研究開発目的では、以下の項目について検査を実施することは適切である。

(1) アルツハイマー病治療薬治験における適切な対象者選択

(2) アルツハイマー病の病態研究、特に早期病態の探索と発症予測因子の解明

９．臨床使用の適正化（２）：不適切な使用

日常臨床で以下の項目について検査を実施することは不適切な使用である。

(1) 進行した重度の認知症症例

(2) 症状・経過が典型的で診断が明らかな場合

(3) Preclinical ADの診断（健常者の検診）

(4) 治療効果の判定

(5) 医療以外の目的（雇用、保険など）

(6) 倫理的配慮/手続きが十分実施できない場合

１０．アミロイドPETの適応まとめ

検査の意義は老人斑密度の推定である。

・陰性所見：アルツハイマー病の除外（単独で主張できる）

・陽性所見：アルツハイマー病の疑い（他所見と併用して判断）

現時点での制限

・単独ではAD診断を支持できない

・発症予測法は未確立

・治療効果判定に使えるかどうかは未確立

１１．アミロイドイメージングの適正使用に関する今後の見通し

現在は根本治療薬実用化前夜であり、現時点における適正使用は、上記に述べたように、日常臨床においては、陰性所見によるアルツハイマー病除外に基づく鑑別診断、アルツハイマー病の早期診断（MCI due to AD：診断、治療のスタンスについては移行期であり議論あり）、開発研究目的では、治療薬治験における対象者選択、アルツハイマー病早期病態研究等があげられる。

しかし、有効性のある根本治療薬が実用化すれば、進行遅延・発症予防治療の対象選択の目的で実施することが想定される。このため、本ガイドラインの適正使用に関する項目は、随時改訂を行っていく必要がある。

（以上）

Ⅴ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

1. 英文原著・症例報告

著者名	論文題名	雑誌名	巻	頁	出版年
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3. 英文単行本
該当なし

4. 邦文原著・症例報告

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VI. 研究成果の刊行物・別刷

J Neurol (2013) 260:1982–1991
DOI 10.1007/s00415-013-6908-0

ORIGINAL COMMUNICATION

Progressive apraxic agraphia with micrographia presenting as corticobasal syndrome showing extensive Pittsburgh compound B uptake

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Received: 13 December 2012 / Revised: 25 March 2013 / Accepted: 27 March 2013 / Published online: 16 April 2013

Abstract A 65-year-old woman developed progressive apraxic agraphia, characterized by poorly formed graphemes, a kanji (Japanese morphograms) recall impairment, relatively preserved oral spelling of kanji characters, and incorrect stroke sequences on writing accompanied by micrographia over a 3-year period. She also showed minor degrees of rigidity, limb-kinetic apraxia, and ideomotor apraxia of the left hand. Although asymmetric rigidity and limb-kinetic apraxia strongly suggested corticobasal degeneration, ^{11}C-Pittsburgh compound B positron emission tomography (PiB-PET) showed the predominantly right-sided accumulation of amyloid β in the cortices and striatum. ^{18}F-fluoro-deoxy-glucose PET and single photon emission computed tomography with a ^{99m}Tc-ethylcysteinate dimer (ECD-SPECT) also revealed predominantly right-sided hypometabolism and hypoperfusion in the primary sensorimotor cortex, posterior cingulate gyrus, temporoparietal cortices, frontal cortices, thalamus, and basal ganglia, a pattern characteristic of both corticobasal degeneration and Alzheimer's disease. The findings suggest that progressive apraxic agraphia with micrographia presenting as corticobasal syndrome can show an Alzheimer's disease pathology. It is also suggested that ideomotor apraxia of the left hand can occur without a callosal lesion, and is caused by hypometabolism or hypoperfusion in the right frontal and parietal cortices, as revealed by PET and SPECT.

Keywords Apraxic agraphia · Non-callosal ideomotor apraxia of the left hand · Micrographia · Corticobasal degeneration · Alzheimer's disease

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Introduction

Apraxic agraphia is a writing disorder of motor processing that is responsible for converting orthographic information into neuromuscular commands for handwriting movements [1]. Apraxic agraphia is defined by the following deficits [2]: (1) illegible graphemes in writing that cannot be explained by sensorimotor dysfunction, (2) grapheme production that improves with copying, (3) preserved oral spelling or typing, and (4) incorrect stroke sequences on writing [3, 4]. From a neuropsychological perspective, apraxic agraphia is assumed to result from damage to the parietal graphemic area in which visuokinesthetic and sequential motor engrams for words and letters are stored, or the disconnection of output from the graphemic area to frontal graphic output programming area [2]. When disruption occurs in the graphemic area, patients can recall the orthography of a word, but cannot spell it. In the latter

disconnection-type agraphia, patients can orally spell a character, but cannot specifically write the stroke sequences [3]. The lesion responsible for apraxic agraphia due to focal damage is in the superior parietal lobule or area surrounding the intraparietal sulcus [4, 5].

Apraxic agraphia also occurs in cortical degenerative diseases. This type of progressive apraxic agraphia has been reported in corticobasal syndrome (CBS) [6, 7] or with an unknown etiology [8]. Given that corticobasal degeneration (CBD) predominantly affects the postcentral gyrus and surrounding area asymmetrically, it is not surprising that CBD presents as progressive apraxic agraphia. However, one reported patient exhibited a progranulin mutation related to frontotemporal lobar degeneration [7]. Thus, the etiology of progressive apraxic agraphia appears to be heterogeneous.

Progressive agraphia generally occurs as an initial symptom or manifests in parallel with other language disorders in cortical degeneration, such as Alzheimer's disease (AD) [9–11], frontotemporal lobar degeneration [12], amyotrophic lateral sclerosis [13], and CBD [14]. In AD, lexical agraphia (a selective spelling impairment of irregular or exceptional words) is common, probably because degeneration involves the temporoparietal junction, including the angular gyrus in the early stage, damage to which causes lexical agraphia. Phonological agraphia (a selective spelling impairment of regular or consistent nonwords) [15] and a semantic impairment with homophone confusion [16] are also known to occur in AD. However, apraxic agraphia has rarely been reported in association with AD because the superior parietal lobule, the responsible lesion, is involved in the later stage of AD.

Here, we report a patient with progressive apraxic agraphia who exhibited the clinical features of CBD, but showed prominent Pittsburgh compound B (PiB) uptake in the cortices and striatum on positron emission tomography (PET), and was thus diagnosed with possible AD.

Materials and methods

Patient profile

The patient, a 65-year-old right-handed housewife who graduated from senior high school, found that she could not write some kanji (Japanese morphograms) characters and the characters that she could write became progressively smaller in December 2009. In June 2010, she could not mentally calculate her change when she went shopping. She had no family or past history of neurological disorders. She consulted the Department of Neurology, Teikyo University, Tokyo. MRI and MRA in November 2010 revealed an enlarged right lateral ventricle, bilateral parietal lobe atrophy, diffuse lacunar infarction in the deep white matter (Fig. 1a), and stenosis of the horizontal portion of the right middle cerebral artery (Fig. 1b) and the right fetal type posterior cerebral artery originating from the internal cerebral artery. Single photon emission computed tomography with a ^{99m}Tc-ethylcysteinate dimer (ECD-SPECT) in October 2010 showed hypoperfusion in the bilateral superior parietal region, which was more extensive on the right. Clopidogrel administration was started from November 2010. In December 2010, she could not tie her apron strings at the back, put clothes on properly, or button her shirt. She began to fall easily during walking. Because of her progressive deterioration, she was referred to the Department of Neurology, Mitsui Memorial Hospital, Tokyo, in March 2011. Neurological and neuropsychological examinations showed: (1) agraphia of kanji characters, (2) acalculia, (3) limb-kinetic apraxia of the left hand, (4) dressing apraxia, (5) bilateral (predominantly left-sided) limb ataxia, and (6) minor degrees of lead pipe rigidity in the left hand. She did not show forced grasping, alien hand sign (a feeling that one limb is foreign, with involuntary motor activity [17]), or utilization behavior.

She achieved a lower score for the performance IQ in the Wechsler Adult Intelligence Scale-Revised (WAIS-R) in May 2011 (Table 1). The Western Aphasia Battery (WAB; Japanese edition) administered in May 2011 revealed isolated agraphia, characterized by impaired kanji character recall, poor grapheme formation, a progressive reduction in the character size during writing (micrographia), the deletion of kana (Japanese phonetic writing) characters, and incorrect stroke sequences (Fig. 2). She stopped spelling while writing and resumed writing from the beginning even when the strokes were correct. This kind of trial and error was particularly observed when writing kanji characters. When copying a sentence, she wrote stroke by stroke; referring to the sample and the spelled graphemes barely improved with copying. Her recognition of orally spelled kanji characters was perfect, whereas oral spelling of auditorily presented kanji characters was within the normal range. She also complained that she could not spell out a character, even though she could recall the visual image of the character. She could correctly arrange kanji sequences with character cards that she could not write in response to dictation. Overall, her language profile was rated as apraxic agraphia with micrographia. In praxis, she did not gesture to command the use of a hammer, or copy the examiner gesturing its use with the left hand, but held the actual hammer and used it properly with either hand. Spontaneous drawing of a cube was without perspective, and copying of the cube was inaccurate. She did not show hemispatial neglect or Bálint syndrome.

Subsequent neuropsychological tests, cerebrospinal fluid and apolipoprotein ε genotyping studies, and a positron emission tomography study were conducted between March and October 2011. A follow-up neuropsychological study was performed between April and January 2013. She

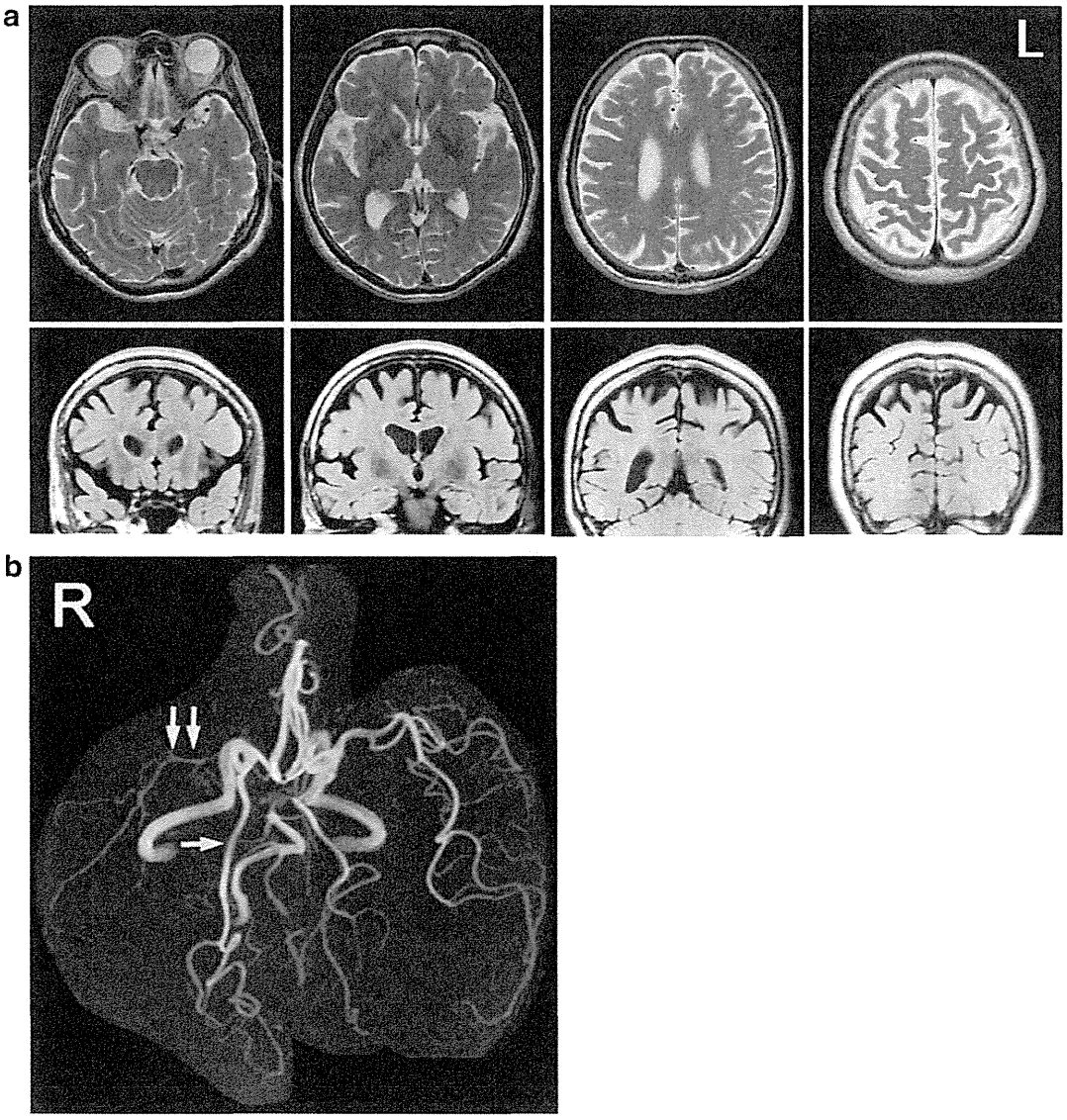

Fig. 1 MRI and MRA of the patient in November 2010. **a** MRI T2-weighted axial and FLAIR coronal images revealed an enlarged right lateral ventricle, bilateral parietal lobe atrophy, and diffuse lacunar infarction in the deep white matter. **b** MRA showed stenosis of the horizontal portion of the right middle cerebral artery (*double arrows*) and right fetal type posterior cerebral artery originating from the internal cerebral artery (*arrow*)

gave written informed consent to each of these studies. The study protocol was approved by the research ethics committee of our hospital, and thus was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Special neuropsychological tests

Reading and writing test

To evaluate the patient's reading and writing performance quantitatively, we conducted a reading and writing test with 100 single-character kanji and kana transcription [18] in March 2011. These characters are taught in the first 3 years of primary school in Japan. The results confirmed the diagnosis of isolated kanji agraphia (Table 1). There were 12 incorrect strokes in kanji and four in kana (Table 2). The trial and error problems described above occurred with 12 kanji and 16 kana characters. Three authors (Y.S, K.H., and I.S.) evaluated the grapheme errors. Among the correct responses, 18 kanji and 15 kana characters were rated as poorly formed, although she complained that all the characters were poorly written. Frequent errors were dislocation (wrong position or direction of each component or stroke) in both kanji and kana.

Table 1 Neuropsychological test scores

Year	2011	2012
WAIS-R		
Verbal IQ	95	93
Digit span forward	6	5
Performance IQ	76	76
WAB		
Spontaneous speech		
Information content (/10)	10	10
Fluency (/10)	10	9
Naming total (/10)	9.4	10
Object naming (/60)	60	60
Repetition (/10)	10	10
Comprehension total (/10)	9.6	9.2
Reading total (/10)	9.7	9.5
Comprehension of sentences (/40)	40	40
Recognition of orally spelled kanji (/6)	6	4
Oral spelling of kanji characters (/6)	3	3
Writing total (/10)	8.15	6.85
Copying of sentences (/10)	8.5[a]	9
Kanji writing from dictation (/6)	2.5	3
Kana writing from dictation (/6)	6	6
Praxis (/10)	rt. 10, lt. 9.7	rt. 10, lt. 9.3
Drawing (/30)	13[a]	16
Calculation (/24)	24	24
100 single-character kanji and kana transcription test (time)		
Kanji reading	100 (2 min 21 s)	100 (2 min 44 s[b])
Kana reading	100 (1 min 10 s)	100 (1 min 24 s)
Kanji writing	56[b] (16 min 34 s[b])	37[b] (24 min 6 s[b])
Kana writing	97[b] (15 min 30 s[b])	88[b] (23 min 3 s[b])
Calculation test		
Mental arithmetic (/40)	28	20
Dictated calculation (/40)	36	37
Electronic calculator (/40)	40	40

[a] More than 2SD below the normal mean [46]

[b] More than 2SD below the normal mean (score) and above the normal mean (time) [4]

An analysis of the visual complexity, concreteness, familiarity, and frequency of the correctly written kanji characters [19] revealed that less complex ($p < 0.001$ by Fisher's exact method), more frequent ($p = 0.0085$ by Fisher's exact method), or more familiar ($p = 0.007$ by Fisher's exact method) characters were written more easily.

Calculation test

As the WAB calculation subtest did not detect acalculia, we performed a supplementary calculation test. The test consisted of an equal number of addition, subtraction, multiplication, and division tasks between two and one digit; half with and half without carrying or borrowing [20]. Mental arithmetic, dictated calculation, and manipulation of an electronic calculator were tested. Mental arithmetic was inferior to dictated calculation (Table 1), which was more attributable to a reduced working memory than to impairment in arithmetic operations.

Test for apraxia

Eight test items were adopted to evaluate limb-kinetic apraxia. The patient could pick up a coin or pencil from a table with her left hand, but it was clumsier than the right hand, and she held a pencil in an awkward manner in her left hand, suggesting slight limb-kinetic apraxia. Furthermore, 10 test items were added to evaluate her use of objects. She had difficulty gesturing and imitating the use of scissors, nail clippers, or a paper fan only with her left hand, whereas the actual use of these tools was preserved. Thus, ideomotor apraxia of the left hand was evident.

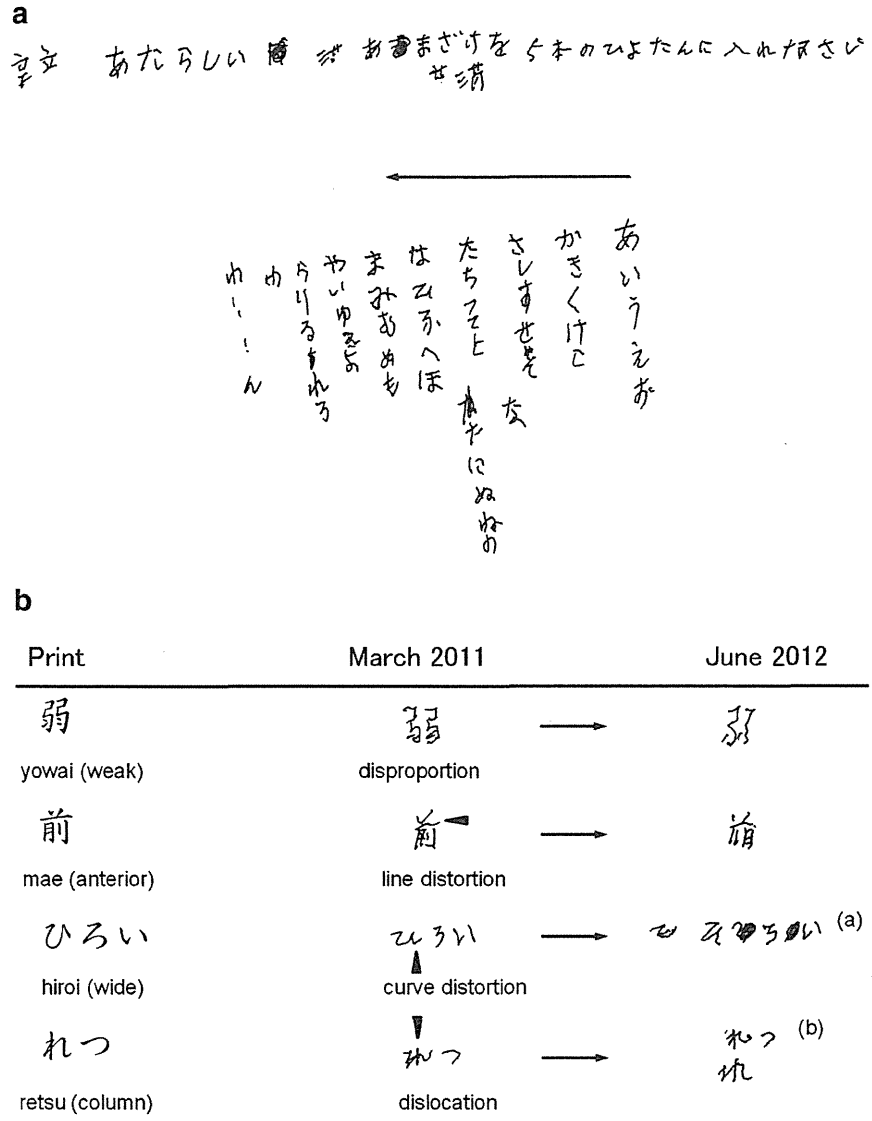

Fig. 2 Patient's writing samples. **a** Writing from the dictation of a sentence (*upper*) showed traces of trial and error, impaired kanji recall (two kanji characters were not recalled), a kana character deletion (ひょうたん a gourd cup → ひょたん), and micrographia. Writing of Japanese syllabary from right to left (*arrow*) also yielded micrographia (*lower*). **b** Examples of grapheme deformities at 1 year and 3 months after the onset and 1 year later. The *arrowhead* denotes the deformed part pointed out by the authors. An evaluation is shown below

Test for cortical tactile disorders

The tactile recognition of objects with blindfolded eyes was normal (right 9/10, left 9/10 of test items). The mean vibration time at the distal interphalangeal joints (DIP) was 14.6 s for the right and 11.4 s for the left: the vibration sense of the left fingers was slightly impaired. There was no left–right difference in two-point discrimination at the tip of the fingers (mean, right 5.4 mm, left 5.8 mm) and graphesthesia at the palm (right 6/10, left 7/10 of trials).

Tests for memory and executive function

Although she did not clinically exhibit amnesia, she could recall only one out of three words in a 5-min delayed recall test, whereas she could recall three visually presented objects completely after 5 min in March 2011. The same result was repeated in January 2013. The Wechsler Memory Scale-Revised test administered in January 2013 (3 years after the disease onset) revealed the following: Verbal Memory Index 77, Visual Memory Index 68, General Memory Index 70, Attention and Concentration 78, and Delayed Recall 79. Thus, her memory remained relatively preserved.

The executive function was evaluated with the Frontal Assessment Battery (FAB) [21] in January 2013. She achieved a score of 15 out of 18. The lost points were similarities (two points) and motor series (Luria's fist-edge-palm test, one point). Her score for lexical fluency was ten (words). No forced grasping, instinctive grasp reaction, such as closing, trapping and magnet response, alien hand sign, or utilization behavior was observed.

Table 2 Types of writing errors and deformities in 100 single-character kanji and kana transcription

Time	March 2011	June 2012
Kanji total errors	44	62
Non-response	13	30
Partial response[a]	13	21
Constructional[a]	14	10
Neographism	0	1
Visual[a]	2	0
Visual/constructional[a]	2	0
Kanji trial and error[b]	12	8
Kanji incorrect stroke sequences[b]	12	17
Kanji deformity total[b]	18	12
Disproportion	2	5
Dislocation	5	4
Line distortion	2	1
Elongation	1	0
Kana total errors	3	12
Non-response	0	1
Partial response	1	1
Constructional	2	9
Neographism	0	1
Kana trial and error[b]	16	20
Kanji incorrect stroke sequences[b]	4	1
Kana deformity total[b]	15	30
Disproportion	1	0
Dislocation	8	5
Line distortion	1	1
Curve distortion	0	4
Elongation	1	0

[a] Partial response. A component of a character was written correctly. Constructional response. Omission or addition of a component of a character. Visual errors. Substitution of another visually similar character, e.g., 角 ([kado], corner) → 負 ([makeru], lose). Visual/constructional errors. Substitution of another visually similar character with the omission or addition of a component of the character

[b] Trial and error and incorrect stroke sequences were evaluated for all characters tested. Trial and error denotes an attempt to write an incorrect or incomplete character repeatedly. Deformity was evaluated only for correct responses. Scores were based on the assessment of the three authors. A character was counted only if two or more authors evaluated the deformity, irrespective of its deformity-type. Deformed characters were chosen when two or more authors' deformity-type assessment was identical. Eventually, the total number of deformities exceeded the sum of each deformity type. Disproportion was the disproportionate size of each component in a character or word, or imbalanced horizontal-to-vertical ratio of a character. Dislocation was the wrong position or direction of each stroke. Distortion was the disruption of a straight line or curve. Elongation was of a line or stroke

Cerebrospinal fluid study and apolipoprotein ε genotyping

The cerebrospinal fluid (CSF) levels of amyloid β 1-42 protein (Aβ), total tau protein (t-tau), and phosphorylated tau-181 protein (p-tau), i.e., standard biomarkers for AD, were measured by ELISA (Innogenetics NV, Zwijndrecht, Belgium) according to the manufacturer's protocol in June 2011. The results revealed that Aβ levels were 632 pg/ml (normal >500), t-tau 1026 pg/ml (normal <300), and p-tau 140 pg/ml (normal <55). Her CSF Aβ concentration was within the normal range, whereas t-tau and p-tau levels were markedly increased. This pattern was exceptional for AD, in which Aβ levels are reduced and t-tau and p-tau levels are elevated [22]. It also differs from that of CBD, in which Aβ levels are decreased and t-tau and p-tau levels are normal [23].

Apolipoprotein ε (ApoE) genotyping was performed with a polymerase chain reaction (PCR) for genomic DNA extracted from the patient's blood sample. The patient was an ε3/ε4 heterozygote.

Neuroimaging study

The patient underwent a follow-up ECD-SPECT at our hospital in April 2011 (Fig. 3). SPECT data were analyzed with statistical parametric mapping (SPM) [24] Version 2. Significance was determined with a two-sample t test for one patient vs. group (normal control) analysis. The normal subject database was provided with the easy Z-score Imaging System (eZIS) version 3 ($n = 18$ for 60–69-year-old women) [25]. Areas showing a significant decrease in cerebral blood flow (uncorrected $p < 0.001$) were shown on standard brain surface images (for details of the method, see Sakurai et al. [19]). Hypoperfusion was noted in the left superior parietal lobule (Brodmann Area 7), right superior and inferior parietal lobules (Areas 7, 39, and 40), right middle occipital gyrus (Area 18), and right superior frontal gyrus (Area 6).

To establish a diagnosis, the patient underwent ^{18}F-2-fluoro-2-deoxy-D-Glucose PET (FDG-PET) and ^{11}C-Pittsburgh compound B PET (PiB-PET) at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, in October 2011. FDG and PiB PET image slices were superimposed on the patient's MRI FLAIR axial images with Dr. View software (AJS, Tokyo, Japan). PiB uptake was evaluated with a standardized uptake value ratio (SUVR) taking the cerebellar cortex as a reference region. FDG-PET revealed diffuse cortical hypometabolism other than in the left occipital lobe. The primary sensorimotor cortex, posterior cingulate gyrus, temporoparietal cortices, frontal cortices, thalamus, and basal ganglia were all involved, and it was more pronounced on the right (Fig. 4a). PiB-PET disclosed diffuse and intensive uptake in the bilateral cortices and striatum, with less intensive uptake in the sensorimotor cortex and occipital lobe. Uptake was more marked on the right (Fig. 4b).

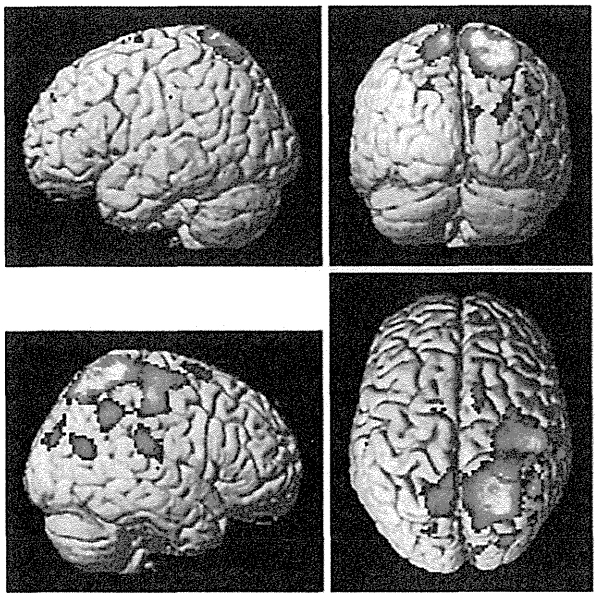

Fig. 3 ^{99m}Tc- ECD SPECT images in April 2011, 1 year and 4 months after the onset. Patient data were compared with those of a normal subject database of the same generation and gender ($n = 22$) with a two-sample t test of SPM2 to show areas with a significant blood flow decrease (uncorrected $p < 0.001$) on standard brain surface images. Hypoperfusion was noted in the left superior parietal lobule, right superior and inferior parietal lobules, right middle occipital gyrus, and right superior frontal gyrus

In August 2011, the patient found that her articulation was poor and myoclonus of the left hand became evident. She was administered donepezil in October 2011. In February 2012, predominantly left-sided rigidity changed from lead pipe to cogwheel. Although she did not go shopping alone and visited our hospital with her husband, she hardly had any difficulties with activities of daily living, except for putting clothes on even 3 years after the onset. Re-examination 1 year later revealed that writing and mental arithmetic had worsened, whereas the general intelligence remained stable (Tables 1, 2). Although she complained that her articulation deteriorated when she spoke for a longer time, only a few phonemic errors (substitution of speech sounds) were noted in the repetition of phoneme sequences such as "pa-ta-ka-pa-ta-ka" (five times) and there was no phonetic distortion (ill-formed phonemes) in spontaneous speech, sentence repetition, or reading in the reassessment using the WAB test. Also, she could stick out her tongue, whistle, and mime blowing out a match. Therefore, neither apraxia of speech nor buccofacial apraxia was noted.

Discussion

The patient developed progressive kanji agraphia with micrographia, acalculia, dressing apraxia, a constructional disorder, and limb-kinetic and ideomotor apraxia of the left hand over a 3-year period. Minor degrees of rigidity were found at the first examination. Agraphia was characterized by poor graphemes, preserved oral spelling, and incorrect stroke sequences. Although the copying of characters did not improve the grapheme forms (which may have been due to a constructional disorder), we can diagnose this disorder as apraxic agraphia. Impaired character recall is sometimes observed in apraxic agraphia [26, 27]; therefore, the coexistence of kanji agraphia due to impaired character recall does not exclude the diagnosis of apraxic agraphia.

Etiological consideration

The patient exhibited limb-kinetic apraxia, ideomotor apraxia, rigidity, and myoclonus of the left hand. Progressive asymmetric rigidity and apraxia, together with a cognitive decline, are consistent with the diagnosis of CBS [28]. FDG-PET revealed hypometabolism in the sensorimotor cortex, thalamus, and basal ganglia, particularly in the right hemisphere, which is characteristic of CBD [29]. However, PiB-PET demonstrated extensive PiB uptake in the neocortex and striatum, which was more prominent on the right. The involvement of the sensorimotor cortex was atypical for AD. However, focal and asymmetric cortical syndromes, such as CBS, have been recognized with an AD pathology that predominantly involves the sensorimotor cortex [30]. Thus, the diagnosis was possible AD (atypical clinical course) with evidence of the AD pathophysiological process [31]. Although multiple lacunes were found on MRI (Fig. 1a), they were too small in size and number to cause the symptoms.

Despite the fact that CSF t-tau and p-tau levels were markedly elevated, Aβ levels were within the normal ranges. The abnormally high CSF t-tau and p-tau levels reflect neuronal degeneration or the formation of tangles in AD [32]. On the other hand, low CSF Aβ levels reflect the deposition of Aβ in plaques [32]. Why our patient had a normal concentration of CSF Aβ with extensive PiB uptake is unclear. However, CSF Aβ values are known to fluctuate by 3–10 % over the course of a day [33]. Also, some patients with AD have normal CSF Aβ levels [34]. Hence, physiological fluctuations, individual differences, and measurement variables may have influenced the result.

A literature review contrasting CBS with an underlying AD pathology (CBS-AD) and that with an underlying CBD pathology (CBS-CBD) [30] revealed that CBS-AD is more strongly associated with a longer disease duration (median 9 vs. 6 years, respectively), a younger age at onset (mean 60 vs. 66 years, respectively), hemisensory neglect, memory impairment, visuospatial difficulties, dressing apraxia, and myoclonus. Our patient was consistent with this view

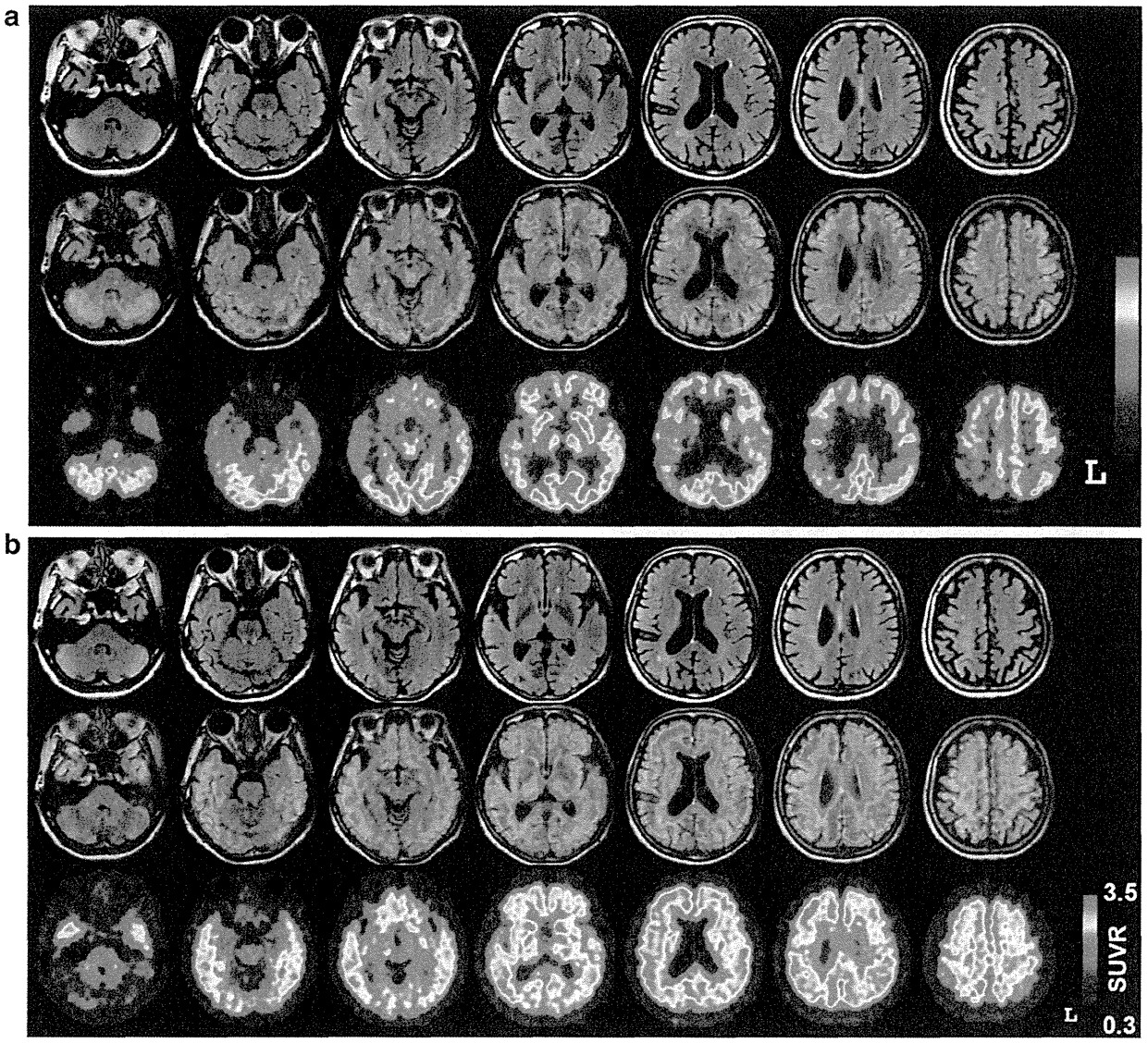

Fig. 4 FDG-PET and PiB-PET images superimposed on the patient's FLAIR images. **a** MRI FLAIR axial images in November 2010 (*upper*), FDG-PET images in October 2011 (*lower*), and PET images superimposed on the patient's FLAIR images (*middle*). FDG-PET revealed diffuse cortical hypometabolism other than in the left occipital lobe, and it was more pronounced on the right. **b** MRI FLAIR axial images in November 2010 (*upper*), PiB-PET images in October 2011 (*lower*), and PET images superimposed on the patient's FLAIR images (*middle*). Diffuse and intensive uptake was observed in the bilateral cortices and basal ganglia, with less intensive uptake in the sensorimotor cortex and occipital lobe. Uptake was more marked on the right. *SUVR* standardized uptake value ratio

of visuospatial difficulties, dressing apraxia, and myoclonus, but she did not show a younger age at onset, hemisensory neglect, or notable memory impairment. In another study [35], initial episodic memory complaints appeared to predict CBS-AD, whereas early frontal-lobe type behavioral symptoms appeared to predict CBS-CBD. However, our patient did not exhibit these symptoms. Therefore, clinical features alone could not be used to predict her pathology. This is because the patient's main lesion was in the predominantly right-sided postrolandic superior parietal cortices, of which the pattern was different from either CBS-CBD or CBS-AD: the patterns of atrophy were noted to be more restricted to posterior frontal regions in CBS-CBD, whereas they were more widespread, including posterior temporal and inferior parietal cortices, in CBS-AD [36].

Substantial evidence has shown that ApoE isoforms differentially affect the aggregation and clearance of Aβ in the brain [37], and the presence of ε4 is associated with increased Aβ in AD [38]. The fact that our patient with one