GLOBAL SCIENCE LIBRARY

Frontiers in Clinical Neurology and Neurosurgery

RESEARCH ARTICLE

Cerebral blood flow-single-photon emission computed tomography and Brodmann mapping may facilitate the evaluation of clinical features of early-onset Alzheimer's disease

Nobuhiko Miyazawa* and Toyoaki Shinohara

Department of Neurosurgery, Kofu Neurosurgical Hospital, Japan

Abstract

A relatively large numbers of studies have reported on the clinical features, classifications, and impairment of cerebral blood flow (CBF) in cases with Alzheimer's disease. However, only few reports have investigated the relationships between clinical tests and lesion areas in the brain with significantly reduced CBF, assessed using single-photon emission computed tomography (SPECT).

This study aimed to assess the correlations between impaired Mini-Mental State Examination (MMSE) scores and reduced CBF using Brodmann area mapping and classify early-onset Alzheimer's disease (EOAD). Thirty-one patients aged <65 years, with memory impairment, were examined using CBF-SPECT, and MMSE during the same period. Twenty patients were diagnosed with EOAD.

We divided the patients into two groups: one with bilateral reduction of CBF in temporo-parietal region and the other with unilateral reduction. The bilateral group had significantly lower MMSE scores than the unilateral reduction group, but it had significantly less family history, significantly poor prognoses, and ten significantly reduced CBF in the Brodmann area (BA) with SPECT. In the bilateral group, there were large correlations between impaired MMSE and reduced CBF regions in the BA. These findings confirm that the classification of EOAD may pave the way to understand patients with EOAD.

Keywords*: early-onset Alzheimer's disease, MMSE, SPECT, 3D-SSP, Brodmann area*

Abbreviations: *AD: Alzheimer's Disease, CDR: Clinical Dementia Rating, EAOD: Early-Onset Alzheimer's Disease, IMP: I-123 iodoamphetamine, IOF: 123I-ioflupane, IWG-2: International Working Group 2, MMSE: Mini-Mental State Examination, SPECT: Single-Photon Emission Computed Tomography*

Introduction

Alzheimer's disease (AD) accounts for 50%–60% of all patients with dementia [1]. Early-onset AD (EOAD) is rare, occurs in people aged <65 years, has a devastating prognosis for patients, and is a major burden for caregivers [2,3]. There have been relatively large numbers of reports regarding clinical features, classifications, and impairment of both cerebral blood flow (CBF) and glucose metabolism [4-7]. However, only a few reports are available in terms of the relationships between clinical tests, such as the Mini-Mental State Examination (MMSE) and Wechler Memory Scale-Revised, and lesion area with significantly reduced CBF assessed using single-photon emission computed tomography (SPECT) [8] CBF analysis with Brodmann area (BA) mapping is thought to be a precise method to diagnose reduced CBF.

Thus, this study aimed to identify a helpful classification of reduced patterns on SPECT to understand the clinical features of EOAD and observe the relationships between reduced patterns on SPECTs with BA mapping and the total and subscales of MMSE.

Methods

Patients

From January 2008 to December 2019, 31 patients aged <65 years with AD patterns on SPECT were examined for memory disturbance or/and other symptoms. Clinical examination, MMSE, and 3T magnetic resonance imaging (MRI) were performed on the same day, and SPECT was conducted approximately after one week. Family and education histories were obtained from the patients or caregivers. The National Institute on Aging and Alzheimer's Association criteria and the International Working Group 2 criteria [9,10] were used to diagnose patients with AD. Patients with cerebral vascular lesions and severe white matter lesions on MRIs were excluded. A medical doctor, certified in Japanese nuclear medicine and dementia examined and evaluated the patterns on SPECT and abnormalities on MRI.

This study was approved by the Ethics Committee of Kofu Neurosurgical hospital and informed consent was obtained from all patients.

Cerebral perfusion SPECT

I-123 iodoamphetamine (IMP)-SPECTwas performed for all patients in our hospital. Three-dimensional stereotactic surface projections with vbSEE software were used to evaluate the reduction of regional CBF. Patients who underwent SPECT were intravenously administered 167–222 MBq of IMP with their eyes open, in a quiet room. Fifteen minutes after administering IMP, SPECT was performed with a triple-head gamma camera (Toshiba GCA93000R, Toshiba, Tokyo, Japan). Images were acquired on a 128 × 128 matrix. Reconstruction was performed using the filtered back projection technique, and ramp filters were utilized for smoothing [11]. We used a severity z-score on the BA mapping to evaluate decreases in CBF. A medical doctor, certified in Japanese nuclear medicine, categorized SPECT findings into three patterns (Figure 1): (I) significant reductions confined to the parietal lobe, and/or the frontal lobe, posterior cingulate cortex, and precuneus cortex (Mild cognitive impairment group); (IIa) significant reductions that extended from the parietal lobe to the temporal lobe bilaterally (Bilateral reduction group); and (IIb) significant reductions that extended from the parietal lobe to the temporal lobe unilaterally (Unilateral reduction group).

Neuropsychiatric examinations

The MMSE and Clinical Dementia Rating (CDR) were administered to all patients. The MMSE consists of several subscales, i.e., orientation (high score: 10), attention (5), late memory (3), language (8), visuospatial recognition (1), and total score (30), which were used for analysis [12] Patients with CDR of 1, 2, and 3 were judged as having dementia and those with CDR of 0.5 and 0 were judged as having mild cognitive impairment (MCI) and no cognitive impairment, respectively.

Table 1: Clinical data of the unilateral and bilateral group

	Bilateral group (n=10)	Unilateral group (n=10)	P-value
Age	45–64 (57.7)	49–64 (58.5)	0.385
Sex	Male: 6; Female: 4	Male: 6; Female: 4	0.5
Fam. Hist.	1	7	0.0062
Educ. Hist.	9–16 (13.7)	9–16 (13.7)	0.5
Prognosis	−4.67	−2.3	0.0484

Fam. Hist.: Family history; Educ. Hist.: Education history; Prognosis: difference in the Mini-Mental State Examination score between first and follow-up examination (1 year later).

Statistical analysis

The Student's t-test and chi-square test were used to compare clinical data between patients within the subgroups. The Pearson' correlation was used to assess relationships between total and subscales of MMSE and reduced CBF areas on BA mappings. P values <0.05 were considered significant.

Results

Clinical and demographic data of patients

Eleven patients had a SPECT pattern of (I), and these patients either had MCI or did not have cognitive impairment based on the CDR. However, 10 patients each had a SPECT pattern of (IIa) and (IIb). All patients with SPECT patterns of (IIa) and (IIb) were considered to have dementia based on CDR.

Firstly, in comparisons between I and (IIa,IIb), The mean age of patients with a SPECT pattern of (I) was 59.1 years and that of those with SPECT patterns (IIa) and (IIb) was 58.1 years. There was no significant difference between the AD (20 cases) and non-AD groups (11 cases) (p = 0.318). The proportion of male and female with specific SPECT patterns was as follows: eight males and one female patient had a SPECT pattern of (1); 12 males and 8 female patients had a SPECT pattern of (IIa, b), but without any significant difference was observed (p = 0.48). There was no significant difference in education history between the two pattern groups (13.7 vs. 13.0 years; p = 0.224). Family history with AD was more frequently observed in the (IIa, b) group (eight patients had a history) than in the (I) group (one patient had a history) (p = 0.0689). In terms of total and subscales of MMSE, there were significant differences in total MMSE scores between the two groups: the (I) group, 27.0 and the (IIa, b) group, 22.6 (p = 0.00112). Orientation, attention, and late memory were significantly worse in the (IIa, b) group than in the (I) group (p = 0.00261, p = 0.0106, p = 0.00404). However, there were no significant differences in language and visuospatial recognition (p = 0.28, p = 0.469).

Secondary, in the comparisons between the (IIa) and (IIb) groups, there was no significant difference in mean ages between the two groups (p = 0.385), and sex-specific distribution was the same (males: six, females: four). More patients had a family history (all had mothers with AD) in the (IIb) group than in the (IIa) group (p = 0.0062). There was no significant difference in education history between the two groups (p = 0.5). Patients in the (IIa) group deteriorated significantly more rapidly than those in the (IIb) group, as assessed using MMSE (p = 0.0484) (Table 1).

Regarding the comparison of the total and subscales of MMSE between the (IIa) and (IIb) groups, there were significant differences in total attention (p = 0.0425, p = 0.0282). There were non-significant differences in language and visuospatial recognition (p = 0.0523, p = 0.075). Moreover, there were no significant differences in orientation and late memory (p = 0.2953, 0.278) (Figure 2).

SPECT findings

In the I group, there was no significant reduction of CBF on SPECT in the BA. In the (IIa) group, a mean z-score of severity >2.0 was judged as a significant reduction of CBF. Significant reductions on SPECT in the BA were recognized in BA7, BA19, BA20, BA21, BA22, BA31, BA37, BA39, BA40, and BA42. The most significant reductions were observed in area 39. Interestingly, left side reduction was dominant in all areas (Figure 3)

In the (IIb) group, each case had a different area of reduction with a z-score >2.0; however, only the mean z-score in BA39 was >2.0.

Correlation of decreased CBF in the SPECT and MMSE scores

In the (IIa) group, reduction of total MMSE scores correlated with right side BA31 (p = 0.0328). That of attention correlated with left BA7, BA19, BA39, and BA40 (p = 0.00283, 0.0105, 0.00971, 0.0107). That of late memory correlated with right BA22 and BA31 (0.0475, 0.0145). That of language correlated with left BA7, BA22, and BA39 and right BA40 (p = 0.00256, 0.046, 0.00156, 0.00269). That of visuospatial recognition correlated with left BA7, BA19, BA31, and BA39 (p = 0.000173, 0.00765, 0.0224, 0.00104). No correlation was found between reduction of orientation and the BA (Figure 4).

In the (IIb) group, there was no correlation between MMSE and reduced BA39.

Discussion

In this retrospective study, patients were divided as having patterns of (I), (IIa), and (IIb) according to reduced CBF on SPECT. Patients with (I) either had MCI or did not have cognitive impairment, and although the mean age and sex-specific distribution were the same for all groups, MMSE scores were significantly higher in the (I) group than in the (IIa, b) group; furthermore, number of cases with family history were significantly lower in the (I) group than in the (IIa, b) group. We focused on patients with dementia who had patterns of (IIa) and (IIb) because of reduced CBF on SPECT. The MMSE total and subscale scores, family histories, and prognoses were significantly different in patients with SPECT patterns of (IIa)

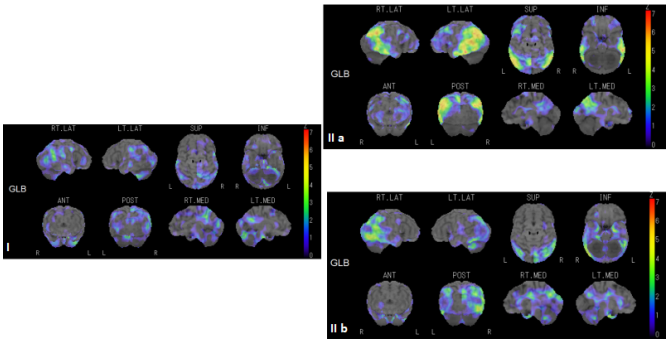

Figure 1: Classification of reduced cerebral blood flow-single-photon emission computed tomography findings. Left: Mild cognitive impairment or without cognitive impairment group.

Upper right: Bilateral reduction group; Lower right: Unilateral reduction group.

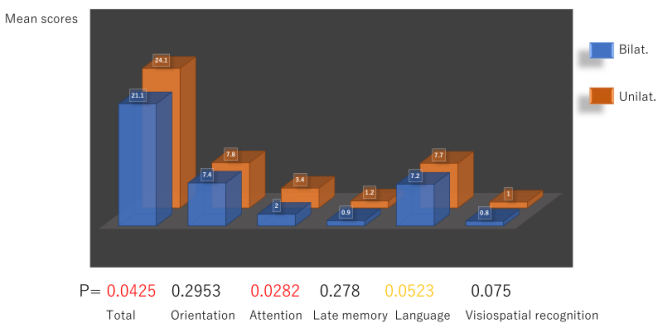

Figure 2: Differences in total and subscales of the Mini-Mental State Examination scores between the bilateral and unilateral reduction group (Left–Right: Total, orientation, attention, late memory, language, visuospatial recognition)

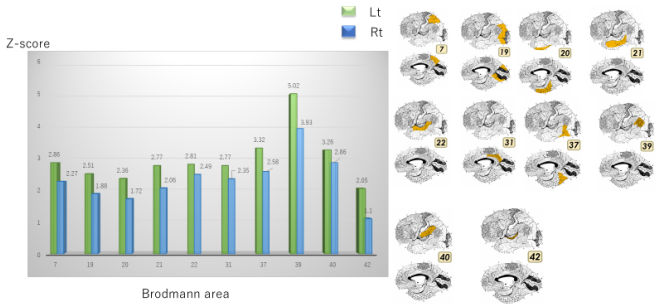

Figure 3: Z-score of reduced cerebral blood flow on Brodmann mapping area in the bilateral reduction group.

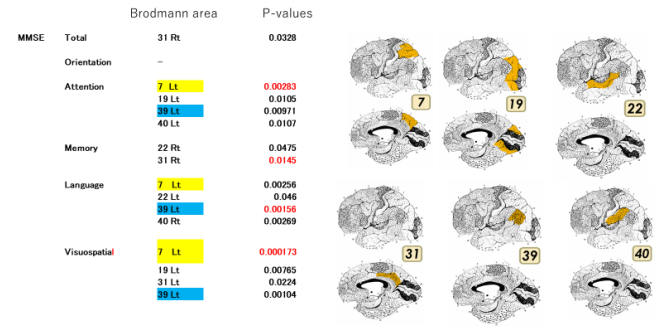

Figure 4: Correlation of Mini-Mental State Examination scores and reduced cerebral blood flow on Brodmann mapping area in the bilateral reduction group.

and (IIb). The significantly reduced CBF regions on BA mapping of patients with a SPECT pattern of (IIa) revealed ten areas and those with a SPECT pattern of (IIb) revealed only one area.

There were significant correlations between MMSE total and subscale scores and reduced CBF regions on BA mapping in patients with a SPECT pattern of (IIa).

In terms of the classification of AD, a recent review and meta-analysis reported that there were four subtypes of AD based on the distribution of tau-related pathology and regional brain atrophy: typical (55%), limbic-predominant (21%), hippocampal-sparing (17%), and minimal atrophy AD (15%) [7]. Regarding the classification of EOAD, typical, language-type, visuospatial-type, and executive function-type have been well recognized [6]. Although this classification mainly depended on clinical signs examined by neurologists, SPECT, PET, and autopsy findings were in line with the examination findings [8]. There have been several reports of reduced glucose metabolism and reduced CBF in patients with EOAD [5,6,11,12,14-17]. Hypometabolism on FDG-PET was noted in the fronto-temporo-parietal association cortices and retrosplenial area in 21 AD patients, and patients with EOAD had a more severe reduction of regional glucose metabolism in the associated cortices [14]. Using the NEUROSTAT program for 40 patients with AD (20 EOAD cases), all patients with AD had significant hypometabolic regions in the bilateral parieto-temporal regions than age-matched individuals, and EOAD patients had more severe hypometabolism in the bilateral parietal and posterior cingulate cortices and precuneus region than late-onset patients [15]. Using BA analysis, bilateral BA20, BA21, BA39, BA40, and right BA23 were judged as having significantly reduced glucose metabolism, compared with the control group without cognitive impairment [16]. Our study showed a reduction of CBF in bilateral BA7, BA19, BA20, BA21, BA22, BA31, BA37, BA39, BA40, and the findings of BA42, and BA20, BA21, BA39, and BA40 were in accordance with those of a FDG study [16]. In a CBF-SPECT study, the parieto-temporal region also appeared to be a significantly reduced region, and in some cases, it showed reduction in occipital region [13,17]. Although there was the report of BA mapping using CBF-SPECT, the mean age of the patients (34 cases) was 70.9 ± 8.1 years; however, bilateral BA38, BA36, BA23, BA25, and BA28 were recognized as significantly reduced CBF areas [5]. Because the distributions of patients' ages were different from our study, the results regarding the reduced areas were not in accordance with our results.

Finally, in terms of correlation between MMSE scores and CBF-SPECT, significant correlations were observed in the posterior cingulate cortex and both temporoparietal association cortices (right-side dominant) of 28 patients with AD [8]. However, Kaneta et al. reported that the mean age of the patients was >79 years and no description of BA mapping and only the total scores of the MMSE were used for correlation analyses. Our study was the first to observe the correlation of both total and subscales of MMSE and reduced CBF areas using BA mapping. In our study, correlations were strongly recognized in patients in the (IIa) group, total of MMSE, subscales (except orientation correlated with a large number of BAs). Among them, left BA7 and left BA39 were correlated with attention, language, and visuospatial recognition. Left BA19 correlated with attention and visuospatial recognition. Right BA31 correlated with total MMSE score and late memory. These BAs are considered as the core part of damages in EOAD [16]. In the (IIb) group, significant reduction was found in BA39; however, no correlation was recognized. In comparison with the prognosis of late-onset AD and EOAD, the decline of CDR suggests that EOAD may show more rapid deterioration [16]. On the other hand, to date, no study has compared CDR within EOAD; thus, our result showed that patients in the (IIa) group deteriorated significantly more rapidly than those in the (IIb) group, as assessed using MMSE ($p = 0.0484$) and the bilateral group might deteriorate more rapidly than the unilateral group. This finding may assist better understanding of clinical features of EOAD.

Despite the strengths of the study, a potential limitation could be the small number of cases analyzed and the use of MMSE, which is slightly less precise. Large number of cases would therefore be needed in future studies, with more precise neuropsychiatric tests same with MMSE subscales.

In conclusion, considering significant differences with family history and prognoses of these unilateral and bilateral groups, classification of the two types is very helpful in understanding the clinical features of EOAD.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1. Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. *Neurol Clin*. 2007; 25: 577-609.
2. Nussbaum RI, Ellis CE. Alzheimer's disease and Parkinson's disease. *New Engl J Med*. 2003; 348: 1356-1364.
3. Querfurth HW, LaFerla FM. Alzheimer's disease. *New Engl J Med*. 2010; 362: 329-344.
4. Garre-Olmo J, Genis Batlle D, del Mar Fernandez M, Marquez Daniel F, de Eugenio Huelamo R, et al. Incidence and subtypes of early-onset dementia in a geographically defined general population. *Neurology*. 2010; 75: 1249-1255.
5. Valotassiou V, Papatriantafyllou J, Sifakis N, Tzavara C, Tsougos I, et al. Clinical evaluation of brain perfusion SPECT with Brodmann area mapping in early diagnosis of Alzheimer's disease. *J Alzheimers Dis*. 2015; 47: 773-785.
6. Vanhoutte M, Semah F, Sillaire AR, Jaillard A, Petyt G, et al. 18F-FDG PET hypometabolism patterns reflect clinical heterogeneity in sporadic forms of early-onset Alzheimer's disease. *Neurobiol Aging*. 2017; 59: 184-196.
7. Ferreira D, Nordberg A, Westman E. Biological subtypes of Alzheimer disease. *Neurology*. 2020; 94: 1-13.
8. Kaneta T, Katsuse O, Hirano T, Ogawa M, Shihikura-Hino A, et al. Voxel-wise correlations between cognition and cerebral blood flow using arterial spin-labeled perfusion in patients with Alzheimer's disease: a cross-sectional study. *BMC Neurol*. 2017; 17: 91-100.
9. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association working groups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7: 263-269.

10. Dubois B, Feldman HH, Jacova C, Jacova C, Hampel H, Molinuevo JL, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014; 13: 614-629.

11. Miyazawa N, Shinohara T, Nagasaka T, Hayashi M. Hypermetabolism in patients with dementia with Lewy bodies. *Clin Nucl Med*. 2010; 35: 490-493.

12. Shigemori K, Ohgi S, Okuyama E, Shimura T, Schneider E. The factorial structure of the mini mental state examination (MMSE) in Japanese dementia patients. *BMC Geriatr*. 2010; 10: 36-42.

13. Mendez MF, Lee AS, Joshi A, Shapira JS. Nonamnestic presentations of early-onset Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2012; 27: 413-420.

14. Yasuno F, Imamura T, Hirono N, Ishii K, Sakaki M, et al. Age at onset and regional cerebral glucose metabolism in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1998; 9: 63-67.

15. Sakamoto S, Ishii K, Sasaki M, Hosaka K, Mori T, et al. Differences in cerebral metabolic impairment between early and late onset types of Alzheimer's disease. *J Neurol Sci*. 2002; 200: 27-32.

16. Kim EJ, Cho SS, Jeong Y, Park KC, Kang SJ, et al. Glucose metabolism in early onset versus late onset Alzheimer's disease: an SPM analysis of 120 patients. *Brain*. 2005; 128: 1790-1801.

17. Kawakatsu S, Kobayashi R, Hayashi H. Typical and atypical appearance of early-onset Alzheimer's disease: a clinical, neuroimaging and neuropathological study. *Neuropathology*. 2017; 37: 150-173.

[*] ***Correspondence:*** Nobuhiko Miyazawa MD, PhD, 1-16-18 Sakaori, Kofu-city, Yamanashi-pref. 400-0805, Japan, Tel: +81-55-235-0995, Fax: +81-55-226-9521, E-mail: nobu_miya9311@yahoo.co.jp

Received: August 26, 2022; **Accepted:** September 26, 2022; **Published:** September 29, 2022

Citation: Miyazawa N, Shinohara T. Cerebral blood flow-single-photon emission computed tomography and Brodmann mapping may facilitate the evaluation of clinical features of early-onset Alzheimer's disease. *Front Neurol Neurosurg*. 2022; 1: 101.