Dementia with Lewy Bodies with Pure Agraphia for Kanji (Japanese Morphograms)

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Abstract:
A 70-year-old dextral woman was admitted to a hospital with agraphia for kanji (Japanese morphograms). She had a history of severe constipation, nightmares, and visual hallucinations. Neurological examinations revealed no obvious Parkinson’s disease symptoms. She showed poor skills in writing the kanji for looking at picture objects, [e.g., writing the Japanese word “inu” (which means dog) when she saw a drawing of a dog] or dictated words. A reduced striatal uptake of [123I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) on single-photon-emission computed tomography and reduced metaiodobenzylguanidine (MIBG) cardiac uptake on myocardial scintigraphy were detected. The accumulation of amyloid beta in the bilateral cerebral cortices was observed on amyloid-positron emission tomography. We herein report a case of Lewy body dementia with pure agraphia for kanji with underlying Alzheimer’s disease pathology.

Key words: dementia with Lewy bodies, agraphia, kanji, Alzheimer’s disease, amyloid beta

Introduction
The Japanese language contains two different systems for reading/writing: kanji (morphograms) and kana (phonograms). Japanese sentences are usually constructed by the combination of kanji and kana. In elementary school, Japanese children learn to read and write approximately 1,000 kanji, and almost 2,100 kanji outlined by the Japanese government are used in daily life.

Agraphia for kanji but not kana has been reported in cases with cerebrovascular disease. Agraphia for kanji is considered to be equivalent to lexical or orthographic agraphia in Western countries (1). Sakurai et al. reported cases of pure agraphia for kanji caused by a lesion in the left posterior middle temporal gyrus (2, 3). However, other lesions resulting in agraphia for kanji have been described in the angular gyrus (4, 5), superior parietal lobule (6), and posterior middle frontal gyrus (7).

Only a few reports have been published concerning agraphia for kanji but not kana in cases with neurodegenerative diseases, such as Alzheimer’s disease (AD) (8-11), and this entity has been described in only one case of dementia with Lewy bodies (DLB), albeit with insufficient imaging data (12).

We herein report a case of probable DLB with pure agraphia for kanji with underlying AD pathology that was confirmed by amyloid positron emission tomography (PET).

Case Report
A 70-year-old, right-handed woman was admitted to our hospital due to agraphia for kanji. She had a history of hypertension. An interview with her husband revealed that her writing of kanji characters had gradually worsened, and she had had difficulty writing her address using kanji since approximately one year prior to admission. She had had severe constipation from 10 years prior to admission, experienced nightmares from 3 years ago, and started to experience visual hallucinations from 1 year ago, reporting that “someone is standing at the front door”.

On admission, she was alert, with a body temperature of...
36.6°C, blood pressure of 146/49 mmHg, and pulse of 56 beats per min. Examinations of the heart, lungs, and abdomen were unremarkable. Neurological examinations did not reveal any notable abnormalities, and there were no obvious symptoms of Parkinson’s disease or ataxia. Blood test results were unremarkable. The Schellong test indicated hypotension. Anosmia was diagnosed because she provided only one correct answer in the Odor Stick Identification Test for Japanese.

Upon cognitive examinations, the patient’s Mini-Mental State Examination (MMSE, Japanese version) (13) score was 21 out of 30 points (orientation, 9 points; registration, 3 points; attention and calculation, 2 points; recall, 1 point; and language, 6 points), and her score for the Hasegawa Dementia Scale-Revised (14) was 24 out of 30 points (age, 1 point; orientation, 5 points; immediate recall of 3 words, 3 points; delayed recall of 3 words, 3 points; calculation, 2 points; backward digit span, 1 point; visual encoding and recall, 4 points; and semantic verbal fluency, 5 points). In the Frontal Assessment Battery (15), she scored 12 out of 18 points (Similarities, 1/3; Lexical fluency, 1/3; Motor series, 1/3; Conflicting instruction, 3/3; Go-No-Go, 3/3; and Prehension behavior, 3/3). She was unable to perform Raven’s Colored Progressive Matrices non-verbal test of abstract reasoning (16) or the Kohs Block-Design Test (17), indicating that her visuospatial abilities were impaired.

We administered the Standard Language Test of Aphasia (Japanese version) (18). She showed poor skills in writing the kanji for looking at picture objects [e.g., writing the Japanese word “inu” (which means dog) when she saw a drawing of a dog] or dictated words, but her skills in writing the kana for picture objects and dictated words were normal. Her oral reading of kanji, kana, and short sentences was normal, as was her reading comprehension of kanji and kana. Her auditory comprehension was almost normal (Fig. 1). In addition, Gogi (word-meaning) aphasia, which is considered a semantic variant of primary progressive aphasia, was not indicated because her comprehension of the meaning of words and sentences was normal.

We performed a writing test involving the kanji characters that Japanese students learn from the first to fourth grades of elementary school (Fig. 2). She provided incorrect answers to 29 out of 70 questions. For the kanji characters learned in the lower grades, she demonstrated phonologic and morphologic paragraphia; her writing errors in kanji included partial responses, in which some of the kanji components were correct, but she did not write the other components. For the kanji characters learned from the fourth grade, the most frequent writing error was a non-response. In addition, her copying of kanji was almost normal. As a result, she was diagnosed with pure agraphia for kanji.

The patient also completed the Visual Perception Test for Agnosia (Japanese version) (19). Her ability to copy figures, draw a clockface with hands, and draw a face was impaired (Fig. 3). Her performance in the pentagon copying test in the MMSE was also impaired (Fig. 3). Topographical agnosia, which is a right hemisphere symptom, was observed because she could not indicate the location of Mt. Fuji or the city in which she lives on an unlabeled map and she sometimes got lost when she tried to return to her room while in the hospital. However, prosopagnosia was not observed because her recognition of familiar faces was good. In addition, her identification of differences between unknown faces was impaired. Furthermore, her ability to match unknown faces, in a test in which a series of facial photographs are presented first and then one photograph is

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| Speaking | 6 | 6  | 6      |
| Speaking | 7 | 7  | 7      |
| Speaking | 8 | 8  | 8      |
| Speaking | 9 | 9  | 9      |

| Reading Comprehension | 1 | 1  | 1      |
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| Reading Comprehension | 3 | 3  | 3      |
| Reading Comprehension | 4 | 4  | 4      |
| Reading Comprehension | 5 | 5  | 5      |

| Writing | 1 | 1  | 1      |
| Writing | 2 | 2  | 2      |
| Writing | 3 | 3  | 3      |
| Writing | 4 | 4  | 4      |
| Writing | 5 | 5  | 5      |
| Writing | 6 | 6  | 6      |
| Writing | 7 | 7  | 7      |

| Arithmetic | 1 | 1  | 1      |
| Arithmetic | 2 | 2  | 2      |
| Arithmetic | 3 | 3  | 3      |
| Arithmetic | 4 | 4  | 4      |
| Arithmetic | 5 | 5  | 5      |

Figure 1. Results of the Standard Language Test of Aphasia (Japanese version). This test from the Japan Society for Higher Brain Dysfunction (download version) was used and partially modified.
Figure 2. Example of the kanji writing task. These are kanji characters learned by third-grade students in elementary school. (a, b) Phonologic paragraphia of kanji. (c) Morphologic paragraphia of kanji [(kyu; correct writing) meaning break⇒(tai; patient’s writing) meaning body]. (d) Partial response: the patient wrote the right component of the character correctly but could not write the left components.

Figure 3. Examples of copying and drawing on request. (a) Pentagon copying test in the MMSE was impaired. (b) Copying a figure (cube). (c) Copying a figure (flower). (d) Drawing a clockface with hands. (e) Drawing a face.

presented and the subject has to select the same person, was impaired; therefore, facial recognition was considered to be slightly impaired.

Magnetic resonance imaging of the brain did not provide clear evidence of ischemic changes, basal ganglia degeneration, or amyloid angiopathy. An analysis utilizing the Voxel-based Specific Regional Analysis System for AD (20) generated a Z-score of 1.71. There was evidence of atrophy in the AD areas of interest in the right medial temporal lobe, including the entorhinal cortex, amygdala, and hippocampus. Further atrophy was detected in a posterior lesion of the inferior temporal lobe and occipital lobes (Fig. 4). Brain atrophy detected by magnetic resonance imaging was predominantly in the right temporal and occipital lobes (Fig. 4).

We used \[^{18}F\]-\(\beta\)-carbomethoxy-\(\beta\)-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) single-photon emission computed tomography (SPECT) and meta-iodobenzylguanidine (MIBG) myocardial scintigraphy to differentiate AD from Parkinson’s disease and Lewy body diseases, such as DLB. FP-CIT SPECT showed that the striatal uptake ratio (SUR) was reduced, as determined using DaTQUANT™ (GE Healthcare, Little Chalfont, UK) (Fig. 5a). MIBG myocardial scintigraphy showed evidence of a reduced cardiac uptake, as the heart-to-mediastinum MIBG uptake ratio was 1.79 in the early phase and 1.44 in the late phase (Fig. 5b).

\[^{99m}Tc\]-ethyl-cysteinate dimer SPECT was also performed. An evaluation with the easy Z-score imaging system indicated decreased perfusion in the bilateral frontal, parietal, and occipital lobes and a posterior lesion of the temporal
Figure 4. Magnetic resonance imaging of the brain. T1-weighted imaging (a) axial section at the level of the cerebral peduncle and (b) coronal section at the level of the thalamus, cerebral peduncle, and pons, showing slight atrophy in the bilateral temporal lobe. (c) A voxel-based specific regional analysis for Alzheimer’s disease. A marked decrease in the volume of gray matter atrophy was observed in the right medial temporal area (medial temporal lobe, including the entorhinal cortex, amygdala, and hippocampus), and a posterior lesion was detected in the inferior temporal lobe and occipital lobe (area 19). Colored areas with Z-scores >2 are overlaid as regions of significant atrophy onto tomographic sections and the cortical surface of a standardized magnetic resonance imaging template.

Figure 5. [123I]-2β-Carbobemthoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) single-photon emission computed tomography (SPECT) and meta-iodobenzylguanidine (MIBG) myocardial scintigraphy. (a) FP-CIT SPECT images showed that the striatal uptake ratio was 0.39 (normal range 1.83±0.33) in the right striatum and 0.58 (normal range 1.81±0.35) in the left striatum using DaTQUANT™, indicating a reduced striatal uptake. (b) MIBG myocardial scintigraphy showed that the heart-to-mediastinum (H/M) uptake ratio was 1.79 in the early phase and 1.44 in the late phase (normal H/M uptake ratio ≥2.2), indicating a reduced cardiac uptake.
Figure 6. $^{99m}$Tc-ethyl-cysteinate dimer single-photon emission computed tomography (SPECT). SPECT images, analyzed with an easy Z-score imaging system, showed a decrease in the blood flow in the bilateral frontal, parietal, and occipital lobes and a posterior lesion of the temporal lobe. Overall, perfusion was decreased more on the right side than on the left side.

Figure 7. Amyloid positron emission tomography (PET) images and fluorodeoxyglucose-PET images. (a) Amyloid PET images using Pittsburgh compound B showed the significant diffuse deposition of fibrillary Aβ peptide throughout the cortex, especially in the right hemisphere. (b) Fluorodeoxyglucose-PET images, analyzed with the easy Z-score imaging system, showed glucose hypometabolism in the bilateral temporal, parietal, and occipital lobes. Hypometabolism was more pronounced in the right hemisphere than in the left hemisphere.

Overall, perfusion was decreased more on the right side than on the left side (Fig. 6).

Amyloid PET with Pittsburgh compound B (Fig. 7a) and fluorodeoxyglucose-PET were performed (Fig. 7b). Amyloid PET imaging revealed the accumulation of amyloid beta (Aβ) with the significant diffuse deposition of fibrillary Aβ peptides in the bilateral cerebral cortices, especially in the right hemisphere. Furthermore, fluorodeoxyglucose-PET imaging showed regions of hypometabolism in the bilateral temporal, parietal, and occipital lobes. Hypometabolism was more pronounced in the right hemisphere than in the left hemisphere.
Discussion

Our case had characteristics of DLB with pure agraphia for kanji (morphograms) - but not for kana (phonograms) - with underlying AD pathology. She was diagnosed with probable DLB using the Diagnostic Criteria for DLB (21). Our case demonstrated one core clinical feature (recurrent visual hallucinations) and two indicative biomarkers [a reduced dopamine transporter uptake in the basal ganglia on SPECT and an abnormal (low) uptake on $^{123}$I-MIBG myocardial scintigraphy]. Amyloid PET with Pittsburgh compound B allows for the in vivo visualization of the Aβ peptide accumulation, which is an important biomarker and useful tool for the diagnosis of AD (22-24). In our case, amyloid PET revealed the accumulation of Aβ.

Our case presented with a combination of DLB and AD pathology, as has been reported previously for many DLB cases (25). In particular, significantly more individuals with DLB have positive amyloid PET findings than those with Parkinson’s disease, Parkinson’s disease with dementia, and normal controls (26), suggesting that amyloid PET may not necessarily be a useful examination for differentiating AD from DLB. Therefore, the diagnosis in our case was considered to be DLB with underlying AD pathology.

In our case, neuropsychological examinations revealed agraphia for kanji and visuospatial deficits. Agraphia for kanji, which is characterized by the impaired recall of characters and is considered to be the equivalent of lexical agraphia in Western languages, has been examined in detail in cases with cerebrovascular disease. Sakurai et al. reported pure agraphia for kanji caused by a lesion in the left posterior middle temporal gyri (Brodmann area 37), which is located above and posterior to the ventral word form area (mid-fusiform/posterior inferior temporal gyri) (2, 3).

Sakurai et al. proposed a dual-route mechanism for writing to dictation (6, 7) consisting of a phonological route and a morphological route. The phonological route proceeds from the primary auditory area and Wernicke’s area to the angular and supramarginal gyri and joins the arcuate fasciculus to reach the motor and premotor hand area. Conversely, the morphological route starts at the posterior inferior temporal cortex and proceeds upward under the angular gyrus and superior parietal lobule to reach the motor and premotor hand area. Under this hypothesis, a lesion in the posterior inferior temporal cortex can induce deficits in writing from dictation because this is where the morphological information on characters and words is stored. Sakurai et al. suggested that damage to the morphological route may yield agraphia for kanji, while damage to the phonological route may yield agraphia for kana (6, 7).

Suzuki et al. reported that two probable AD patients with a slowly progressive visuospatial impairment demonstrated a peculiar type of visuocostructive deficit and agraphia for kanji, which consisted of an inability to perform task-dependent narrowing and fixation of visual attention (8).

Saito et al. reported agraphia for kanji in a case with AD, suggesting that it might have resulted from a disturbance of visual image processing of the characters and an impairment in writing kinesthesia (9). Kanemoto et al. described a patient with AD showing corticobasal syndrome who had agraphia for kanji (10); the clinical features consisted of an inability to recall the form of kanji but without apraxic agraphia. Koyanagi et al. reported agraphia for kanji in an AD patient with visuospatial impairment and constructive disturbance (11). This patient did not meet the diagnostic criteria for posterior cortical atrophy (PCA), but their symptoms were similar to those of PCA.

We considered the possibility of PCA in the present patient. PCA generates visual symptoms and is a form of dementia that has significant posterior atrophy of the cerebrum and impaired visual and spatial cognition, but the anterograde memory is relatively preserved. In addition, there is an absence of early parkinsonism and hallucinations. AD is the underlying cause of almost all cases of PCA, but corticobasal degeneration, DLB, and prion disease have also been reported (27, 28). In addition, cognitive dysfunction in DLB is characterized by the marked impairment of attention, visuospatial ability, and executive function, with mild memory impairment. The visuospatial ability is reportedly more impaired in patients with DLB than in those with AD (29, 30). Although visuospatial deficits were also a characteristic symptom in our case, visual complaints were absent, and hallucinations were present from the early stage of the disease. Therefore, we considered a diagnosis of DLB to be more appropriate than PCA in our case.

In the present case, the most frequent writing error was a non-response when performing a writing test of kanji characters. There was a possibility of a disorder of construction and visuospatial abilities because her writing of kanji characters had worsened over time. Therefore, we considered her agraphia for kanji to be the result of an inability in recalling the form of kanji together with visuospatial impairment and constructive disturbance.

Although the most frequent writing error of the present case was a non-response, some paragraphia was observed. As shown in Fig. 2a, b, her errors in kanji were phonological equivalents; however, she understood the meaning of the kanji symbols. As shown in Fig. 2c, when writing kanji, she substituted another kanji symbol that had a visual resemblance to the target kanji character, although she understood the meaning of the target character.

Hayashi et al. reported that phonologically plausible spelling errors of kanji were detected in a case with AD, similar to phonologically plausible spelling errors in lexical agraphia (31). The phonologically equivalent errors of kanji that occurred were the result of writing the kanji characters using only the phonological process, since it was not possible to produce the correct kanji form. In addition, the errors differed from the phonologically plausible spelling errors encountered in Gogi (word-meaning) aphasia, which is considered to be a semantic variant of primary progressive apha-
In our case, the comprehension of the meaning of words was normal. Therefore, her paragraphia was considered the result of phonologically equivalent errors and could be distinguished from the paragraphia of semantic variant primary progressive aphasia with word meaning deficits.

In our case, hyperperfusion of \(^{18}\)F-fluorodeoxyglucose-PET imaging were observed in the left posterior inferior temporal cortex. Therefore, the pure agraphia for kanji was considered to have been caused by a lesion in the left posterior inferior temporal gyrus (Brodman area 37), as in previous reports (2, 3). However, since we observed right hemisphere dominant cerebral atrophy, hyperperfusion of \(^{18}\)F-fluorodeoxyglucose-PET imaging, and the accumulation of Aβ, we considered the relationship between these imaging findings and crossed agraphia for kanji.

Although cases of crossed agraphia are rare, some have been reported. Mizuta reported alexia with agraphia for kanji due to subcortical hemorrhaging in the right posterior inferior temporal area. In that case, the patient was unable to write spontaneous or dictated kanji but was able to copy kanji. This may have been caused by anomalous lateralization in the right hemisphere (32).

Other reports have suggested the involvement of the right medial frontal lobe in the selection and arrangement of components in the final process of writing kanji (33) and the participation of the right parietal lobe in the kinesthetic movements of writing (34). In addition, the cases of Suzuki et al. and Koyanagi et al. showed right hemisphere-dominant imaging findings, although these reports did not mention anomalous lateralization in the right hemisphere (8, 11).

Taking into account these previous cases, the present patient might have had crossed agraphia for kanji, given the right hemisphere-dominant imaging findings. The mechanism underlying crossed agraphia might be involved anomalous lateralization in the right hemisphere. However, whether or not the cause of agraphia for kanji is located in the right hemisphere in cases with right hemisphere-dominant imaging findings is unclear. Therefore, we are interested in studying hemispheric lateralization and need to accumulate more cases with agraphia in which right hemisphere-dominant atrophy and the brain function are remarkable and to examine the localization of the function.

The authors state that they have no Conflict of Interest (COI).

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