A characteristic and the assessment of the writing impairments in subjects with Alzheimer's disease

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A characteristic and the assessment of the writing impairments in subjects with Alzheimer's disease

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Abstract

Background. Among the language deficits seen in Alzheimer's disease (AD), dysgraphia emerges relatively early. As the number of mild AD patients living at home is expected to increase, a method of evaluating the writing of AD patients is needed.

Methods: Free writing and writing from dictation were used to to test the writing ability of AD patients and healthy elderly controls who were asked to write on paper over a graphics tablet. The data were analyzed using customized writing analysis software. Various factors were compared between the AD and elderly groups. Single and multiple logistic regression analyses were then performed.

Results: The elderly group included 34 individuals aged ≥ 65 years and the AD group consisted of 28 individuals diagnosed by a doctor as suffering from AD. While there were no differences between the two groups in terms of age, years of education, or handedness, there was a significant difference in mean MMSE scores (AD group, 17.8 ± 4.4 points; elderly group, 28.5 ± 2.8 points). Among six factors evaluated in free writing, including number of characters, horizontal sentence length, number of mistakes in character formation, number of mistakes in character usage, text slant, and the writing time, there were significant differences between the AD and elderly groups for five factors except the writing time. The number of characters and the horizontal sentence length were significantly smaller in the AD group, and the numbers of mistakes in character formation and in character usage and text slant were significantly larger in the AD group ($p<0.05$). Among five factors evaluated in writing from dictation including horizontal sentence length, number of mistakes in character formation, number of mistakes in character usage, text slant, and the writing time, there were significant differences between the AD and elderly groups for four factors except horizontal length of sentence. The numbers of mistakes in character formation and in character usage and text slant were significantly larger in the AD group, and the writing time was significantly longer in the AD group ($p<0.05$). On multiple regression analysis, number of characters, number of mistakes in character usage, and text slant were characteristic of AD on free writing, while number of mistakes in character usage and text slant were identified for writing from dictation. On ROC analysis, an area under the curve (AUC) was 0.90 for free writing, while for writing from dictation, the AUC was 0.85.

Conclusions: In the present study, the factors related to writing ability that were characteristic of AD were identified. Further studies are needed to further evaluate the utility of this approach in AD.

Key words

Alzheimer's disease, writing ability, cognitive function, quantitative evaluation, writing impairment

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Introduction

It is well known that dysgraphia appears as one type of communication disturbance as dementia progresses. Among the language deficits seen in Alzheimer's disease (AD), dysgraphia emerges comparatively early. It has been reported that vocabulary is impaired despite the maintenance of the phoneme system,[1,2] and that AD subjects frequently make spelling mistakes that are phonetically similar.[3] In narrative writing tasks, AD subjects use fewer words and made more mistakes when describing a visual scene.[4] In free writing, the severity of AD increase the number of mistakes, although it makes no difference in the number of words.[5]

Japanese uses a unique writing system consisting of Chinese characters (*kanji*) and phonetic characters (*kana*). Tsuruta[6] reported that spontaneous writing is most severely affected in the breakdown process of writing in AD, and that *kanji* were seen to suffer impairment earlier than *kana*. Akanuma *et al.*[7] analyzed the number of characters, mistakes in *kanji* and *kana* character formation, and character usage in terms of clinical dementia rating (CDR) severity. They found that the number of characters used tended to decrease with increasing severity, and that mistakes in both *kanji* and *kana* formation and character usage increased. According to Hayashi *et al.*[8], subjects with early or mild AD had no problems writing down dictated *kana* and copying *kanji*, but they had more difficulty in writing down dictated *kanji*, particularly in remembering how to form them. There have been few studies of dysgraphia in AD to date, particularly with respect to Japanese or to the quantitative evaluation of dysgraphia.

Exercises with the aim of improving writing actions usually fall under the remit of occupational therapy, and improving the communication abilities of dementia sufferers is important in this approach. Kawashima[9] has also shown that the use of learning therapy focused on reading, writing, and calculations is effective in improving dementia in elderly dementia subjects, suggesting that the action of writing is an extremely important activity for elderly sufferers from dementia.

The Orange Plan recently set out by the Ministry of Health, Labour and Welfare calls for early support for dementia sufferers in their homes,[10] and this is likely to increase opportunities for writing at home. A method of evaluating the writing of AD subjects is therefore required. It will be necessary to elucidate what kinds of factors are involved in dysgraphia among AD subjects, and how these factors can be explained in AD subjects.

In this study, writing analysis software was used to perform quantitative measurements of features of dysgraphia such as writing time, horizontal sentence length, and text slant in AD subjects and healthy elderly individuals. Factors such as mistakes in *kanji* and *kana* character formation and mistakes in character usage such as spelling mistakes were also analyzed. Furthermore, the factors in writing ability that may be specific to AD were also examined, working on the hypothesis that text slant, which may be affected by attention deficit or visuospatial disturbance, may be characteristic.

Methods

1. Subjects

Subjects had no history of central neurological disorder or finger damage. They also had sufficient hearing to participate in everyday conversation, and no difficulties in linguistic comprehension. The elderly group included 34 individuals aged ≥65 years (mean age 79.5 ± 8.3 years, 5 men and 29 women, mean educational history 11.6 ± 2.4 years). They were users or volunteers of two day service centers. The AD group consisted of 33 individuals who entered one of two geriatric health services facilities or a group home. They were diagnosed by doctor as suffering from AD. Because 5 of 33 people were incapable of both free writing and writing from dictation, they were excluded from the study. Therefore, the AD group consisted of 28 subjects (mean age 82.6 ± 4.3 years, 2 men and 26 women, mean educational history 9.9 ± 2.4 years). All subjects were right-handed in both groups. There were no differences between the two groups in terms of age, years of education ($p<0.05$, compared t-test). The subjects in each group were from different facilities and were referred for enrollment by the facility staff at the request of the investigator.

Subjects and their families were provided in

advance with an oral and written explanation of the purpose and content of the study, its physical burden, handling of results, and privacy protection, and they participated in tests after having provided consent. This study was authorized by the Ethics Committee of Kanazawa University (approval no. 204).

2. Experimental procedure

The methods used for writing were free writing, one of the test items in the Mini-Mental State Examination (MMSE), and writing from dictation, which requires the use of short-term memory. These two methods were chosen to investigate the writing ability of AD subjects because it was thought that they would reveal the features of writing by AD subjects.

MMSE was first administered to all subjects. For the free writing item in the MMSE, subjects used a special ballpoint pen for use with a graphics tablet (ZP-130, WACOM, Saitama, Japan) to write on a sheet of A4 paper placed on top of a graphics tablet (Intuos 3 PTZ-930, WACOM) connected to a personal computer (PC). Subjects wrote in ballpoint pen on white paper, and the data on their writing were imported by the investigator into the PC via the graphics tablet. This writing analysis was performed using customized writing analysis software (LabVIEW, National Instruments Corporation, Tokyo, Japan). This software starts measuring time in millisecond increments when the pen is first pressed down to start writing a character on the graphics tablet, and it stops measuring when the pressure ends. Writing was recorded as one plot per fortieth of a second, and the length of the sentence was measured from the left-hand margin of the first character to the right-hand margin of the final character plotted on the X-axis. The center points of the first and last characters plotted on the X- and Y-axes were calculated in order to calculate the text slant. Text slant was calculated by dividing the difference between the central point on the Y axis from its difference on the X-axis, with text written perfectly horizontally having a slant of 0. Text slants were expressed as absolute values.

1) Free writing

The investigator (an occupational therapist with 12 years' clinical experience) asked the subjects to engage in free writing on the white paper placed over the graphics tablet connected to the PC by giving them the oral instruction, "Write a sentence here. It doesn't matter what you write." The number of individual characters, the number of mistakes in *kanji* or *kana* character formation, and the number of mistakes in *kanji* or *kana* suffix usage were measured. The other parameters measured were horizontal sentence length (mm) as the distance between the left-hand margin of the first character and the right-hand margin of the last character on the X-axis, text slant, and writing time (sec) from the start to the end of writing.

2) Writing from dictation

The investigator then asked the subjects to write from dictation on the graphics tablet by giving them the oral instruction "Write the sentence *takai yama ni noborimashita* ['I climbed a high mountain'] here, using *kanji*." The subjects were given this instruction slowly and in a loud voice. As for the free writing, the number of individual characters, the number of mistakes in *kanji* or *kana* character formation, and the number of mistakes in *kanji* or *kana* suffix usage were measured. As for the number of mistakes in character usage, the cases in which the subjects could not use *kanji* were also counted as mistakes. The other parameters measured were horizontal sentence length (mm), text slant, and writing time (sec).

3. Statistical analysis

1) Free writing

A t-test was used to compare six factors (number of characters, number of mistakes in character formation, number of mistakes in character usage, horizontal sentence length, writing time, and text slant) between the AD and elderly groups. Single logistic regression analysis was performed with AD as the dependent variable, and the six variables from the free writing were selected. Multiple logistic regression analysis was then performed by the forced entry method, and variables were then chosen by the stepwise method. The cut-off point for determining AD was calculated from the receiver operating characteristic (ROC) curve.

2) Writing from dictation

A t-test was used to compare five factors (number of mistakes in character formation, number of mistakes in character usage, horizontal sentence length, writing

time, and text slant) between the AD and elderly groups. Single logistic regression analysis was performed with AD as the dependent variable, and the five variables from the writing from dictation test were selected. Multiple logistic regression analysis was then performed by the forced entry method, and variables were then chosen by the stepwise method. The cut-off point for determining AD was calculated from the ROC curve.

JMP9.0.0(SAS. Institute Japan, Tokyo, Japan) was used for statistical analysis.

Results

1. Comparison of MMSE scores between the elderly and AD groups

There was a significant difference in mean MMSE scores between the AD (17.8 ± 4.4 points; MAX, 28; MIN, 12) and elderly groups (28.5 ± 2.8 points; MAX, 30; MIN, 22) ($p < 0.05$). The score for the five subjects who were excluded was 4.6 ± 1.5 points, and all of them scored <10 points.

2. Comparison of individual factors between the elderly and AD groups

Table 1 shows the results for free writing, and Table 2 shows the results for writing from dictation. Figure 1 shows an example of the characters written by a subject of the AD group, and Figure 2 of those written by a subject of the elderly group. The characteristic parts of each written text are circled.

In free writing, there were significant differences between the AD and elderly groups for all factors except the writing time. The number of characters and the horizontal sentence length were significantly smaller in the AD group, and the numbers of mistakes in character formation and in character usage and text slant were significantly larger in the AD group ($p<0.05$).

In writing from dictation, there were significant differences between the AD and elderly groups for all factors except the horizontal sentence length. The numbers of mistakes in character formation and in character usage and text slant were significantly larger in the AD group, and the writing time was significantly longer in the AD group ($p<0.05$).

As shown in Figure 1, some subjects of the AD group made mistakes in *kanji* usage or were unable to write *kanji* from dictation (particularly the character nobori, "climb"). Some also made mistakes in *kanji* formation by missing part of the character. In addition, as shown in Fig. 2, most of the elderly group subjects had no mistake in character formation and in character usage, and they also had no text slant.

3. Analysis of factors for determining AD

1) Free writing

The results are shown in Table 3. When single logistic regression analysis was performed with AD as the dependent variable, six character-related variables were selected. When multiple logistic

Table 1. Free writing

	AD	Healthy	p value
Number of characters	11.2 ± 6.5	15.9 ± 6.2	**
Number of mistakes in character formation	0.86 ± 1.23	0.06 ± 0.24	**
Number of mistakes in character usage	0.46 ± 0.79	0.15 ± 0.36	*
Horizontal length of sentence (pt)	116.0 ± 46.1	154.2 ± 49.7	**
Writing time (sec)	40.5 ± 36.6	38.2 ± 28.2	N.S.
Text slant	0.073 ± 0.094	0.029 ± 0.018	**

N.S., not significant
$p<0.05$ * $p<0.01$ **

Table 2. Writing from dictation

	AD	Healthy	p value
Number of mistakes in character formation	0.64 ± 0.95	0.12 ± 0.33	**
Number of mistakes in character usage	0.75 ± 1.00	0.16 ± 0.36	**
Horizontal length of sentence (pt)	100.7 ± 30.4	94.0 ± 31.2	N.S.
Writing time (sec)	26.7 ± 18.7	18.1 ± 9.2	*
Text slant	0.073 ± 0.076	0.029 ± 0.021	**

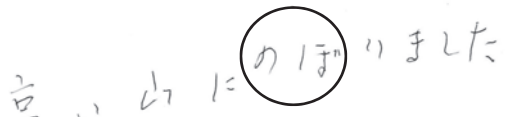
N.S., not significant
$p<0.05$ * $p<0.01$ **

regression analysis was performed by the forced entry method, factors that did not exert an influence were selected, and the stepwise method was therefore used. When the variance inflation factor (VIF) value was investigated to avoid the multicollinearity of independent variables, three variables were selected: number of characters, number of mistakes in character usage, and text slant. R^2 was 0.38.

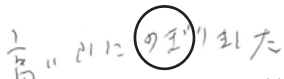
2) Writing from dictation

The results are shown in Table 4. When single logistic regression analysis was performed with AD as the dependent variable, five character-related variables were selected. When multiple logistic regression analysis was performed by the forced entry method, factors that did not exert an influence appeared, and the stepwise method was therefore

86-year-old woman. Slant: 0.05. Mistakes in character usage: 1 (the character 飯 has been written as 飲)



89-year-old woman. Slant: 0.11. Mistakes in character usage: 1 (unable to write the character 登)

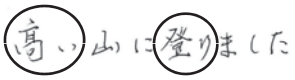


93-year-old woman. Slant: 0.04. Mistakes in character usage: 1 (unable to write the character 登), mistakes in character formation: 1 (vertical stroke missing in the character ぼ)

※The characteristic parts of each written text are circled.

Figure 1. Writing by AD patients

85-year-old woman. Slant: 0. Other mistakes: 0



88-year-old woman. Slant: 0. Other mistakes: 0

※The characteristic parts of each written text are circled.

Figure 2. Writing by healthy elderly individuals

Table 3. Multiple logistic regression analysis (free writing)

	Estimated value	Odds ratio	p value	VIF value
Number of characters	− 0.211	0.81	0.003**	1.1109
Character usage	2.79	16.33	0.008**	2.0153
Slant	58.2	1.88×10^{-25}	0.008**	1.9658

p<0.01 **

Table 4. Multiple logistic regression analysis (writing from dictation)

	Estimated value	Odds ratio	p value	VIF value
Character usage	1.53	4.61	0.012*	1.0157
Slant	44.1	$1\ 39 \times 10^{-19}$	0 006**	1 0157

p<0.05 * p<0.01 **

used. When the VIF value was investigated to avoid the multicollinearity of independent variables, two variables were selected: number of mistakes in character usage and text slant. R^2 was 0.31.

4. Cut-off points for determining AD

The optimum cut-off points for determining AD from the ROC curves were investigated.

1) Free writing

The ROC curve is shown in Figure 3. The area under the curve (AUC) was 0.90, and the cut-off point was 0.24. This had sensitivity of 0.96, specificity of 0.71, and predictive value of 0.79. The linear predictor was − 0.39 − 0.21 × (number of characters) + 2.79 × (number of mistakes in character usage) + 58.19 × (text slant). The value of linear predictor corresponding to the cut-off point was − 1.14. Values greater than this value were likely to indicate AD.

2) Writing from dictation

The ROC curve is shown in Figure 4. The AUC was 0.85, and the cut-off point was 0.46. This had sensitivity of 0.74, specificity of 0.79, and predictive value of 0.77. The linear predictor was − 2.67 + 1.53 × (number of mistakes in character usage) + 44.1 × (text slant). The value of linear predictor corresponding to the cut-off point was − 0.16. Values greater than this value were likely to indicate AD.

Discussion

In this study, writing analysis software was used to perform a quantitative analysis of the writing ability of AD subjects and elderly individuals, and the correlations between MMSE scores and writing ability were investigated. The factors related to writing ability that were characteristic of AD were also identified.

1. Correlation between writing in the elderly and AD groups and MMSE scores

In this study, 5 of the 33 subjects of the AD group were incapable of both free writing and writing from dictation. The mean MMSE score for these 5 patients was 4.6 ± 1.5 points, clearly lower than that for the other AD subjects. This was a predictable result, as writing is certainly the highest-level higher brain function within language function. Nevertheless, 28 of the 33 subjects of this group were able to complete this test despite scoring significantly lower on the MMSE than the elderly group subjects.

Writing ability is a necessary skill in every day life for purposes such as signing documents, irrespective of age, but little is known about the level at which elderly individuals and AD subjects are capable of writing, or the relationship between decline in cognitive abilities and writing. In this sense the results of this study are highly significant because they

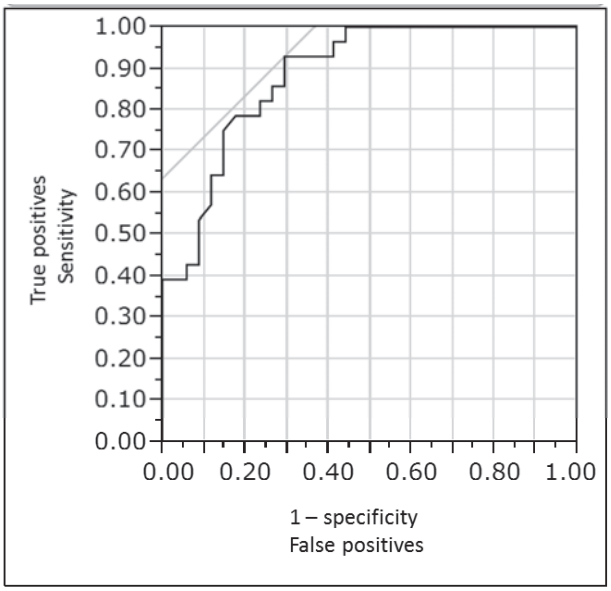


Figure 3. ROC curve (free writing)

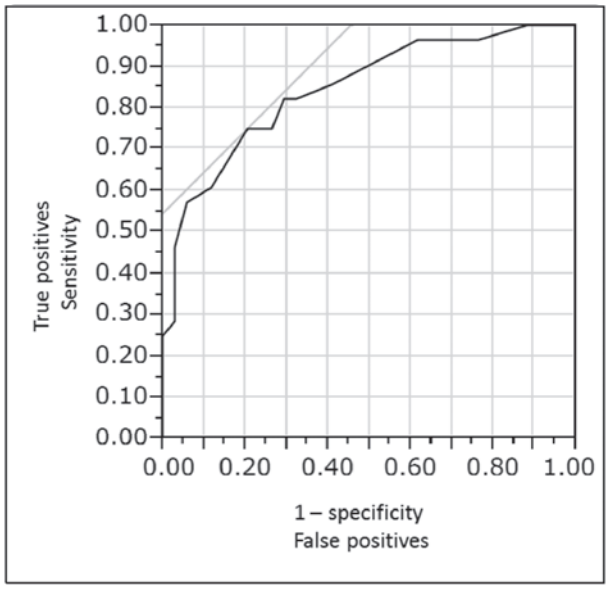


Figure 4. ROC curve (writing from dictation)

clarify the writing abilities of AD subjects and elderly individuals.

2. Analysis of factors for determining AD

Multiple logistic regression analysis to investigate which variables related to writing ability differentiate AD subjects from healthy elderly individuals identified the three variables of number of characters, number of mistakes in character usage, and text slant in free writing, and the two variables of number of mistakes in character usage and text slant in writing from dictation.

With respect to the number of characters, Henderson *et al*.[4] have previously reported that AD subjects used fewer words and made more mistakes when describing a visual scene. Akanuma *et al*.[7] also reported that the number of characters used tended to decrease with increasing CDR severity. They also found a significantly higher rate of mistakes in character usage in subjects with CDR +1 compared with those with CDR 0 (healthy individuals).

In this study, the three variables of number of characters, number of mistakes in character usage, and text slant in free writing in particular were capable of distinguishing AD subjects with a high predictive value, suggesting that they may be useful when predicting which patients have AD from their writing.

Tsuruta[6] suggested that dysgraphia in AD subjects involves visuospatial cognitive disturbances such as apraxic agraphia, including the breakdown of character style and scribbled writing, or abnormal placement. These, however, are difficult to measure quantitatively, and no quantitative method of evaluation has yet been reported. Slanted text is also frequently evident in written sentences, and it is possible that the visuospatial cognitive disturbances and decreased attention during writing of AD subjects[11] may be involved in such breakdown of character style, scribbled writing, and slanted text. The sort of quantitative assessment of text slanting performed in this study may be as important for understanding the characteristics of writing by AD subjects as the number of mistakes in character usage or the number of words in free writing.

3. Cut-off points for determining AD

The cut-off points for determining AD were also calculated from the ROC curves. In free writing, the cut-off point was 0.24 for a model involving the three variables of number of characters, number of mistakes in character usage, and text slant, and this had a high predictive value of 0.79. In writing from dictation, the cut-off point was 0.46 for a model involving the two variables of number of mistakes in character usage and text slant, and this also had a high predictive value of 0.77. Further investigation of these cut-off points involving a greater number of subjects is required in the future, but the results of the present study suggest that the three variables of number of characters, number of mistakes in character usage, and text slant in free writing and the two variables of number of mistakes in character usage and text slant in writing from dictation may be factors capable of explaining the dysgraphia evident in AD, and they may have validity as a method of evaluating writing ability.

4. Potential as a method of evaluating writing ability in AD

The writing is an important action that is intimately connected with people's everyday lives, and it accurately reflects cognitive function. It may be important to perform a quantitative evaluation of writing ability along with the MMSE in order to understand cognitive function in AD subjects.

The sentence that subjects were instructed to write from dictation in this study was *Takai yama ni noborimashita* ['I climbed a high mountain']. Akanuma *et al*.[7] used the sentence *Watashi wa ie ni kaeritai* ['I want to go home'], the dictation task from the Cognitive Abilities Screening Instrument (CASI). Both tasks include *kanji* that are learned between the ages of 6 and 9 years, and in Japan, which has a high literacy rate, this task is of an appropriate level of difficulty. The length of the writing task was not evaluated in the present study. Future studies of tasks of varying lengths may be required.

Of the factors that may explain writing in AD that emerged from the present study (number of characters, number of mistakes in character usage, and text slant), the number of characters and number of mistakes in character usage are easily determined at a glance. With respect to quantitatively measured text slant, however, further studies will be required

to ascertain whether it can be determined visually in practice, in order for it to be used as a simple means of evaluation in clinical and everyday settings.

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アルツハイマー型認知症者の書字障害の特徴と評価法

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藤田　高史****，中谷　　謙*****，井上　克己*

要　旨

はじめに：アルツハイマー病（以下AD）で見られる言語障害において，書字障害は比較的早期に現れる．今後AD患者の数が増加すると予想されるためAD患者の書字能力を評価する方法が必要である．**方法**：AD群と高齢者群に自由書字と書き取りによる書字をコンピューターに接続したペンタブレット上の用紙に書かせた．データを書字分析ソフトウェアを使用して分析，書字に関する様々な因子を2群間で比較した．またこれらのどの因子がADに特徴的かを判断するためロジスティック重回帰分析を行った．**結果**：65歳以上の高齢者34名を高齢者群，AD患者28名をAD群として分析できた．自由書字では，AD群と高齢者群間において，評価した6つの因子のうち，「書字時間」以外の5つの因子で有意差を認めた．すなわち，「文字数」，「文章の横の長さ」ではAD群が有意に小さく，「文字形態の誤りの数」,「文字運用の誤りの数」,「文章の傾き」ではAD群が有意に大きかった（$p<0.05$）．書き取りでの書字では，評価した5つの因子のうち，「文章の横の長さ」以外の4つの因子で有意差を認めた．すなわち，「文字形態の誤りの数」，「文字運用の誤りの数」，「文章の傾き」ではAD群が有意に大きく，「書字時間」ではAD群が有意に長かった（$p<0.05$）．ロジスティック重回帰分析により，自由書字においては「文字数」が少なく，「文字運用の誤り」が多く，「文章の傾き」が大きいことがAD群に特徴的であることが明らかになった．また書き取りでの書字においては「文字運用の誤り」が多く,「文章の傾き」が大きいことがAD群に特徴的であることが明らかになった．**結論**：本研究にてAD症例の書字能力を説明しうる因子を特定した．この評価の有用性を評価するためには今後更なる研究が必要である．