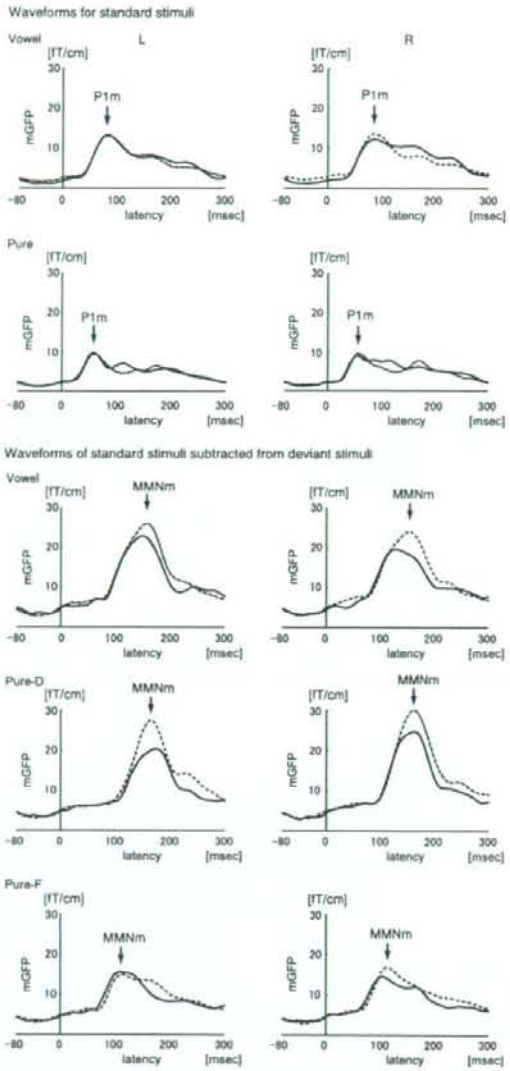

Figure 4. Grand mean mGFP waveforms of P1m (upper four panels) and MMNm (lower six panels) averaged for each group (major depressive disorder patients [solid line] and healthy volunteers [dashed line]), for each condition (vowel across-category change condition [Vowel], pure-tone [Pure], pure-tone duration change condition [Pure-D] and pure-tone frequency change condition [Pure-F]), and for each hemisphere (right [R], left [L]).

properties. They elicited MMNm in response to duration changes of pure-tone stimuli (standard: 100-ms duration, 1000-Hz frequency; duration deviant: 250-ms duration, 1000-Hz frequency), whereas we elicited MMNm in response to duration changes of pure-tone stimuli (standard: 50-ms duration, 1000-Hz frequency; duration deviant: 100-ms duration, 1000-Hz frequency). Without appropriate control conditions, exogenous/obligatory responses contributing differently to the repetitive standard stimulus and the rare deviant stimulus affect the results (Kujala, Tervaniemi, & Schröger, 2007). As in their studies, we did not control this effect; thus, the difference between our results and their results may be due to the non-MMN contribution such as offset-N1.

The absence of group differences in the mGFP powers and latencies of P1m in this study is also in disagreement with the results of Kähkönen et al. (2007). Whereas they found a shorter P1m latency in the major depressive disorder patients and its significant negative correlation with the HDRS scores, no such significant differences or correlations were obtained in this study. These differences cannot be explained by the differences in the

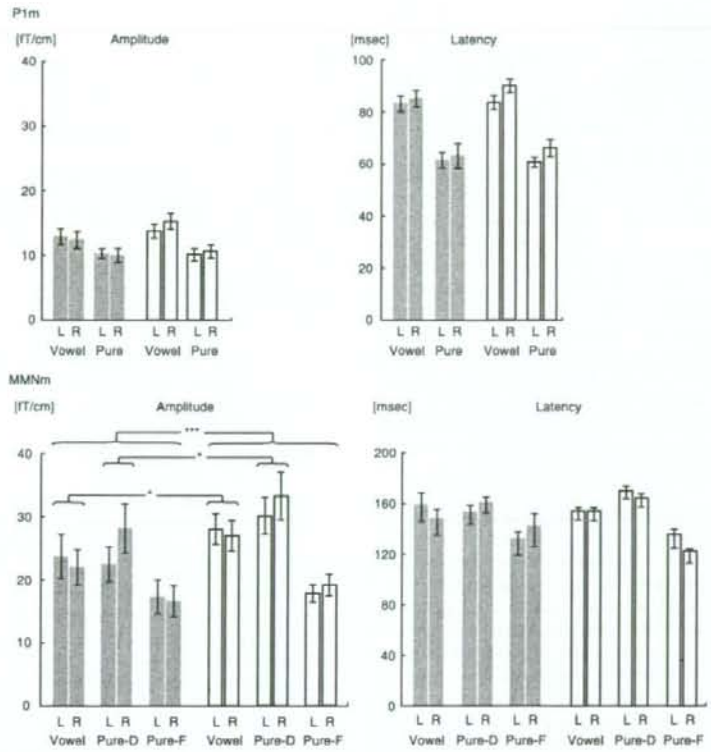

Figure 5. mGFP powers and latencies of P1m (upper panels) and MMNm (lower panels) averaged for each group (major depressive disorder patients [gray], healthy volunteers [white]), for each condition (vowel across-category change condition [Vowel], pure-tone duration change condition [Pure-D], and pure-tone frequency change condition [Pure-F]) and for each hemisphere (right [R], left [L]). Each error bar indicates standard error: $^{*}p < .1$; $^{**}p < .05$; $^{***}p < .01$.

task conditions described above. The differences in the severity of the depressive symptoms between the patients in the two studies may be one of the possible reasons for the difference in the results. The HDRS scores in this study were smaller those in the study by Kähkönen et al.

In the child subjects, Lepistö et al. (2004) found unchanged MMN amplitude and smaller MMN latency in major depressive disorder patients. In addition, Ogura et al. (1995) examined the N200 component in adult major depressive disorder and bipolar disorder and found small amplitudes of the early N200 component that is assumed to correspond to MMN. The results of this study are in agreement with those of Ogura et al. (1995) but not with those of Lepistö et al. Differences in task designs and in the age, severity of depressive symptoms, and medication status of the subjects may partly explain these discrepancies.

Relationship between MMN and Clinical Variables

The absence of significant correlations between MMNm power and doses of antidepressants, anxiolytics, and hypnotics in this study suggests that a smaller MMNm power in major depressive disorder patients is not due to the effects of psychotropic medication. In addition, although the MMN amplitude has been reported to be reduced in Alzheimer's disease and dementia (Pekkonen, 2000; Schroeder, Ritter, & Vaughan, 1995), MMNm power reduction in this study is not assumed to be due to intellectual decline in the subjects, because the subjects suspected of having dementia were excluded from our study on the basis of their MMSE scores.

The clinical significance of the MMNm power reduction in major depressive disorder patients can be speculated considering the lack of significant correlations of MMNm power with clinical variables. The lack of a significant correlation between MMNm power and clinical symptoms may suggest that the MMNm power reduction is not a state-dependent finding. The lack of a significant correlation between MMNm power and illness duration or age of onset may suggest its nonprogressive nature. Taken together, MMNm power reduction in major depressive disorder patients may be assumed to reflect the trait for developing major depressive disorder or the morbid process of developing major depressive disorder.

Shuchaku-Seikaku (*Shuchaku* the tendency for obsessive preoccupation with certain thoughts and affairs; *Seikaku* character) is a type of personality often observed as a premorbid personality of depression, particularly in Japan. MMN (N2a component) amplitude reduction in *Shuchaku-Seikaku* patients supports this interpretation (Ogura et al., 1991). This interpretation should be examined in future studies with more subjects and detailed personality assessments.

On the other hand, MMN amplitude for a pure-tone frequency change condition in schizophrenia was demonstrated to correlate with illness duration in a meta-analysis (Umbricht & Krljes, 2005), and MMN amplitude in schizophrenia was demonstrated to be reduced in recent-onset and chronic patients but not in first-episode patients (Umbricht, Bates, Lieberman, Kane, & Javitt, 2006). These findings support the deteriorating nature of MMN through the illness course. On the other hand, MMN amplitude has been reported to be reduced in adolescent-onset schizophrenia (Oades et al., 2006), which may suggest the trait-dependent or morbid-process-related nature of MMN reduction. Moreover, MMN amplitude reduction in schizophrenia may be interpreted to indicate state-dependent neurodegeneration based on the finding that MMN amplitude in a nonaffected member of twin pairs discordant for schizophrenia is unchanged when compared with that in healthy subjects (Ahveninen et al., 2006).

The results of the MMNm dipole location suggest an additional significance of MMNm abnormalities in major depressive disorder patients. The MMNm dipole has been estimated to be located more laterally in schizophrenia patients than in healthy volunteers in some studies (Kasai et al., 2003; Oades et al., 2006; Pekkonen et al., 2002), and the location shift is interpreted to reflect functional and structural abnormalities in the temporal lobe. The unchanged dipole location of MMNm in major depressive disorder patients in this study suggests that MMNm abnormalities in major depressive disorder patients are more functional than structural. However, this finding should be regarded as preliminary because correction for brain size was not considered. Preserved P1m power in this study also suggests additional significance of MMNm power reduction in major depressive disorder patients. Major depressive disorder patients may be relatively spared in sensory function (P1m) but more impaired in higher cognitive function, including preattentive level (MMNm), as compared with schizophrenia in which both P1m and MMNm powers are reduced (Ahveninen et al., 2006).

P1m Results

Some of the results obtained in this study are different among the three task conditions. As for P1m, both its mGFP and latency were significantly smaller in the pure-tone condition than in the vowel across-category change condition. As for MMNm, its mGFP and latency were significantly smaller in the pure-tone frequency change condition than in the pure-tone duration change condition and the vowel across-category change condition. These results suggest that P1m may be affected mainly by the physical property of the sound, whereas in the case of MMNm, it may be affected by the task conditions in a more complex manner.

This assumption is also supported by the estimated locations of the dipoles. Although the locations of the P1m dipole were not estimated differently across the task conditions, the locations of MMNm were estimated more anteriorly in the vowel across-category change condition than in the pure-tone duration change condition but not in the pure-tone frequency change condition. Comparison between P1m and MMNm resulted in the differences in the location: The MMNm dipole is located more superiorly than the P1m dipole. These results suggest again that the location of MMNm is affected not only by the physical property of the sound but also by the task condition.

Limitations of This Study

The limitations of this study are as follows: (1) The number of subjects is small; (2) the results were drawn from patients with mild to moderate symptoms; and (3) although we found no significant correlation of MMNm or P1m finding with psychotropic medication except mood stabilizers, the effect of psychotropic medication cannot be completely excluded because almost all the patients took psychotropic drugs. In the future, studies with more subjects in various mood states in a drug-free condition and longitudinal follow-up cohort studies including premorbid patients will be performed.

Conclusions

We investigated preattentive information processing in major depressive disorder patients by MEG using MMNm and P1m. The MMNm power was smaller in major depressive disorder patients than in healthy volunteers. This result suggests the functional dysfunction of preattentive information processing irrespective of clinical symptoms and psychotropic medication in major depressive disorder patients; this dysfunction is not due to the dysfunction at the lower level of information processing.

REFERENCES

Ahveninen, J., Jaaskelainen, I. P., Osipova, D., Huttunen, M. O., Ilmoniemi, R. J., Kaprio, J., et al. (2006). Inherited auditory-cortical dysfunction in twin pairs discordant for schizophrenia. *Biological Psychiatry, 60,* 612–620.

Alho, K., Winkler, I., Escera, C., Huotilainen, M., Virtanen, J., Jääskeläinen, I. P., et al. (1998). Processing of novel sounds and frequency changes in the human auditory cortex: Magnetoencephalographic recordings. *Psychophysiology, 35,* 211–224.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Austin, M. P., Ross, M., Murray, C., O'Carroll, R. E., Ebmeier, K. P., & Goodwin, G. M. (1992). Cognitive function in major depression. *Journal of Affective Disorders, 25,* 21–29.

Beyer, J. L., & Krishnan, K. R. (2002). Volumetric brain imaging findings in mood disorders. *Bipolar Disorders, 4,* 89–104.

Giard, M. H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. *Psychophysiology, 27,* 627–640.

Hämäläinen, M., Hari, R., Ilmoniemi, R., Knuutila, J., & Lounasmaa, O. V. (1993). Magnetoencephalography: Theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics, 65,* 413–497.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23,* 56–62.

Hari, R., Hämäläinen, M., Ilmoniemi, R., Kaukoranta, E., Reinikainen, K., Salminen, J., et al. (1984). Responses of the primary auditory cortex to pitch changes in a sequence of tone pips: Neuromagnetic recordings in man. *Neuroscience Letters, 50,* 127–132.

Honea, R., Crow, T. J., Passingham, D., & Mackay, C. E. (2005). Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry. *American Journal of Psychiatry, 162,* 2233–2245.

Inagaki, A., & Inada, T. (2006). Dose equivalence of psychotropic drugs. Part XVIII: Dose equivalence of psychotropic drugs: 2006 Version. *Rinsyo Seisin Yakuri, 9,* 1443–1447.

Kähkönen, S., Yamashita, H., Rytsälä, H., Suominen, K., Ahveninen, J., & Isometsä, E. (2007). Dysfunction in early auditory processing in major depressive disorder revealed by combined MEG and EEG. *Journal of Psychiatry & Neuroscience, 32,* 316–322.

Karaaslan, F., Gonul, A. S., Oguz, A., Erdinc, E., & Esel, E. (2003). P300 changes in major depressive disorders with and

without psychotic features. *Journal of Affective Disorders, 73*, 283–287.

Kasai, K., Yamada, H., Kamio, S., Nakagome, K., Iwanami, A., Fukuda, M., et al. (2003). Neuromagnetic correlates of impaired automatic categorical perception of speech sounds in schizophrenia. *Schizophrenia Research, 59*, 159–172.

Kawasaki, T., Tanaka, S., Wang, J., Hokama, H., & Hiramatsu, K. (2004). Abnormalities of P300 cortical current density in unmedicated depressed patients revealed by LORETA analysis of event-related potentials. *Psychiatry and Clinical Neurosciences, 58*, 68–75.

Knuutila, J. E. T., Ahonen, A., Hämäläinen, M. S., Kajola, M. J., Laine, P. P., Lounasmaa, O. V., et al. (1993). A 122-channel whole-cortex SQUID system for measuring brain's magnetic field. *IEEE Transactions on Magnetics, 29*, 3315–3320.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology, 38*, 557–577.

Kreitschmann-Andermahr, I., Rosburg, T., Meier, T., Volz, H. P., Nowak, H., & Sauer, H. (1999). Impaired sensory processing in male patients with schizophrenia: A magnetoencephalographic study of auditory mismatch detection. *Schizophrenia Research, 35*, 121–129.

Kujala, T., Tervaniemi, M., & Schröger, E. (2007). The mismatch negativity in cognitive and clinical neuroscience: Theoretical and methodological considerations. *Biological Psychology, 74*, 1–19.

Lehmann, D., & Skrandies, W. (1980). Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalography and Clinical Neurophysiology, 48*, 609–621.

Lepistö, T., Soininen, M., Čeponiené, R., Almqvist, F., Näätänen, R., & Aronen, E. T. (2004). Auditory event-related potential indices of increased distractibility in children with major depression. *Clinical Neurophysiology, 115*, 620–627.

Lyytinen, H., Blomberg, A. P., & Näätänen, R. (1992). Event-related potentials and autonomic responses to a change in unattended auditory stimuli. *Psychophysiology, 29*, 523–534.

McGee, T. J., King, C., Tremblay, K., Nicol, T. G., Cunningham, J., & Kraus, N. (2001). Long-term habituation of the speech-elicited mismatch negativity. *Psychophysiology, 38*, 653–658.

Näätänen, R. (1992). The mismatch negativity (MMN). In R. Näätänen (Ed.), *Attention and brain function* (pp. 136–200). Hillsdale, NJ: Lawrence Erlbaum Associates.

Näätänen, R., Gaillard, A. W., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica, 42*, 313–329.

Oades, R. D., Wild-Wall, N., Juran, S. A., Sachsse, J., Oknina, L. B., & Ropcke, B. (2006). Auditory change detection in schizophrenia: Sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. *BMC Psychiatry, 6*, 7.

Ogura, C., Nageishi, Y., Fukao, K., Shimoji, Y., Hirano, K., Hokama, H., et al. (1991). Deviate N200 component of event-related potentials in shuchaku-seikaku, a premorbid personality of depression. *Japanese Journal of Psychiatry and Neurology, 45*, 641–651.

Ogura, C., Nageishi, Y., & Omura, F. (1995). Reduced mismatch negativity and hyperactivation of N2b in depression. *Electroencephalography and Clinical Neurophysiology Supplement, 44*, 218–223.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*, 97–113.

Papageorgiou, C. C., Alevizos, B., Ventouras, E., Kontopantelis, E., Uzunoglu, N., & Christodoulou, G. (2004). Psychophysiological correlates of patients with delusional misidentification syndromes and psychotic major depression. *Journal of Affective Disorders, 81*, 147–152.

Pekkonen, E. (2000). Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. *Audiology & Neuro-otology, 5*, 216–224.

Pekkonen, E., Katila, H., Ahveninen, J., Karhu, J., Huotilainen, M., & Tiihonen, J. (2002). Impaired temporal lobe processing of preattentive auditory discrimination in schizophrenia. *Schizophrenia Bulletin, 28*, 467–474.

Roschke, J., & Wagner, P. (2003). A confirmatory study on the mechanisms behind reduced P300 waves in depression. *Neuropsychopharmacology, 28*(Suppl 1), S9–12.

Schroeder, M. M., Ritter, W., & Vaughan, H. G., Jr. (1995). The mismatch negativity to novel stimuli reflects cognitive decline. *Annals of the New York Academy of Science, 769*, 399–401.

Tervaniemi, M., Kujala, A., Alho, K., Virtanen, J., Ilmoniemi, R. J., & Näätänen, R. (1999). Functional specialization of the human auditory cortex in processing phonetic and musical sounds: A magnetoencephalographic (MEG) study. *NeuroImage, 9*, 330–336.

Tham, A., Engelbrektson, K., Mathé, A. A., Johnson, L., Olsson, E., & Åberg-Wistedt, A. (1997). Impaired neuropsychological performance in euthymic patients with recurring mood disorders. *Journal of Clinical Psychiatry, 58*, 26–29.

Trejo, L. J., Ryan-Jones, D. L., & Kramer, A. F. (1995). Attentional modulation of the mismatch negativity elicited by frequency differences between binaurally presented tone bursts. *Psychophysiology, 32*, 319–328.

Umbricht, D., Koller, R., Schmid, L., Skrabo, A., Grübel, C., Huber, T., et al. (2003). How specific are deficits in mismatch negativity generation to schizophrenia? *Biological Psychiatry, 53*, 1120–1131.

Umbricht, D., & Krljes, S. (2005). Mismatch negativity in schizophrenia: A meta-analysis. *Schizophrenia Research, 76*, 1–23.

Umbricht, D. S., Bates, J. A., Lieberman, J. A., Kane, J. M., & Javitt, D. C. (2006). Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biological Psychiatry, 59*, 762–772.

Urretavizcaya, M., Moreno, I., Benlloch, L., Cardoner, N., Serrallonga, J., Menchon, J. M., et al. (2003). Auditory event-related potentials in 50 melancholic patients: Increased N100, N200 and P300 latencies and diminished P300 amplitude. *Journal of Affective Disorders, 74*, 293–297.

Veiel, H. O. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology, 19*, 587–603.

Woldorff, M. G., Hillyard, S. A., Gallen, C. C., Hampson, S. R., & Bloom, F. E. (1998). Magnetoencephalographic recordings demonstrate attentional modulation of mismatch-related neural activity in human auditory cortex. *Psychophysiology, 35*, 283–292.

Yucel, G., Petty, C., McCarthy, G., & Belger, A. (2005). Graded visual attention modulates brain responses evoked by task-irrelevant auditory pitch changes. *Journal of Cognitive Neuroscience, 17*, 1819–1828.

Zakzanis, K. K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 11*, 111–119.

(Received October 17, 2007; Accepted April 21, 2008)

Novel Augmentation Therapy with Cilostazol for the Geriatric Major Depressive Disorder Patient with Deep White Matter Hyperintensities on T_2-Weighted Brain MRI: A Case Report

K. Takahashi[1], A. Oshima[1], K. Inoue[2], H. Takeyoshi[1], M. Fukuda[1], M. Mikuni[1]

[1]Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, Gunma, Japan

[2]Gunma Prefectural Psychiatric Medical Center, Gunma, Japan

In our search of a new augmentation therapy for geriatric patients with intractable depression, we administered cilostazol, an antiplatelet agent, in addition to conventional antidepressants to a patient with persistent major depressive disorder showing deep white matter hyperintensities on a T2-weighted magnetic resonance image and evaluated cerebral blood flow before and after the administration of cilostazol by ^{99m}Tc-ethylcysteinate dimer single photon emission computed tomography. This patient showed improvements of depressive symptoms as well as an increase in cerebral blood flow. These findings suggest a potential efficacy of cilostazol as a new drug for use in augmentation therapy for depressed patients with deep white matter hyperintensities.

Introduction

It has been reported that patients with geriatric depression exhibit a higher percentage of cerebrovascular disorder including asymptomatic cerebral infarction than the non-depressed population [5]. Cerebrovascular disorder has been considered to be deeply related to the condition of geriatric depression, and Alexopoulus et al. [1] and Krishnan et al. [6] proposed the concept of vascular depression in 1997. Thus, the importance of cerebrovascular lesions has been emphasized for understanding the pathophysiology of mood disorder in the elderly. Treatment of depressed patients with cerebrovascular lesions including asymptomatic ones is often difficult because many patients with this condition respond poorly to antidepressants, frequently develop side effects, and are more susceptible to chronicity or recurrence. Therefore, a new therapeutic approach that takes into account cerebrovascular factors is required. Cilostazol is an antiplatelet agent with a vasodilating effect that results in an enhancement of cerebral blood flow [7]. The drug has mainly been used for chronic arterial occlusion but also for preventing recurrent cerebral infarction because its effectiveness to prevent recurrence of cerebral infarction has been demonstrated in a large-scale study [2]. To the best of our knowledge, however, there has been no report yet of its efficacy in depressed patients with asymptomatic cerebrovascular lesions. In this study, we examined the possibility of a new augmentation therapy by concomitantly administering cilostazol and conventional antidepressants to a patient with a major depressive disorder and a silent cerebrovascular disorder.

Case Presentation

The subject is a 79-year-old female patient who was diagnosed as having recurrent major depressive disorder for 22 years on the basis of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR); she showed deep white matter hyperintensities on a T_2-weighted magnetic resonance image (MRI), no microhemorrhage on T_2*-weighted MRI of the brain, and presented with persistent depressive symptoms for 3 years in the current episode. Somatic complications were excluded by regular physical examination and laboratory tests at the time of admission, and the patient was free from any other medications. Brain ^{99m}Tc-ethyl cysteinate dimer single photon emission computed tomography (^{99m}Tc-ECD SPECT) images were obtained prior to cilostazol administration and five weeks after its initiation. The Hamilton Depression Rating Scale (HDRS) (Japanese version of the Structured Interview Guide for the HDRS (SIGH-D) [8]) was used to evaluate the symptoms. The Institutional Review Board of Gunma University Hospital approved this study. The subject gave her written consent to participate after procedures and possible side effects were explained to her.

In the current episode, the patient was hospitalized to our department after a suicide attempt. Despite antidepressant and anxiolytic medication, the patient continued to present with hypochondriacal complaints, hypobulia, and suicidal ideation, and adverse reactions often emerged due to abnormal activity of the metabolic liver enzyme cytochrome P450 2D6 (CYP2D6), which was discovered later. The drug treatment remained difficult and did not lead to remission. Although ECT relieved her depressed condition transiently, delirium arose and worsened, making it difficult to continue the ECT. After improvement of the delirium, hypochondriacal complaints, anxiety, restlessness, and diminished activity persisted. The doses of the drugs used at this point (15 mg/day, milnacipran; 250 mg/day, carbamazepine; 2.5 mg/day, olanzapine; and 50 mg/day, tiapride) were fixed 4 weeks prior to cilostazol administration, and brain MR imaging and ^{99m}Tc-ECD SPECT studies were conducted. T_2-weighted brain MRI showed many deep white matter hyperintensities, and the pre-cilostazol ^{99m}Tc-ECD SPECT showed a decrease in cerebral blood flow (**Fig. 1**). The HDRS score 2 weeks prior to cilostazol administration was 21. The concomitant treatment with cilostazol at 50 mg/day reduced the hypochondriacal complaints, improved activity, and decreased the HDRS score from 21 (at treatment initiation) to 15 (1 week later), and further to 6 (5 weeks later); thus, the patient was discharged. Mean cerebral blood flow (mCBF: mL/100 g/min) measured by ^{99m}Tc-ECD SPECT improved from 36.52 (2 weeks before cilostazol) to 40.14 (5 weeks after cilostazol). The plasma concentration of carbamazepine was 5.6 μg/mL (at treatment initiation) and 5.5 μg/mL (5 weeks later).

Discussion

We report here a case with difficult-to-treat major depressive disorder with asymptomatic deep white matter hyperintensities on the brain T_2-weighted MRI. The concomitant administration of cilostazol was effective in this patient.

Cilostazol improves cerebral blood flow in patients with chronic cerebral infarction, and has been reported to improve cerebral function evaluated by P300 event-related potential [7], and the

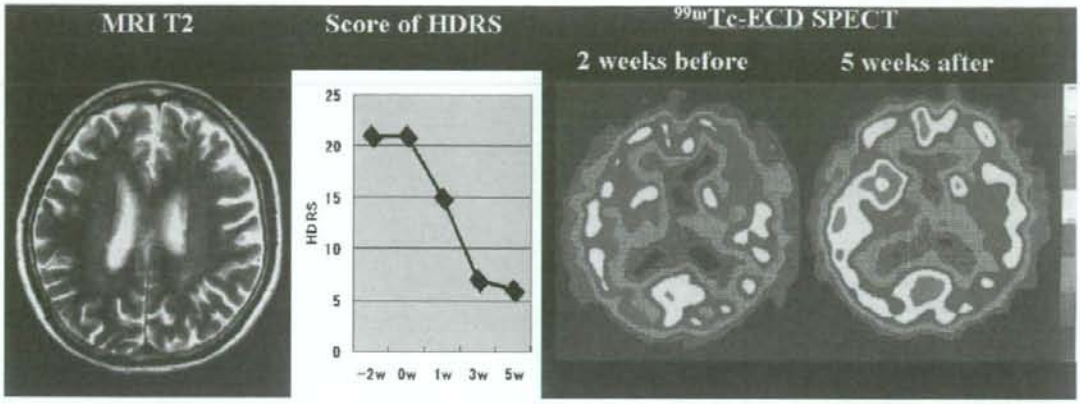

Fig. 1 This case showed broad deep white matter hyperintensities on the T_2-weighted brain MRIs. The HDRS score cerebral blood flow as shown by ^{99m}Tc-ECD SPECT, improved after cilostazol administration.

enhancing effect on cerebral blood flow may have led to the improvement of depressive symptoms in this case. Moreover, cilostazol inhibits PDE3; it has been confirmed in platelets [4] and vascular smooth muscle cells [11] that cilostazol inhibits the degradation of cAMP to AMP and increases the intracellular cAMP concentration. Moreover, in the white matter of rats with artificial chronic cerebral ischemia, increases in phosphorylated cAMP response element binding protein (CREB), Bcl-2, and COX-2 expression levels were reported in the cilostazol-treated group compared with the control group [12]. Furthermore, recent studies have revealed that chronic administration of antidepressants facilitates CREB phosphorylation [10] and transcription of target genes such as brain-derived neurotrophic factor (BDNF) [9] in the rat brain. Taken together, it may be postulated that the activation of these intracellular signaling molecules by cilostazol enhances neural activity, resulting in an increased cerebral blood flow and the eventual recovery from a depressive episode.

There is also a possibility that the plasma level of cilostazol may be affected by drugs like carbamazepine which induce liver enzymes, because cilostazol undergoes extensive hepatic metabolism. However, this is unlikely in the present case, as the plasma concentrations of carbamazepine were almost identical and low (5.5–5.6 μg/mL) before and after cilostazol treatment, and liver enzyme induction may be rather weak at this level.

In general, as in the case presented here, depressed patients with cerebrovascular lesions including asymptomatic lesions poorly respond to antidepressants and often develop adverse reactions, and the depressive symptoms tend to persist or recur [3]. For these major depressive disorder patients with cerebrovascular lesions, cilostazol may be promising as a new drug for augmentation therapy and merits further investigation.

Acknowledgments

We thank Dr. I. Ida, Dr. H. Kumano, Dr. M. Ito, Dr. M. Aihara, Dr. T. Majima, Dr. M. Amanuma, and Dr. K. Endo for their collaboration in this study. Funding for this study was provided by a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Japanese Ministry of Health, Labor and Welfare (MM).

References

1 *Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M.* Vascular depression hypothesis. Arch Gen Psychiatry 1997; 54: 915–922
2 *Gotoh F, Tohgi H, Hirai S, Terashi A, Fukuuchi Y, Otomo E, Shinohara Y, Itoh E, Matsuda T, Sawada T, Yamaguchi T, Nishimaru K, Ohashi Y.* Cilostazol Stroke prevention study: A placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis 2000; 9: 147–157
3 *Kales HC, Maixner DF, Mellow AM.* Cerebrovascular disease and late-life depression. Am J Geriatr Psychiatry 2005; 13: 88–98
4 *Kimura Y, Tani T, Kanbe T, Watanabe K.* Effect of cilostazol on platelet aggregation and experimental thrombosis. Arzneimittelforschung 1985; 35: 1144–1149
5 *Krishnan KR, Goli V, Ellinwood EH, France RD, Blazer DG, Nemeroff CB.* Leukoencephalopathy in patients diagnosed as major depressive. Biol Psychiatry 1988; 23: 519–552
6 *Krishnan KR, Hays JC, Blazer DG.* MRI-defined vascular depression. Am J Psychiatry 1997; 154: 497–501
7 *Mochizuki Y, Oishi M, Mizutani T.* Effects of cilostazol on cerebral blood flow, P300, and serum lipid levels in the chronic stage of cerebral infarction. J Stroke Cerebrovasc Dis 2001; 10: 63–69
8 *Nakane Y, Williams JBW.* Japanese version of structured interview guide for the Hamilton Depression Rating Scale (SIGH-D). Jpn J Clin Psychopharmacol 2003; 6: 1353–1368
9 *Nibuya M, Morinobu S, Duman RS.* Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995; 15: 7539–7547
10 *Nibuya M, Nestler EJ, Duman RS.* Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J Neurosci 1996; 16: 2365–2372
11 *Tanaka T, Ishikawa T, Hagiwara M, Onoda K, Itoh H, Hidaka H.* Effects of cilostazol, a selective cAMP phosphodiesterase inhibitor on the contraction of vascular smooth muscle. Pharmacology 1988; 36: 313–320
12 *Watanabe T, Zhang N, Liu M, Tanaka R, Mizuno Y, Urabe T.* Cilostazol protects against brain white matter damage and cognitive impairment in a rat model of chronic cerebral hypoperfusion. Stroke 2006; 37: 1539–1545

received 29.06.2007
revised 24.08.2007
accepted 03.09.2007

Bibliography
DOI 10.1055/s-2007-993208
Pharmacopsychiatry 2008;
41: 37–39

ISSN 0176-3679

Correspondence
K. Takahashi, MD, PhD
3-39-22 Showa-machi
Maebashi
371-8511 Gunma
Japan
Tel.: +81/27/220 81 90
Fax: +81/27/220 81 87
tkeisuke@showa.gunma-u.ac.jp

ELSEVIER

Journal of Affective Disorders 111 (2008) 46–51

Journal of Affective Disorders

www.elsevier.com/locate/jad

Research report

Executive dysfunction in medicated, remitted state of major depression

Yoshiyuki Nakano [a,1], Hajime Baba [a,*,1], Hitoshi Maeshima [a], Akiyoshi Kitajima [b], Yoshie Sakai [a], Kanako Baba [a], Toshihito Suzuki [a], Masaru Mimura [c], Heii Arai [a]

[a] *Department of Psychiatry, Juntendo University, School of Medicine, Tokyo, Japan*
[b] *Genkikai Yokohama Hospital, Kanagawa, Japan*
[c] *Department of Neuropsychiatry, Showa University, School of Medicine, Tokyo, Japan*

Received 27 October 2007; received in revised form 17 January 2008; accepted 30 January 2008
Available online 4 March 2008

Abstract

Background: Past neuropsychological studies on depression have documented executive dysfunction and it has been reported that some dysfunction persists even after depressive symptoms disappear. Studies have shown a correlation between cerebrovascular lesions and executive dysfunction in depression among the elderly. The aim of the present study was to focus on executive functions in remitted major depressive disorder (MDD) patients, and to investigate whether remitted young and elderly patients show different patterns of executive dysfunction, and to ascertain the relationships with vascular lesions.
Methods: Subjects were 79 inpatients with MDD and 85 healthy controls. Each subject received Wisconsin Card Sorting Test (WCST), Stroop test, and Verbal Fluency Test (VFT) in a remitted state. Both the MDD and control groups were divided into young and elderly groups, and the performances between 4 groups were compared.
Results: For Stroop test, the scores of the MDD group were significantly lower than controls. In addition, as for VFT, the scores for the elderly MDD group were significantly lower than the other groups. Multiple regression analysis showed that VFT scores were affected by the presence of vascular lesions.
Conclusions: The results of the present study demonstrated that executive dysfunction remained even in a remitted state in MDD patients, but the patterns of impairment were different between young and elderly patients. The results also suggested that vascular lesions affect executive dysfunction, particularly in elderly depressive patients.

Keywords: Depression; Remission; Executive function; Elderly; Vascular

1. Introduction

It is well known that patients with major depressive disorder (MDD) present with cognitive deficits, in particular executive dysfunctions (Fromm and Schopflocher, 1984; Franke et al., 1993; Channon, 1996; Veiel, 1997; Degl'Innocenti et al., 1998). Lockwood et al. (2002) compared executive dysfunction between young

* Corresponding author. Juntendo Koshigaya Hospital, 560 Fukuroyama, Koshigaya, Saitama, Japan 343-0032. Tel.: +81 48 975 0321; fax: +81 48 978 7821.
E-mail address: hbaba@med.juntendo.ac.jp (H. Baba).
[1] Y Nakano and H Baba contributed equally to this work.

0165-0327/$ - see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2008.01.027

and elderly MDD patients while on depressive episodes, and reported that selective and sustained attention exhibited no age and depression interaction whereas the elderly depressed patients alone demonstrated the slowed psychomotor speed and impaired performance on tasks requiring set sifting, problem solving and initiating novel responses. Recent studies have also documented that executive dysfunction may at least in part remain unresolved even after remission of depressive episodes (Trichard et al., 1995; Paradiso et al., 1997; Reischies and Neu, 2000; Neu et al., 2001; Biringer et al., 2005; Paelecke-Habermann et al., 2005).

Neural bases for residual executive dysfunction in remitted MDD patients are not well understood. One plausible account is existence of deep white matter vascular changes, which have reportedly been associated with executive dysfunction in elderly patients with MDD (Boone et al., 1992; Lesser et al., 1996; Aizenstein et al., 2002). White matter changes are more prevalent and severe in depressed elderly patients than in age-matched controls, and mainly occur in subcortical regions and their frontal white-matter projections (Coffey et al., 1990; Krishnan, 1993; Greenwald et al., 1996; Krishnan et al., 1997; Tupler et al., 2002; Taylor et al., 2003).

Although reports regarding executive dysfunction in remitted state of depression are increasing, few studies have investigated the possibly dissociable patterns between young and elderly patients. The aim of the present study was to explore differences in executive dysfunctions between young and elderly MDD patients in a remitted state and elucidate how cerebrovascular changes may affect these functions.

2. Subjects and methods

2.1. Subjects

Seventy-nine depressive inpatients (38 males and 41 females; mean age, 52.4 years; age range, 25–78 years) were recruited from Juntendo Koshigaya Hospital. All the patients previously met the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria for MDD. Thirty-eight patients experienced a single episode, 32 patients experienced recurrent episodes. For remaining nine patients it was unable to determine the number of episodes. At the time of the study, however, the patients were considered in remission, which was confirmed by the fact that they no longer met the DSM-IV criteria for MDD. In addition, their Hamilton Rating Scale for Depression (HAM-D) scored below 7 points (Hamilton, 1960). Patients were excluded if they had a history of other psychiatric disorders including delusions, severe or acute medical illnesses, neurological disorders, or use of drugs that may cause depression. All the patients were on antidepressant medication at the time of the study (Table 1).

Detailed demographic and clinical features of the participants are shown in Table 1. Presumed IQ was computed using the Japanese Adult Reading Test (JART) (Matsuoka et al., 2006). The patients were examined using the brain computed tomography (CT) to assess low density areas indicating white matter cerebrovascular changes. The brain CT of each patient was read by two reading specialists independently of and blindly to the results of the neuropsychological tests. Patients with large organic changes that may directly affect psychiatric features were excluded. The CT data were assessed using the Fazekas criteria by Krishnan et al. (1997). These criteria introduced a modified Fazekas classification system (Greenwald et al., 1996), which provided a rough assessment of the extent of subcortical gray matter, deep white matter, and periventricular changes on brain CT. Patients were classified as having vascular lesions if a score of ≥ 2 on either deep white matter low densities or subcortical gray matter ratings was obtained. Based on this criterion, 7% of young and 54% of elderly patients were classified as having vascular lesions.

Eighty-five healthy control participants (15 males and 70 females) matched for age and education were also recruited. All the controls were recruited from the employees of Genkikai Yokohama Hospital. Based on recent studies having reported individuals ≥ 60 years as geriatric subjects (Lockwood et al., 2002; Murphy et al., 2006), we divided both the MDD patients and controls into two age groups (young, <60 years and elderly, ≥ 60 years) and the neuropsychological performances were compared between the four groups. Presumed IQ was higher in the young MDD patients as compared to young controls ($p<0.05$). There were more females in the young controls than in the young MDD group ($p<0.001$). Subjects who had clinical evidence of dementia or whose Mini-Mental State Examination (MMSE) score <24 were excluded. Twelve MDD patients and 19 healthy subjects had hypertension.

The study was approved by the Medical Ethics Committee of Juntendo University, and was performed in accordance with the regulations outlined by Juntendo University. All the participants signed an informed consent form.

2.2. Executive function tests

Three executive function tests were given to each participant; the Wisconsin Card Sorting Test (WCST), Stroop and Verbal Fluency Test (VFT). For the WCST,

Table 1
Demographic of the subjects

	Young (<60 years)		Elderly (≥60)	
	Control (N=60)	MDD (N=55)	Control (N=25)	MDD (N=24)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	44.0 (11.4)	45.1 (8.3)	66.6 (4.5)	68.9 (4.5)
Sex (M/F)	12/48	32/23	3/22	6/18
Education (years)	13.2 (3.0)	14.2 (2.0)	12.1 (2.9)	11.5 (2.8)
Presumption IQ	101.2 (11.6)	105.5 (10.6)	95.7 (13.1)	97.3 (13.0)
On-set age (years)		40.5 (8.6)		63.0 (10.6)
Number of depressive episodes		1.8 (1.2)		2.1 (1.6)
Total duration of depressive phase (months)		25.8 (38.2)		43.0 (120.0)
Total duration of medication (months)		27.65 (42.1)		47.7 (116.4)
Vascular lesions		4(7%)		13(54%)

two indices of Categories Achieved (CA) and Perseverative Errors (PE) were selected as measures. The PE were useful for documenting problems in forming concepts, profiting from correction, and conceptual flexibility (Lezak et al., 2004). A computerized version of the test was used in the present study. We used modified Japanese version of Golden's (1978) 'Stroop Color and Word Test'. In the Stroop test Part I, the participant read aloud color words printed in ink of different colors (congruent condition). Part II required the participant to name the incongruent printed color of the color words (incongruent condition). Time difference between Part I and II (Part II–Part I) was evaluated (Golden, 1978). This difference has been attributed to a response conflict and to a failure of response inhibition (Lezak et al., 2004). For the VFT, we used the Japanese characters "a," "ka," and "sa" as prompts, and the score was the sum of all acceptable words produced within three one-minute trials. Successful performance in this test depends in part on the participant's ability to "organize output in terms of clusters of meaningfully related words" (Lezak et al., 2004). Fluency tests requiring word generation according to an initial letter provide subjects with the greatest scope for seeking a strategy to guide the search for words (Estes, 1974; Lezak et al., 2004).

2.3. Data analysis

Statistical analysis was performed using 2 (diagnosis; MDD vs. controls)×2 (age group; young vs. elderly) analysis of variance (ANOVA) at a significance level of $p<0.05$. Performances on each executive function test between MDD and controls were compared using two-tailed unpaired Student's t-test for post hoc analysis within each age group. Bonferroni correction was applied, and 0.25% level of significance was adopted.

Multiple regression analysis was conducted using neuropsychological test scores as dependent variables and age, gender, education level, and vascular lesions as independent variables. Statistical procedures were performed using Japanese version of SPSS v15.1 (SPSS Japan Inc. Tokyo, Japan).

3. Results

The means and standard deviations of the executive function tests are presented in Table 2, along with the

Table 2
Results of the four groups on the neuropsychological tests

	Young (<60)		Elderly (≥60)		Main effect of age		Main effect of diagnosis		Interaction between age×diagnosis	
	Control (N=60)	MDD (N=55)	Control (N=25)	MDD (N=24)						
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F (1,160)	p	F (1,160)	p	F (1,160)	p
WCST										
CA	3.3 (2.0)	3.4 (2.1)	1.96 (1.5)	2.0 (1.9)	14.84	<0.001	0.08	0.782	0.27	0.869
PE	5.6 (5.0)	6.0 (6.0)	9.6 (5.0)	7.9 (4.7)	8.95	0.003	0.43	0.515	1.20	0.275
Stroop test	55.2 (20.6)	78.5 (36.9)**	82.6 (31.0)	122.2 (77.8)*	26.73	<0.001	20.98	<0.001	1.41	0.236
VFT	32.1 (8.9)	32.7 (10.0)	29.8 (12.9)	22.2 (9.2)*	14.24	<0.001	4.19	0.042	5.73	0.018

Two-tailed paired Student's t-test for post hoc analysis within each age group. *$p<0.025$, **$p<0.001$.

Table 3
Results of multiple regression analysis

	WCST				Stroop test		VFT	
	CA		PE					
	β	p	β	p	β	p	β	p
Age	−0.27	0.129	0.05	0.780	0.54	0.001	−0.17	0.225
Sex	0.13	0.347	−0.21	0.153	0.11	0.370	0.09	0.398
Education	0.18	0.229	−0.15	0.335	−0.05	0.735	0.34	0.005
Vascular lesions	0.04	0.845	−0.02	0.923	−0.14	0.324	−0.33	0.015

main effects of age and diagnosis, and the interaction between the two. For both CA and PE on the WCST, two-way ANOVA revealed a significant main effect for age, but not for diagnosis. The age × diagnosis interaction was not significant.

For the Stroop test, the main effects of both age and diagnosis were significant, indicating that MDD patients performed poorer than controls, irrespective of age. However, age × diagnosis interaction was not significant. Post hoc analysis confirmed that both young ($p<0.001$) and elderly ($p=0.024$) patients with MDD showed poorer performance in the Stroop test as compared to their age-matched counterpart.

For the VFT, significant main effects of age and diagnosis were obtained. In addition, an interaction between age and diagnosis reached significant level, suggesting that the elderly MDD group alone performed more poorly than the other three groups. This was confirmed by the post-hoc analysis which indicated that only elderly depressives performed poorer than elderly controls.

Multiple regression analysis showed that age had a significant effect on the Stroop test, while education level and the presence of vascular lesions had a significant effect on VFT scores (Table 3).

4. Discussion

Lockwood et al. (2002) investigated executive dysfunction in young and elderly MDD patients in depressed phase, and found that only elderly, but not young patients in current depression present with difficulty in set shifting as indexed by PE in the WCST. In contrast, Biringer et al. (2005) reported that the performance on the WCST of recovered patients with MDD were comparable to healthy controls. Our present results are in according with Biringer et al. (2005) study in that the two indices of the WCST were not affected by the previous episodes of depression. Although we did not directly compare WCST performance of MDD patients in depressed and remitted states, by combining previous findings and ours, one may speculate that deficient set shifting of elderly patients observed during depressive state resolves as depressed symptoms improve. One may further speculate that within the subdivisions of the prefrontal cortex (PFC), dorsolateral PFC activity which is most sensitively indexed by WCST set shifting abilities is recoverable after remission.

In the present study, performances on the Stroop test were affected both by age and diagnosis. For both young and elderly groups, remitted MDD patients performed more poorly than age-matched controls. The results were consistent with previous findings suggesting residual impaired performance on Stroop even after remission of MDD (Trichard et al., 1995; Paradiso et al., 1997; Paelecke-Habermann et al., 2005). Recent functional neuroimaging studies have suggested that the PFC and the anterior cingulate cortex (ACC) are particularly impaired in MDD patients (Bench et al., 1992; Ito et al., 1996; Mayberg, 1997; Mayberg et al., 1997; Davidson et al., 2002). In addition, studies documented that dysfunctions of PFC, ACC and amygdala may remain even in a remitted state, suggesting pathological influence within fronto-subcortical networks persist in remission (Drevets, 2000; Harrison, 2002; Holthoff et al., 2004). Within such functional abnormalities of amygdala-ACC-PFC projection, we consider that dysfunction of the ACC is most crucial in pathogenesis of MDD and reasonably persists in remitted stage (Ishizaki et al., 2008). Recent fMRI study using Stroop task paradigm demonstrated inefficiency of ACC and dorsolateral PFC in MDD (Wagner et al., 2006). Our findings, together with those of Paelecke-Habermann et al. (2005), are in line with such fMRI experiment suggesting residual pathophysiological dysfunction of the ACC in remitted MDD, which is most sensitively indexed by poor Stroop performance.

Concerning the VFT, we found a different pattern; i.e., performances of only elderly, but not young patients with MDD were impaired even in remitted state. Such dissociable findings between young and elderly patients with remitted depression were observed by Trichard

et al. (1995). Their MDD patients with an average age of 47.0 years, which approximated that of our young patients (45.2 years), showed severe impairment in the VFT on admission. However, such impairment in the VFT resolved to a comparable level to healthy controls at discharge. In addition, our study suggests that VFT scores were influenced by vascular lesions independent of age, gender, and education level. These vascular lesions associated with executive dysfunction are more prevalent and severe in depressed elderly individuals than age-matched controls, and mainly occur in subcortical regions and their frontal white-matter projections.

Neuropsychological and functional neuroimaging studies have documented that VFT is tightly linked with the left PFC, including Broca's and adjacent areas, together with the premotor cortex and insula (Tucha et al., 1999; Baldo et al., 2001). In addition, PET and fMRI studies have suggested that not only the left, but also the right frontal lobe, may play a crucial role in voluntary speech intention and/or attentional resources. Interconnected areas such as these are implicated in organizing a functional language network subserving word output (Perani et al., 2003). In the present study, VFT scores were found to be poor only for elderly depressives, and these poor results correlated to the presence of white matter lesions. This suggests that the vascular lesions associated with elderly depression may lead to impairment of the language-related frontal lobe functions.

5. Limitations

There are several limitations in the present study. First, the patients were treated with one or two different antidepressants, which may possibly have exerted deleterious effects on cognition. Executive dysfunction in our patients may have been influenced by an adverse effect of anticholinergic medication. Accordingly, drug-free euthymic patients should be investigated in future research.

Second, in the present study, neuroimaging information was obtained using brain CT only for MDD patients. In addition, CT images were assessed using rating scales, not with more quantified method. When compared to MRI, the detection rate of white-matter lesions is lower for CT, and in reality, more patients may have had vascular lesions in the present study than were detected. Additional research is warranted in order to investigate the relationship between executive dysfunction and the degree of white matter changes using MRI, with more quantified measurement. Also, direct comparison of vascular lesions between MDD patients and controls are warranted.

6. Conclusion

In MDD patients, executive dysfunction persisted even when in a remitted state; however, impairment patterns differed between young and elderly MDD. And the results suggest that vascular lesions affect executive dysfunction, particularly in elderly depressive.

Role of the funding source

This research was supported in part by a Health and Labor Science Research Grant for Special Research from the Japanese Ministry of Health, Labor and Welfare (MM); the Japanese Ministry of Health, Labor and Welfare had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgement

This research was supported in part by a Health and Labor Science Research Grant for Special Research from the Japanese Ministry of Health, Labor and Welfare (MM).

References

Aizenstein, H.J., Nebes, R.D., Meltzer, C.C., Fukui, M.B., Williams, R.L., Saxton, J., Houck, P.R., Carter, C.S., Reynolds III, C.F., DeKosky, S.T., 2002. The relation of white matter hyperintensities to implicit learning in healthy older adults. International Journal of Geriatric Psychiatry 17, 664–669.

Baldo, J.V., Shimamura, A.P., Delis, D.C., Kramer, J., Kaplan, E., 2001. Verbal and design fluency in patients with frontal lobe lesions. Journal of International Neuropsychological Socciety 7, 586–596.

Bench, C.J., Friston, K.J., Brown, R.G., Scott, L.C., Frackowiak, R.S., Dolan, R.J., 1992. The anatomy of melancholia-focal abnormalities of cerebral blood flow in major depression. Psychological Medicine 22, 607–615.

Biringer, E., Lundervold, A., Stordal, K., Mykletun, A., Egeland, J., Bottlender, R., Lund, A., 2005. Executive function improvement upon remission of recurrent unipolar depression. European Archives of Psychiatry and Clinical Neuroscience 255, 373–380.

Boone, K.B., Miller, B.L., Lesser, I.M., Mehringer, C.M., Hill-Gutierrez, E., Goldberg, M.A., 1992. Neuropsychological correlates of white-matter lesions in healthy elderly subject. A threshold effect. Archives of Neurology 49, 549–554.

Channon, S., 1996. Executive dysfunction in depression: the Wisconsin card sorting test. Journal of Affective Disorders 39, 107–114.

Coffey, C.E., Figiel, G.S., Djang, W.T., Weiner, R.D., 1990. Subcortical hyperintensity on magnetic resonance imaging: a comparison of normal and depressed elderly subjects. American Journal of Psychiatry 147, 187–189.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: perspectives from affective neuroscience. Annual Review of Psychology 53, 545–574.

Degl'Innocenti, A., Agren, H., Backman, L., 1998. Executive deficits in major depression. Acta Psychiatrica Scandinavica 97, 182–188.
Drevets, W.C., 2000. Neuroimaging studies of mood disorders. Biological Psychiatry 48, 813–829.
Estes, W.K., 1974. Leaning theory and intelligence. American Psychologist 29, 740–749.
Franke, P., Maier, W., Hardt, J., Frieboes, R., Lichtermann, D., Hain, C., 1993. Assessment of frontal lobe functioning in schizophrenia and unipolar major depression. Psychopathology 26, 76–84.
Fromm, D., Schopflocher, D., 1984. Neuropsychological test performance in depressed patients before and after drug therapy. Biological Psychiatry 19, 55–72.
Golden, C.J., 1978. Stroop color and word test: a manual for clnical and experimental uses. Stoelting, Chicago.
Greenwald, B.S., Kramer-Ginsberg, E., Krishnan, R.R., Ashtari, M., Aupperle, P.M., Patel, M., 1996. MRI signal hyperintensities in geriatric depression. American Journal of Psychiatry 153, 1212–1215.
Hamilton, M., 1960. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23, 56–62.
Harrison, P.J., 2002. The neuropathology of primary mood disorder. Brain 125, 1428–1449.
Holthoff, V.A., Beuthien-Baumann, B., Zundorf, G., Triemer, A., Ludecke, S., Winiecki, P., Koch, R., Fuchtner, F., Herholz, K., 2004. Changes in brain metabolism associated with remission in unipolar major depression. Acta Psychiatrica Scandinavica 110, 184–194.
Ishizaki, J., Yamamoto, H., Takahashi, T., Takeda, M., Yano, M., Mimura, M., 2008. Changes in regional cerebral blood flow following antidepressant treatment in late-life depression. International Journal of Geriatric Psychiatry 23, 805–811.
Ito, H., Kawashima, R., Awata, S., Ono, S., Sato, K., Goto, R., Koyama, M., Sato, M., Fukuda, H., 1996. Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. Journal of Nuclear Medicine 37, 410–414.
Krishnan, K.R., 1993. Neuroanatomic substrates of depression in the elderly. Journal of Geriatric Psychiatry and Neurology 6, 39–58.
Krishnan, K.R., Hays, J.C., Blazer, D.G., 1997. MRI-defined vascular depression. American Journal of Psychiatry 154, 497–501.
Lesser, I.M., Boone, K.B., Mehringer, C.M., Wohl, M.A., Miller, B.L., Berman, N.G., 1996. Cognition and white matter hyperintensities in older depressed patients. American Journal of Psychiatry 153, 1280–1287.
Lezak, M.D., Howieson, D.B., Loring, D.W. (Eds.), 2004. Neuropsychological assessment. Oxford University Press, Inc.
Lockwood, K.A., Alexopoulos, G.S., van Gorp, W.G., 2002. Executive dysfunction in geriatric depression. American Journal of Psychiatry 159, 1119–1126.
Matsuoka, K., Uno, M., Kasai, K., Koyama, K., Kim, Y., 2006. Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: Japanese version of National Adult Reading Test. Psychiatry and Clinical Neurosciences 60, 332–339.
Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. Journal of Neuropsychiatry and Clinical Neurosciences 9, 471–481.
Mayberg, H.S., Brannan, S.K., Mahurin, R.K., Jerabek, P.A., Brickman, J.S., Tekell, J.L., Silva, J.A., McGinnis, S., Glass, T.G., Martin, C.C., Fox, P.T., 1997. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8, 1057–1061.
Murphy, C.F., Gunning-Dixon, F.M., Hoptman, M.J., Lim, K.O., Ardekani, B., Shields, J.K., Hrabe, J., Kanellopoulos, D., Shanmugham, B.R., Alexopoulos, G.S., 2006. White-matter integrity predicts stroop performance in patients with geriatric depression. Biological Psychiatry 61, 1007–1010.
Neu, P., Kiesslinger, U., Schlattmann, P., Reischies, F.M., 2001. Time-related cognitive deficiency in four different types of depression. Psychiatry Research 103, 237–247.
Paelecke-Habermann, Y., Pohl, J., Leplow, B., 2005. Attention and executive functions in remitted major depression patients. Journal of Affective Disorders 89, 125–135.
Paradiso, S., Lamberty, G.J., Garvey, M.J., Robinson, R.G., 1997. Cognitive impairment in the euthymic phase of chronic unipolar depression. Journal of Nervous and Mental Disease 185, 748–754.
Perani, D., Cappa, S.F., Tettamanti, M., Rosa, M., Scifo, P., Miozzo, A., Basso, A., Fazio, F.A., 2003. fMRI study of word retrieval in aphasia. Brain and Language 85, 357–368.
Reischies, F.M., Neu, P., 2000. Comorbidity of mild cognitive disorder and depression—a neuropsychological analysis. European Archives of Psychiatry and Clinical Neuroscience 250, 186–193.
Taylor, W.D., Steffens, D.C., MacFall, J.R., McQuoid, D.R., Payne, M.E., Provenzale, J.M., Krishnan, K.R., 2003. White matter hyperintensity progression and late-life depression outcomes. Archives of General Psychiatry 60, 1090–1096.
Trichard, C., Martinot, J.L., Alagille, M., Masure, M.C., Hardy, P., Ginestet, D., Feline, A., 1995. Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. Psychological Medicine 25, 79–85.
Tucha, O.W., Smely, C.W., Lange, K.W., 1999. Verbal and figural fluency in patients with mass lesions of the left or right frontal lobes. Journal of Clinical and Experimental Neuropsychology 21, 229–236.
Tupler, L.A., Krishnan, K.R., McDonald, W.M., Dombeck, C.B., D'Souza, S., Steffens, D.C., 2002. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. Journal of Psychosomatic Research 53, 665–676.
Veiel, H.O., 1997. A preliminary profile of neuropsychological deficits associated with major depression. Journal of Clinical and Experimental Neuropsychology 19, 587–603.
Wagner, G., Sinsel, E., Sobanski, T., Kohler, S., Marinou, V., Mentzel, H.J., Sauer, H., Schlosser, R.G., 2006. Cortical inefficiency in patients with unipolar depression: an event-related FMRI study with the Stroop task. Biological Psychiatry 59, 958–965.

Neuropathology 2008; **28**, 652–659 doi:10.1111/j.1440-1789.2008.00905.x

Case Report

An atypical autopsy case of Lewy Body disease with clinically diagnosed major depression: A clinical, radiological and pathological study

Shuji Iritani,[1,3] Kuniaki Tsuchiya,[2] Tetsuaki Arai,[3] Haruhiko Akiyama[3] and Kenji Ikeda[4]

[1]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, [2]Department of Laboratory Medicine and Pathology, Tokyo Metropolitan Matsuzawa Hospital, Tokyo, [3]Department of Psychogeriatrics, Tokyo Institute of Psychiatry, Tokyo and [4]Department of Psychiatry, Zikei Hospital, Okayama, Japan

We report an 84-year-old woman who was clinically diagnosed with late-life major depression (LLMD) and having a diffuse type of dementia with Lewy bodies (DLB) neuropathologically. Clinically, this case showed depressive mood, anxiety, and irritation, but did not show cognitive dysfunction, visual hallucination, fluctuation of alertness and parkinsonism, which define the criteria for diagnosing DLB. Neuropathological examination demonstrated abundant Lewy-related pathology including Lewy bodies and neurites in the hippocampal region and the cerebral cortex, and moderate levels in brain stem nuclei including the substantia nigra, locus ceruleus and dorsal raphe nucleus. These findings suggest the possibility that Lewy-related pathology is associated with the depressive symptoms. Furthermore, it must be noted that some patients diagnosed with LLMD clinically may develop pathology of DLB without the typical or usual clinical symptoms.

Key words: amygdala, α-synuclein, depression, Late life, Lewy body disease.

INTRODUCTION

The term Lewy body disease (LBD) is an all-inclusive clinical concept that includes Parkinson disease, Parkinson disease with dementia and dementia with Lewy bodies (DLB). LBD is neuropathologically categorized into four types: (i) brainstem type; (ii) transitional type; (iii) diffuse type; and (iv) cerebral type, according to the distribution of Lewy-related pathology in the brain.[1,2] LBD cases, in which the dominant symptom is dementia, have been referred to as DLB. Besides, DLB has been classified as pure form, common form or AD form according to the degree of Alzheimer pathology, thought to be a distinctive pathological entity that can be differentiated from Alzheimer's disease (AD).[3]

Dementia with Lewy bodies is known to be the second most frequent neurodegenerative dementia following AD.[4] According to the diagnostic consensus guidelines for DLB,[5] visual hallucination and/or the fluctuation of attention or consciousness and idiopathic parkinsonism are commonly observed as core neuropsychiatric symptoms along with progressive cognitive dysfunction. However, it should be noted that memory disturbance and visual hallucination are seldom observed as the initial sign of DLB.[6]

Late life major depression (LLMD) is frequently associated with cognitive impairment, and increases the risk for subsequent dementia. It is sometimes difficult for psychogeriatric clinicians to distinguish deterioration of cognition due to neurodegenerative disorders due to LLMD at the bedside. Furthermore, depressive mood is sometimes observed in the initial stage or during the clinical course of many neurodegenerative diseases including AD, DLB, and multiple system atrophy (MSA).[7–9]

We report here an atypical case that was diagnosed as LLMD without dementia symptoms clinically and as a diffuse type of DLB neuropathologically. This case indicates that some cases of LLMD might have the brain pathology of DLB.

CASE REPORT

An 84-year-old woman died and was autopsied. She had lived alone in her house for 20 years after her husband had

Correspondence: Shuji Iritani, MD, PhD, Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan. Email: iritani@med.nagoya-u.ac.jp

Received 26 October 2007; revised 18 January, 2008; accepted 20 January 2008.

died, but had two married daughters living in the neighborhood within walking distance. She had no appreciable disease either physically or mentally throughout life, and there was no hereditary burden. Furthermore, she had no alcohol drinking habits.

She was basically active and usually participated in many community events such as dance parties or walking circles. At 81 years, she felt dizziness without the loss of consciousness during a community activity event. She consulted the local hospital, but various examinations including brain neuroimaging could not identify an obvious cause of dizziness. After that incident, she became withdrawn within her house, and tended not to go out unless necessary. She gradually began to express hypochondriac complaints with anxiety. She called to her daughters frequently due to unbearable feelings of loneliness. She consulted her general physician, who prescribed some minor tranquilizers and a low dose of antidepressant under a diagnosis of anxiety neurosis. These medications were never effective and gradually her anxiety became exaggerated, increasing her dependence on her daughters, and she frequently complained that she could not bear to be home alone. Thus, her anxiety gradually became severe over time.

At 84 years (about 2 years after her initial symptoms), her appetite gradually decreased and she could not take care of herself due to anxiety and agitation. During this time, her walk was observed as awkward and she tended to topple over. At one point she injured her head by falling to the floor. Her daughters provided limited care and made the patient visit a psychogeriatric hospital.

The condition at the time of the initial examination was diagnosed as follows. There were no abnormal neurological signs. She could speak fluently and answered questions promptly although her voice was listless. Her facial expression disclosed depressed without vital feeling. Her weight had decreased by 10 kg during the previous year. The patient's score on the Mini Mental State Examination[10] was 29/30 and the score on the revised Hasegawa dementia scale[11] was 28/30 (full score 30 points, cut off 19/20). There were no disorientation and memory disturbance (short, long and visual memory). She did not show symptoms of micrographia that patients with parkinsonism often display. She complained of her anxiety about living alone and showed a pesimistic and depressive mood. She also expressed a lack of appetite. Based on these findings, she was clinically diagnosed with major depression and was admitted to the psychogeriatric unit of the psychiatry hospital.

The course of hospitalization was as follows. Her appetite was very poor and she was constipated. Because her only intake was a small amount of ice cream or jelly, she was sometimes given an intravenous drip injection to maintain minimum nutrition. Her blood examination showed: total protein, 5.5 mg/dL; blood sugar, 128 mg/dL; hemoglobin, 13.8 g/dL; and blood urea nitrogen, 30 mg/dL. She was not in a starvation state but showed slight dehydration. Other blood examination data were within normal limits. Her blood pressure and pulse rate indicated 115/67 mmHg, 72 times/minute, respectively, at the time of admission, and 134–110/98–67 mmHg, 68–90 times/minute, respectively, during the hospitalization. Postural hypotension was not observed. Brain CT showed slight diffuse cortical atrophy and enlargement of the inferior horn of the lateral ventricle, which were new findings compared to those from the previous neuroimaging examination (Fig. 1).

On the morning of the seventh day after admission, she was unexpectedly found dead in bed. The total duration of illness was about 3 years. Her clinical diagnosis was major depression (onset at late life) according to the criteria of DSM-IV-TR.[12]

Pathological findings

There were no obvious findings indicating the cause of death.

The weight of the brain was 1040 g before fixation in 10% neutral formalin.

Macroscopic observation (Fig. 2)

There was no evident atrophy in the cortex or white matter of the brain (Fig. 2A–D). Slight atherosclerosis was found in the basilar artery. Depigmentation of the substantia nigra and the locus ceruleus were significantly evident (Fig. 2E). The obvious enlargement of ventricles was not detected.

Microscopic observation (Figs 3, 4, 5)

For microscopic observation, 10 μm brain sections were stained by HE, KB, modified Gallyas-Braak, and the immunohistochemical method using primary antibodies to ubiquitin (rabbit polyclonal, DAKO, Carpintaria, CA, USA) and α-synuclein (mouse monoclonal, Wako, Osaka, Japan).

Cerebral cortex and hippocampal area

There was obvious neuronal loss in the cerebral cortex and the hippocampus. Slight neuronal loss was also observed in the parahippocampal cortex. Lewy bodies were found mainly throughout the deep layer of the cerebral cortex (Fig. 3,III) and amygdala (Fig. 3,II,C). Lewy bodies and Lewy neuritis were especially abundant in the amygdala. Many Lewy neurites were observed in the area of CA2-3 (Fig. 3,III,D). Moderate number of neurofibrillary tangles

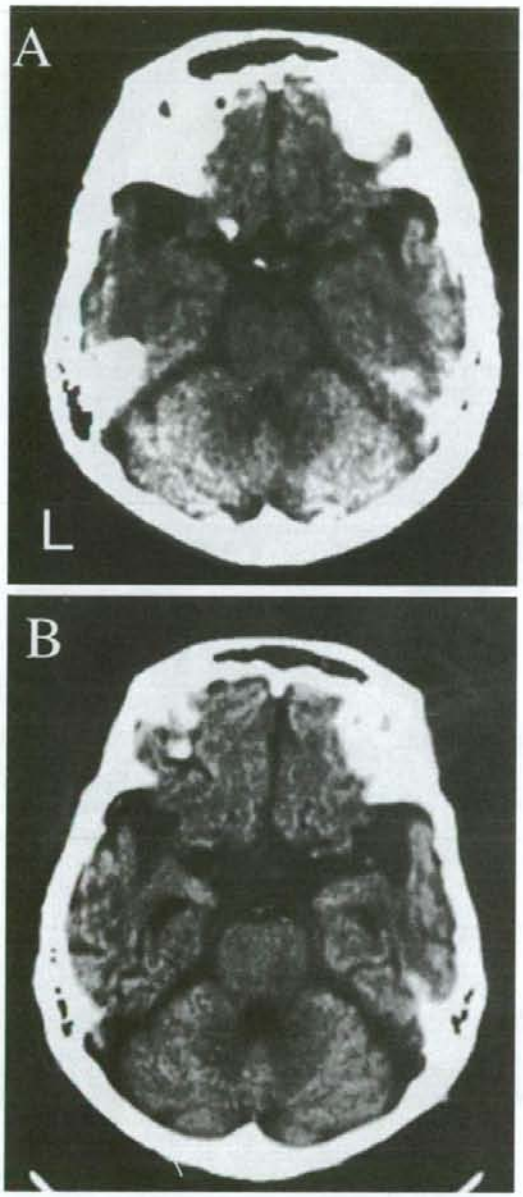

Fig. 1 CT scan of the patient at the age of 76 years (8 years before death) (A) and at 84 years (2 months before death) (B), showing moderate diffuse atrophy of the limbic cortex and moderate enlargement of the inferior horn of both lateral ventricles.

was observed in the hippocampus (Fig. 4A), parahippocapal cortex. Senile plaques were moderately found in the hippocampus and parahippocampal cortex (Fig. 4B), and observed also in the precentral gyrus. Besides, neurofibrillary tangles and senile plaques were moderately observed in the amygdala. The upper layers of the temporal, insular and parahippocampal cortex demonstrated spongiform changes (Fig. 5).

Basal ganglia

There was neuronal loss in the basal ganglia including the nucleus basalis of the Meynert. Lewy bodies were found in the nucleus basalis of the Meynert (Fig. 3,II,B). Neurofibrillary tangles were observed in the nucleus basalis of the Meynert, thalamus, hypothalamus and nucleus subthalamicus. Senile plaques were moderately found in the caudate nucleus and putamen. In the brain stem, slight neuronal loss was noted; free melanin and moderate amount of Lewy bodies and Lewy neurites were observed in the substantia nigra (Fig. 4C–F) and the locus ceruleus; also Lewy body inclusions were found in the nucleus raphes. Some Lewy bodies, moderate gliosis and scarce neuronal loss were observed in the posterior nucleus of the vagus nerve. The sympathetic ganglion was not available in this section.

Based on the observations described above, this case was diagnosed with DLB neuropathologically and the condition of AD pathology disclosed that Braak stage[13] was III for neurofibrillary tangles and C for senile plaques. This case was considered the so-called common form of DLB.[3]

The schematic distribution of Lewy bodies is shown in Figure 3. The score of Lewy bodies[14] is indicated in Table 1. Lewy-related pathology score was defined according to the third report of the DLB Consortium[5] and is shown in Table 2. Marked Lewy-related pathology was detected in the amygdala, cingulate cortex and transentorhinal cortex.

DISCUSSION

We report here a unique case that was diagnosed clinically as major depression without dementia and any neurological signs, and pathologically as the diffuse type of LBD or the common form of DLB. To our knowledge, such a case has not previously been reported in the literature. Although five cases of LBD lacking parkinsonism have been reported, all cases showed memory disturbance as the initial symptom.[15–18] However, it is interesting that one of these five cases showed depression and anxiety. At the initial stage of the diffuse type of LBD, memory disturbance and parkinsonism are frequently observed, while depressive symptoms are less frequent.[6]

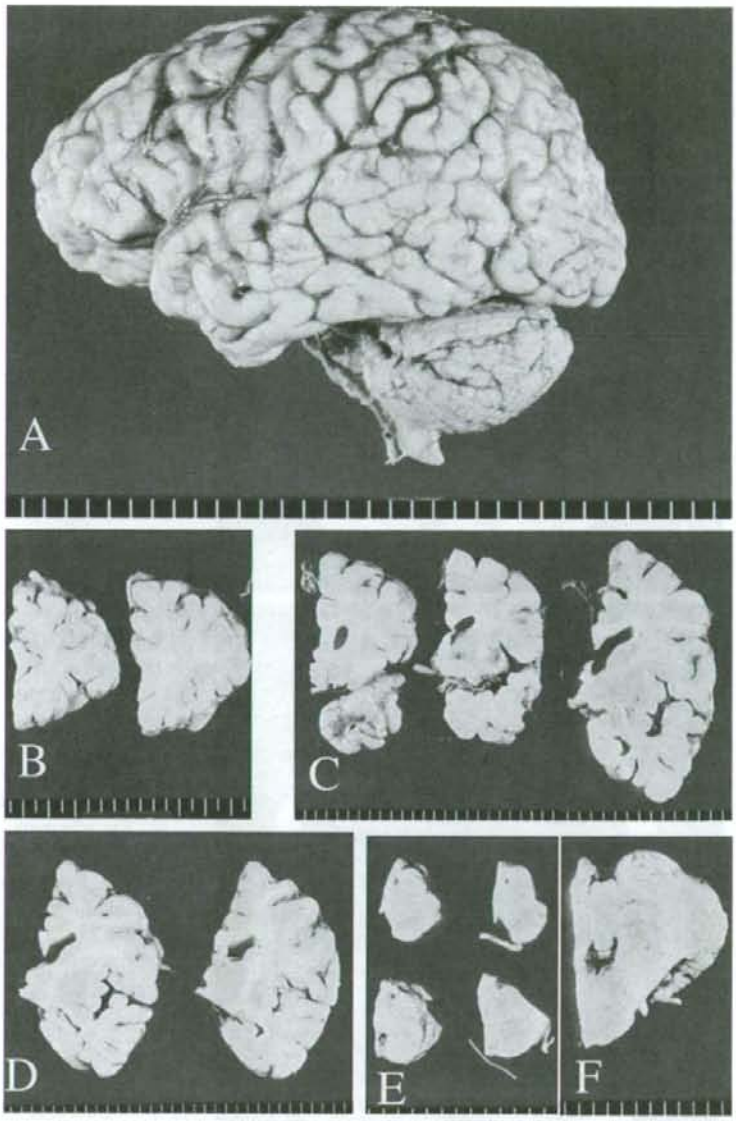

Fig. 2 The external lateral view, coronal sections of the left hemisphere (A–D) and transverse sections of the mid brain (E,F). There is an absence of marked brain atrophy. Observe the clear boundary between the cortical layer and the white matter. The depigmentation of substantia nigra and the locus ceruleus is obvious (E). (One graduation was 5 mm).

There have been many studies concerning the association between major depression and AD. A past history of major depression in the elderly was reported to increase the risk of AD.[19–21] Another report demonstrated that more severe AD pathology was observed neuropathologically in patients with a history of major depression compared to those without such a history.[22] In the present case, AD pathology was mild but Lewy-related pathology was remarkable. This may suggest that LLMD is associated with the risk of LBD as well as AD.

One of the important questions is which areas of the brain are involved in depressive symptoms in our case. Degenerative changes of the noradrenergic neuronal network in the locus ceruleus or the monoaminergic neuronal system in the nucleus raphe may be involved.[23] Another possibility is involvement of the amygdala, since

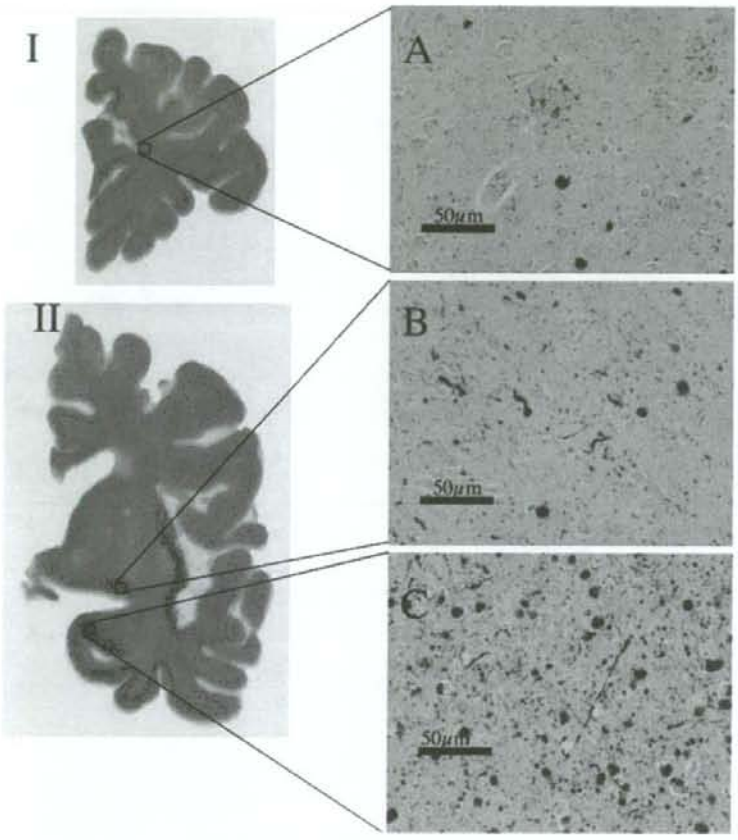

Fig. 3 Distribution of Lewy-related pathology that was detected by α-synuclein immunohistochemistry. Dots indicate the Lewy bodies (One dot indicates one Lewy body). (I) Coronal section at the frontal cortical level, (II) coronal section at the amygdala level, (III) coronal section at the hippocampal level, (IV) midbrain section including the substatia nigra, (V) midbrain section including the locus ceruleus. (A) Lewy bodies in the medial cortex of the frontal cortex. Lewy bodies are scattered mainly in the deep layer of the cortex. (B) Lewy bodies in the nucleus basalis of Meynert. (C) Abundant Lewy bodies and neurites were observed in the amygdala. (D) Abundant Lewy neurites were observed in the CA2-3 area of the hippocampus. Inset photo shows high magnification observation. (E) Lewy bodies and neurites in the subsatntia nigra of the midbrain. Inset photo shows high magnification observation. (F) Lewy bodies and neurites in locus ceruleus in the mid-brain. Inset photo shows high magnification observation.

Table 1 Lewy body score[14]

Category	Transentorhinal	Cingulate	Temporal	Frontal	Parietal	Total
Count number of LB (Lewy body) (Using HE stained specimen)	9	38	16	8	6	
Score	2	2	2	2	2	10 (neocortical type)
Count number of LB in the same area (Using ubiquitin immunohistochemical stained specimen)	47	166	70	57	38	
Count number of LB in the same area (Using α-synuclein immunohistchemcal stained specimen)	67	187	73	66	Not available	

Lewy body score according to the criteria of Ellison[14] observed on HE-stained specimens, and also showing the actual number of Lewy bodies in the same area observed on ubiquitin immunohistochemical-stained specimens and α-synuclein immunohistochemical-stained specimens. Many Lewy bodies were detected in the cerebral cortices.

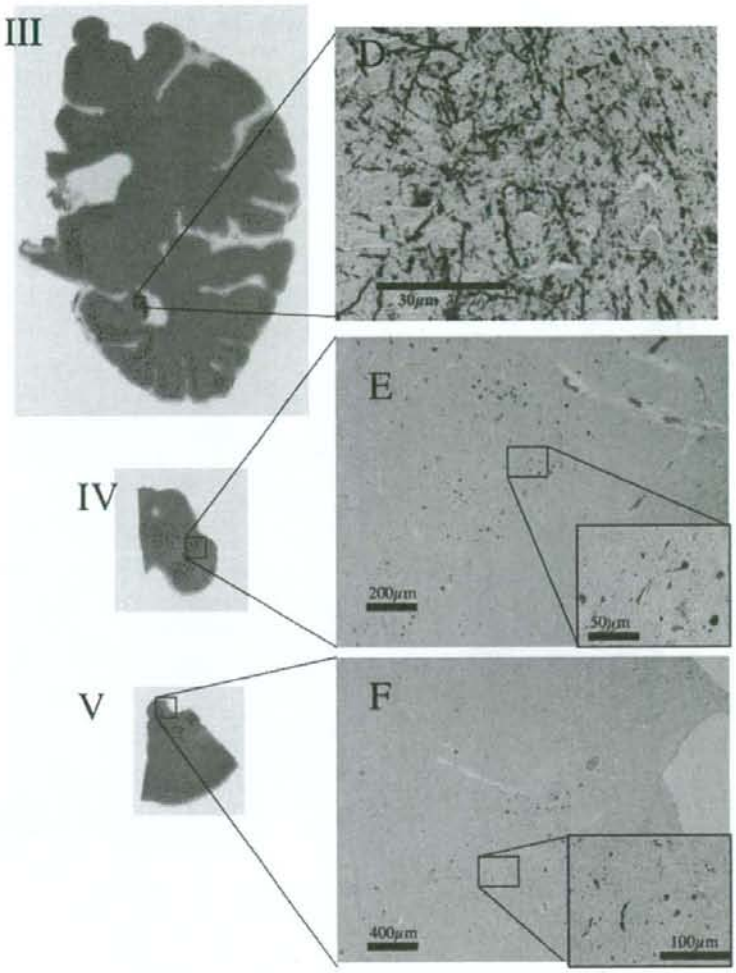

Fig. 3 *Continued*

Table 2 Lewy-related pathology score according to the third report of the DLB Consortium[5]

Locus ceruleus	3
Substantia nigra	3
Nucleus basalis of Meynert	3
Amygdala	4
Transentorhinal cortex	4
Cingulate cortex	4
Temporal cortex	3
Frontal cortex	3
Parietal cortex	2

Marked Lewy-related pathology was detected in the cerebral neocortex and amygdala.

its function has been reported to be associated with affection,[24,25] panic disorder,[26] and anxiety.[27] It has been reported that transmissional metabolism or neurotransmission may be changed in the amygdala in depressive patients.[28] Lewy-related pathology in the amygdala has been reported to be related to depression in AD.[29] Thus, severe Lewy-related pathology in the amygdala of the present case may correlate with the depressive symptoms.

In conclusion, the results of the present study suggest that some patients clinically diagnosed with LLMD may develop pathology of DLB without typical or usual clinical symptoms. Further studies including the development biological markers are needed to establish accurate clinical diagnostic criteria of DLB.

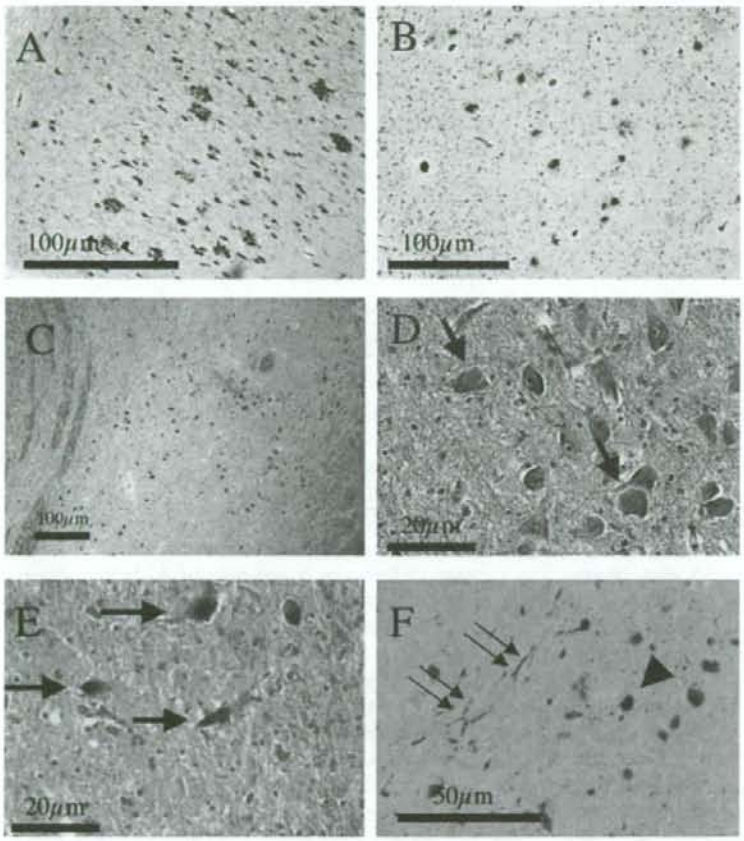

Fig. 4 (A) Senile plaques and neurofibrillary tangle changes were observed in the subiculum of the hippocampus (modified Gallyas-Braak stain). (B) Senile plaques in the parahippocampal cortex (modified Gallyas-Braak stain). (C) Neurons in the substantia nigra showing slight neuronal losses (KB stain). (D) Neurons with Lewy bodies (arrow) were observed in the substantia nigra, but neurons were relatively preserved (HE stain). (E) Some free melanins were observed in the substantia nigra (arrow) (HE stain). (F) Lewy body (arrow head) and Lewy neuritis (arrows) were observed in the substantia nigra (α-synuclein immunohistochemical stain).

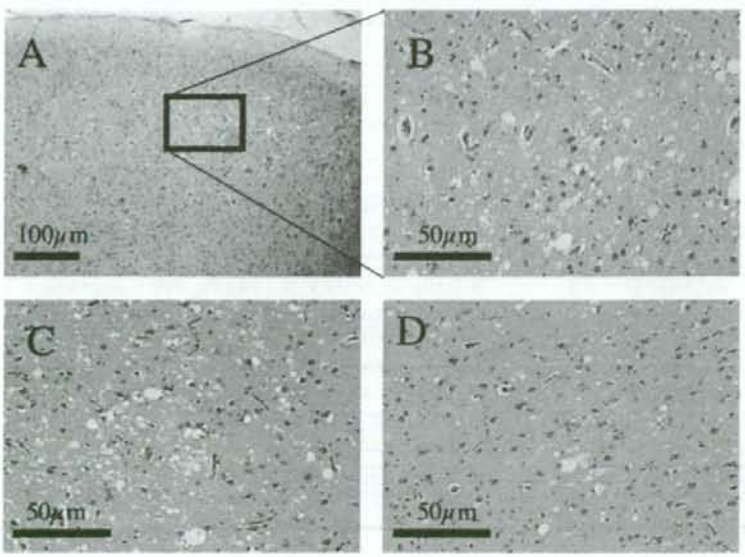

Fig. 5 Spongiform change was observed in the upper layer of the insular cortex (A). High magnification of the square inset of A (B), temporal cortex (C) and parahippocampal cortex (D). (HE stain).