.001	1.67±0.87	1.71±0.82	0.570 n.s.
whole brain atrophy rate (%)	7.63±3.20	9.51±5.00	0.084 n.s.	7.68±5.04	8.98±5.21	0.080 n.s.
entorhinal atrophy rate (%)	52.34±36.28	67.64±35.61	0.002	32.86±27.31	33.42±25.98	0.855 n.s.
entorhinal/whole brain atrophy ratio	6.96±5.11	7.88±5.54	0.357 n.s.	4.60±4.35	5.18±7.33	0.696 n.s.

Data are the mean±SD
1st : at the initial examination
2nd : after the follow-up

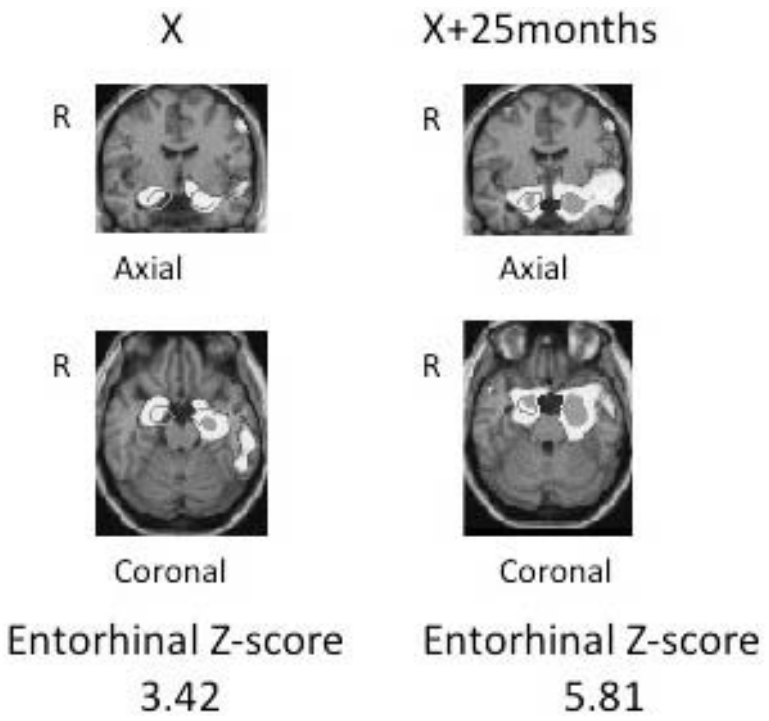

Figure 1 Follow-up of Voxel-based Specific Regional Analysis System for Alzheimer's Disease(VSRAD)in a patient with Alzheimer's disease (AD).
VSRAD of a 63-year-old male showed the largest increase of entorhinal Z-score in this study.
Gray scale Z-score maps ranging from 2 to 6 were displayed by overlaying topographic sections of the spatially normalized MRI template.
Entorhinal Z-score was 3.42 at the first examination and 5.81, after 25 months of follow-up.
MMSE was 17 at the first examination and 7 after the follow-up. The clinical impression of change was a marked worsening.

The entorhinal Z-score, whole brain atrophy rate, entorhinal atrophy rate, and entorhinal/whole brain atrophy ratio in the two groups were not significantly different at the initial examination (Table 3).

3 Comparison of the VSRAD indicators between before and after the follow-up in the progress group and the stable group

Table 3 shows the change of each VSRAD indicator between the initial examination and after the follow-up, respectively, in the progress and stable groups.

The entorhinal Z-score increased significantly after the follow-up in the progress group, while it showed no significant change in the stable group between the initial examination and after the follow-up. A comparison between at the initial examination and after the follow-up in a typical case of the progress group is shown in Figure 1.

The whole brain atrophy rate tended to increase after the follow-up in both groups. However, there was no statistically significant change.

The entorhinal atrophy rate increased significantly after the follow-up in the progress group, while there was no significant change in the stable group.

The entorhinal/whole brain atrophy ratio showed no recognizable difference between the initial examination and after the follow-up.

Since the average period for the follow-up was almost the same in both groups (Table 2), the comparison was made between before and after the follow-up without correcting for the length of the

Table 4 The comparison of the changes of the VSRAD indicators before and after the follow–up between in the progress group and the stable group

	progress group (20 cases)	stable group (18 cases)	p value
change of entorhinal Z–score	0.65±0.64	0.05±0.33	0.001
change of whole brain atrophy rate (%)	1.88±4.61	1.30±2.97	0.653 n.s.
change of entorhinal atrophy rate (%)	15.30±18.14	0.56±12.71	0.007
change of entorhinal/whole brain atrophy ratio	0.92±4.35	0.58±6.15	0.843 n.s.

Data are the mean±SD

follow–up period. Table 4 shows the comparison of the changes of each indicator in both groups.

The average increase in the entorhinal Z–score was 0.65±0.64 in the progress group and 0.05±0.33 in the stable group. The average increase of the Z –score in the progress group was larger than that in the stable group, and statistically significant difference was found between the two groups.

The average increase in the whole brain atrophy rate was 1.88±4.61% in the progress group and 1.30 ±2.97% in the stable group, and there was no significant difference between the two groups.

The entorhinal atrophy rate increased after the follow up in the progress group, while there was no significant change in the stable group. The average increase was 15.30±18.14% in the progress group and 0.56±12.71% in the stable group. These findings show the change was significantly larger in the progress group. The average increase in the entorhinal/whole brain atrophy ratio was 0.92±4.35 in the progress group and 0.58±6.15 in the stable group. Accordingly, there was no significant difference between these two groups regarding the changes before and after the follow–up.

The summary of the results of each VSRAD indicator

1. Entorhinal Z–score

As a whole, the Z–score increased with time. It increased significantly with time in the progress group, but there was no significant change in the stable group. The change in the entorhinal Z–score before and after the follow–up was larger in the progress group in comparison to the change in the stable group.

2. Whole brain atrophy rate

As a whole, the ratio of the atrophy area increased with time. The changes before and after the follow–up showed no significant difference between the progress and the stable group.

3. Entorhinal atrophy rate

As a whole, the ratio of the atrophy area increased with time. The ratio of the atrophy area in the entorhinal cortex increased with time in the progress group, while it showed no significant change in the stable group. The change before and after the follow–up was larger in the progress group in comparison to the change in the stable group.

4. The entorhinal/whole brain atrophy ratio

As a whole, there was no change with time. The change before and after the follow–up showed no significant difference between the progress group and stable group.

Discussion

Matsuda[10] reported that the entorhinal Z–score is high in AD and it also increases with time in the follow–up period in the same patient. The Z–score supposed assumed to increase along with the progression of AD. The current results showed that the mean entorhinal Z–score value increased from 2.10 to 2.46 in 38 AD patients in 1.26 years. This result also proves that the entorhinal Z–score value increases with time in AD.

Matsuda[10] also reported that even in AD the entorhinal Z–scores are low in some patients. Watanabe et al.[11] reported that they found 13 cases with the entorhinal Z–scores more than 2.0 out of 95 cases of healthy senior citizens. This report indicated that some healthy individuals could also have high entorhinal Z–scores. These reports suggest that it is impossible to diagnose AD merely depending upon the entorhinal Z–score

value in a one-time examination.

The progress group in the current series, represents the patients with rapid symptomatic progression and the stable group represents the patients with slow symptomatic progression. The results indicate that the patients with rapid symptomatic progression show a larger increase of the entorhinal Z-score than the patients with slow symptomatic progression. It is suggested that the increase of the entorhinal Z-score could be larger in the patients in whom clinical symptoms make rapid progress ; in other words, the progression of the atrophy in the entorhinal cortex could be more rapid in patients with rapid symptomatic progression.

It is impossible to diagnose AD only with the value of the entorhinal Z score. However, the data suggest that the progression of AD can be confirmed by examining the change of entorhinal Z-score with time. Confirming the increase of the entorhinal Z-score by VSRAD can raise the reliability of the diagnosis of AD. In addition, the level of increase in the entorhinal Z-score might therefore be useful for predicting the progression of clinical symptoms.

The mean age in the stable group was about 5 years older than in the progress group, which is not statistically significant. It is impossible to differentiate non-Alzheimer type dementia such as argyrophilic grain disease or senile dementia of the NFT type from AD using current diagnostic techniques. Since these non-Alzheimer type dementia are reported to increase with age and to develop in a significant population of latter-stage elderly people, the older group (stable group) could contain non-Alzheimer type dementia. The difference between AD and these non-Alzheimer type dementia should be studied with VSRAD in the future.

In this study, the comprehensive diagnosis by a psychiatrist was used to divide the patients into two groups. It might be more objective to divide the patients into two groups by the CDR and MMSE values. However, the CDR and MMSE values alone are not sufficient to identify a minute symptomatic change over a short term. For this reason, the comprehensive evaluation by the psychiatrist was used for the evaluation in this study. Hopefully, prospective studies will be conducted in the future with more precise and objective evaluation methods. For example, a clinical global assessment should be performed by a person other than the primary physician to ensure objectivity of the evaluation. In addition, a clearer statistical difference could be available by controlling the levels of dementia of the two groups more precisely for comparison.

Since VSRAD was developed using the 1.5 Tesla MRI machine, Matsuda[9] recommend using the 1.5 Tesla MRI machine for VSRAD. However, because this is a retrospective study using the results of MRI performed as a general examination in our hospital, it was impossible to designate 1.5 Tesla MRI machine as the machine to use (1.0 Tesla MRI machine was also used.). A preliminary experiment[12] using two MRI machines (1.0 Tesla and 1.5 Tesla) showed that the VSRAD for the same patient showed almost the same value. In addition, there are other reports using the 1.0 Tesla machines, which show no significant difference from the results using the 1.5 Tesla machine.[13][14] Therefore, it is unlikely that the difference in the MRI machines exerted an influence on the results. However, it is preferable to use the same machine to make a more accurate comparison in the future.

Acknowledgement

We thank Mr. R. Nakamuta, Mr. S. Morimoto and Ms. H. Higashi for their technical assistance.

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(Received on June 25, 2009,
Accepted on September 9, 2009)