Clinical characteristics of elderly depressive patients with low MIBG uptake

Running title: Features of low MIBG uptake patients

Shintaro Takenoshita, MD,[1] Seishi Terada, MD, PhD,[1] Etsuko Oshima, MD, PhD,[1] Megumi Yamaguchi, MED,[1] Satoshi Hayashi,[1] Kenji Hinotsu,[1] Satoru Esumi, PhD,[2] Takayoshi Shinya, MD, PhD,[3] Norihito Yamada, MD, PhD[1]

[1]*Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama, Japan*

[2]*Department of Pharmacy, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama, Japan*

[3]*Department of Pediatric Radiology, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama, Japan*

Correspondence should be addressed to: Dr. Seishi Terada MD, PhD, Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Email: terada@okayama-u.ac.jp.

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ABSTRACT

Backglound: Recently, depression with Lewy body pathology before the appearance of parkinsonism and cognitive dysfunction has been drawing attention. Low cardiac metaiodobenzylguanidine (MIBG) uptake is helpful for early differentiation of Lewy body disease (LBD) from late-onset psychiatric disorders even before parkinsonism or dementia appears. In this study, we used MIBG uptake as a tool in suspected LBD, and evaluated the relationship of MIBG results to clinical characteristics and depressive symptoms.

Methods: Fifty-two elderly inpatients with depression were included in this study. The Hamilton Depression Rating Scale (HDRS) was administered at admission, and ^{123}I-MIBG cardiac scintigraphy was performed. Of 52 patients, 38 had normal and 14 had reduced MIBG uptake.

Results: Correlation analyses of the late phase heart-to-mediastinum (H/M) ratio on the MIBG test and each item of the HDRS revealed that the H/M ratio was significantly correlated with scores of “agitation”, “anxiety-somatic”, and “retardation” on the HDRS. Mean HDRS composite scores

of “somatic and psychic anxiety (Marcos)” and “somatic anxiety/somatization factor (Pancheri)” were higher in the low uptake group than in the normal uptake group.

Conclusion: Elderly patients with depression who manifested an obvious somatic anxiety tend to show low MIBG uptake, and are more likely to have Lewy body pathology.

Key words

depression, elderly, metaiodobenzylguanidine, Lewy body disease, somatic anxiety

INTRODUCTION

A close relationship of Lewy body disease (LBD) with depression has been repeatedly reported,[1-3] and major depression occurs in around one-fourth to one-third of patients with Parkinson disease (PD).[1,4] Dementia with Lewy bodies (DLB) produces more depressive signs than Alzheimer's disease (AD),[2] and the coexistence of major depression is also more frequent in DLB than in AD.[3] Mild cognitive impairment (MCI) with LBD is associated with neuropsychiatric symptoms including depression, similar to those established for DLB.[5]

Recently, early non-motor, non-cognitive symptoms associated with LBD, such as REM sleep behavior disorder (RBD), olfactory dysfunction, autonomic dysfunction, and depression, have become very frequently reported.[6,7] RBD, olfactory dysfunction, autonomic dysfunction, and depression often appear before parkinsonism or cognitive dysfunction become obvious.[1,8] In the field of geriatric psychiatry especially, depression with Lewy body pathology before the appearance of parkinsonism and cognitive dysfunction has been drawing attention.[8-10] Using low metaiodobenzylguanidine (MIBG) uptake as an indicator of LBD, late

onset depression without DLB criteria was reported to be one of the early manifestations of LBD.[11] Further, the concept of a "pure psychiatric presentation (PPP) of LBD" was proposed, and the typical presentation of PPP was reported to be depression with elderly onset.[9] Therefore, the clinical importance of Lewy body-related mental symptoms in patients without dementia and parkinsonism is strongly suggested.[8]

Although the importance of depression in LBD has been repeatedly emphasized, there have been relatively few reports on the frequency of LBD in aged patients with depression.[12] It is not easy to infer Lewy body pathology before dementia or parkinsonism emerge. However, recently it was reported that a low cardiac MIBG uptake, but not a decreasing binding ratio on a dopamine transporter single photon emission computed tomography (DAT-SPECT), was helpful for early differential diagnosis of LBD from late-onset psychiatric disorders, even before parkinsonism or dementia appear.[13] In another study, it was reported that low cardiac MIBG uptake is detected before the diagnosis of probable DLB.[14] The high specificity of MIBG to detect LBD was repeatedly reported.[15] Therefore, in this study, we used MIBG scintigraphy as a tool to identify suspected LBD

in patients, and evaluated the relationship of MIBG results to clinical characteristics and depressive symptoms.

METHODS

Ethics

This study was approved by the Internal Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (1506-006). After a complete description of the study to the subjects and their relatives, written informed consent was obtained.

Subjects

Eighty-three elderly patients with major depression (≥ 60 years old) entered the psychiatric ward of Okayama University Hospital between June 2010 and January 2018. Of the 83 patients, 52 fulfilled the following inclusion and exclusion criteria. They all (1) were 60 years old or over, (ii) fulfilled the F32 or F33 codes of the International Classification of Diseases-10 (ICD-10) criteria, (iii) had not experienced a manic or hypomanic episode; (iv) underwent ^{123}I-MIBG myocardial scintigraphy as well as magnetic resonance imaging (MRI) or computed tomography (CT) of the head, and (v) received a Hamilton depression rating scale (HDRS) score.

We excluded patients who met the following exclusion criteria for ^{123}I-MIBG scintigraphy: (i) taking tricyclic antidepressants, reserpine, and/or norepinephrine reuptake inhibitor, (ii) cardiac failure, (iii) ischemic heart disease that developed within six months of participation, (iv) poorly controlled diabetes mellitus (HbA1c >7.0%) or receiving insulin therapy, (v) severe kidney dysfunction or receiving hemodialysis, and (vi) a history of neoplasm within five years of participation.[15]

Other exclusion criteria were: (i) diagnosis of dementia or Parkinson disease at and before hospitalization, (ii) Huntington disease, normal pressure hydrocephalus, progressive supranuclear palsy, epilepsy, subdural hematoma, multiple sclerosis, or head injury with aftereffect, (iii) infection or focal regions revealed by MRI such as cerebral infarction or brain tumor that affects cognitive function, (iv) use of a cardiac pacemaker, aneurysm clips, prosthetic valves, cochlear implants, or other metal implants, (v) a history of alcohol or drug abuse, deficiency of vitamin B12 or folic acid, syphilis, or thyroid dysfunction, (vi) patients judged by a chief clinician to be inappropriate due to severe physical illness, and (vii) patients receiving drugs causing depression (steroids, α-methyl-dopa, clonidine, tamoxifen,

and cimetidine).[15]

Of 52 depressive patients, 38 patients with a normal MIBG uptake (heart-to-mediastinum (H/M) ratio ≥2.0 in the late image) were classified as the normal uptake group, and 14 patients with reduced MIBG uptake (H/M ratio <2.0 in the late image) were classified as the low uptake group.[16]

Hamilton Depression Rating Scale (HDRS) and Global Assessment of Functioning Scale (GAF)

The HDRS was originally published in 1960.[17] It is a standard measure of depression severity, with 17 items that evaluate behavioral, physical, and mental symptoms of depression. The HDRS was rated by the chief psychiatrist of the patient at admission.

Several studies reported factor analyses of the HDRS. Marcos and Salamero performed a factor analysis of the HDRS in aged people, and they extracted three factors.[18] The factors were (1) inhibition and melancholic depression (items 1, 7, 8, 10, 14), (2) insomnia (items 4, 5, 6), and (3) somatic and psychic anxiety (items 11, 12, 13, 15). Pancheri et al.

performed a factor study of the HDRS in unipolar depressed outpatients and identified four factors: (1) somatic anxiety/somatization (items 4, 5, 6, 11, 13, 15), (2) a psychic anxiety dimension (items 2, 9, 10, 17), (3) a pure depressive dimension (items 1, 7, 8), and (4) an anorexia factor (items 12, 16).[19] The total sums of all items in each factor were taken as the score of the factor.

The overall level of functioning was evaluated with the GAF.[20] The scale values range from 1, which represents the hypothetically sickest individual, to 100, which represents the hypothetically healthiest. The GAF was scored by the chief clinician at both admission and discharge.

Evaluation of clinical information

Age, age at onset, sex, height, weight, and years of education were obtained from the medical records. Suspected parkinsonism at admission, visual hallucination, fluctuation of cognition, and RBD were evaluated using inpatient charts and nursing records by investigators who were blind to the MIBG uptake. Diagnoses of Parkinson disease and dementia at discharge were taken from the medical records. The antidepressants used at the time

of MIBG cardiac scintigraphy were obtained from the medical records.

^{123}I-MIBG cardiac scintigraphy and image analysis

Cardiac planar images were acquired 15 min (early image) and 4 h (late image) after intravenous injection of 111 MBq of ^{123}I-MIBG (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) using a triple-head gamma camera equipped with a parallel-hole low-energy high-resolution collimator (GCA9300A/DI; Toshiba, Tokyo, Japan) before March 2014 (n= 27). After March 2014, we used a dual-head hybrid SPECT/CT system (Discovery NM/CT670 Pro, GE Healthcare, Chicago, IL, USA) equipped with an extended low energy general purpose (ELEGP) collimator and diagnostic multi-detector spiral CT (n= 25).

The cardiac uptake of MIBG was determined by setting a region of interest (ROI) in the left cardiac ventricle and upper mediastinum using a semi-automatic ROI setting software program.[21] The average counts per pixel in the H and M were determined within each ROI to calculate the H/M ratio at 15 min (early image) and 4 h (late image). The MIBG wash-out rate was calculated as follows:

(early H – early M) – (late H – late M) / K / (early H – early M)

where K represents the decay correction factor.

Head MRI

Of the 52 elderly depressive patients, 51 subjects underwent T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI with a 3-T scanner (Siemens, Erlangen, Germany) at the Okayama University Hospital during their hospitalization. Periventricular hyperintensities (PVH), and deep and subcortical white matter hyperintensities (DSWMH) were defined as hyperintensity areas on T2 and FLAIR images without any abnormality on T1 images in patients without neurological signs and/or symptoms.[22] PVH and DSWMH were evaluated as five grades from 0 to 4 using the grading scale released by the Japanese Brain Dock Society (http://jbds.jp/guideline.html) outlined by two reports.[23,24] All images were read and assessed by two investigators who were blind to the MIBG uptake results.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 software program (SPSS Inc., Chicago, IL, USA). Comparisons of continuous variables between the two independent groups were performed by independent sample *t*-tests. Comparison between proportions of two independent groups was calculated using Fisher's exact test (2x2 table). Correlation between the H/M ratio of late-phase MBG and HDRS scores was evaluated by Spearman's correlation coefficient. A value of $p<0.05$ was accepted as significant.

Comparisons of the scores of HDRS items between two independent groups were performed by Mann-Whitney's U test. Among the synthetic factor scores of the HDRS, a test for normality (Shapiro-Wilk test) did not reject the hypotheses of normal distribution of the factor scores in "inhibition and melancholic depression" and "somatic and psychic anxiety" of the study of Marcos and Salamero, and "somatic anxiety/somatization factor" and "a psychic anxiety dimension" of the study of Pancheri et al.[18,19] Therefore, comparison of those factor scores of the two groups was performed using a t-test, and other factor scores of the two groups were compared using Mann-Whitney's U test.

RESULTS

Sex, age, years of education, core features of DLB, and antidepressants

No significant differences were found between the low and normal uptake groups with respect to sex, age, years of education, height, or weight (Table 1).

Parkinsonism was suspected at the time of admission in 15 cases, but only 4 cases were diagnosed as Parkinson's disease at discharge, and others were diagnosed as parkinsonism due to antipsychotic drugs or psychiatric symptoms. Suspected parkinsonism at admission ($p=0.013$) and diagnosed Parkinson disease at discharge were more frequently observed in the low uptake group than in the normal uptake group ($p=0.004$). No significant differences were found between the low and normal uptake groups in the frequency of visual hallucination ($p=0.069$), fluctuation of cognition ($p=0.470$), RBD ($p=0.269$), dementia diagnosis at discharge ($p=0.291$) and calcium channel blockers ($p=0.659$). No significant differences were found as to the type of antidepressants between low and normal uptake groups (Table 1).

Neuroimaging findings

The mean H/M ratio of early to late phases of MIBG uptake in the low uptake group was significantly lower than that in the normal uptake group, and the MIBG wash-out rate in the lower uptake group was significantly higher than that in the normal uptake group (Table 1).

No significant differences were found between the low and normal uptake groups with respect to PVH grade scores or DSWMH grade scores of head MRI (Table 1).

HDRS scores and GAF scores

Spearman's correlation analysis between the H/M ratio of the late phase and each item of the HDRS revealed that the H/M ratio was significantly correlated with the scores of "agitation" and "anxiety-somatic" of the HDRS ("agitation", correlation coefficient= -0.381, p= 0.005; "anxiety-somatic", correlation coefficient= -0.386, p= 0.005) in all 52 patients. There was also a significant correlation between the H/M ratio of the late phase and the scores of "agitation" and "anxiety-somatic" of the HDRS ("agitation", correlation coefficient= -0.509, p= 0.002; "anxiety-somatic",

correlation coefficient= -0.455, p= 0.006) in 35 patients who did not have clinical features of DLB (parkinsonism, visual hallucination, fluctuation of cognition, RBD) .

Spearman's correlation analysis between the H/M ratio of the late phase and composite scores of the HDRS revealed that the H/M ratio was significantly correlated with "somatic and psychic anxiety" (Marcos) (correlation coefficient= -0.425, p= 0.002) and "somatic anxiety/somatization factor" (Pancheri)(correlation coefficient= -0.341, p= 0.013) in all 52 patients. There was also a significant correlation between the H/M ratio of the late phase and composite scores of the HDRS "somatic and psychic anxiety" (Marcos) (correlation coefficient= -0.497, p= 0.002) in 35 patients who did not have clinical features of DLB.

There were no significant differences between low and normal uptake groups in the total and item scores of the HDRS (Table 2). As to HDRS composite scores, mean scores of "somatic and psychic anxiety" (Marcos), "somatic anxiety/somatization factor" (Pancheri), and "pure depressive dimension" (Pancheri) in the low uptake group were higher than those in the normal uptake group (Table 2).

There was no significant difference between mean GAF scores at admission of low and normal uptake groups, but improvement of GAF scores of the low uptake group were lower than those of the normal uptake group (Table 1).

DISCUSSION

During the investigation period, 83 elderly patients with major depression entered the psychiatric ward. Of the 83 patients, 52 underwent MIBG scintigraphy, and 14 patients showed low MIBG uptake. Therefore, 26.9% (14/52) of the patients who took the examination and at least 16.9% (14/83) of the elderly inpatients with depression showed a low MIBG uptake. An autopsy study of 124 elderly people who did not have dementia reported that brainstem Lewy bodies were associated with late-life depressive symptoms, and that in a subscore analysis of depressive symptoms were associated with somatic symptoms. [25] In another study of 36 autopsy brains with a history of depression, at least four brains (11.1%) showed moderate or severe Lewy body pathology in the substantia nigra or locus ceruleus.[26] Of 9 patients with depression who developed the first episode after the age of 60, four subjects (44%) received the neuropathological diagnosis of DLB.[27] In a clinical setting, of consecutive 167 inpatients over 50 years of age with mood disorder, 23 subjects (13.8%) were finally diagnosed with DLB.[12] Moreover, while the sensitivity of the MIBG test to detect DLB is moderate, the specificity is very high.[15] Therefore, there may have been

some persons with LBD in the normal uptake group. Considering our study and these past reports together, it is possible that more than 10% of aged patients with major depression may suffer from Lewy body pathology. In elderly patients with depression, there are many cases that it is difficult to distinguish them from dementia and mild cognitive impairment, and there is a possibility that this study may include MCI patients with DLB pathology.

Lewy body pathology is not rare in aged people. However, according to a community-based autopsy study in Japan, the frequency of Lewy body pathology including incidental Lewy bodies in the brain is 0% in the sixties and 10–15% in the seventies.[27] In this study, if the subjects are limited to those in their sixties, of 34 patients with major depression, 20 underwent MIBG scintigraphy, and five patients showed low MIBG uptake. Therefore, 25.0% (5/20) of the patients who took the examination and at least 14.7% (5/34) of the elderly in-patients with depression showed low MIBG uptake. Therefore, the proportion of elderly depressed patients with low MIBG intake is higher than that of the general population, and that the proportion of people with Lewy body pathology is also higher than the general

population.

A significant relationship was found between the H/M ratio of MIBG and several HDRS item scores by correlation analysis in this study. The lower the H/M ratio was, the higher the scores of agitation, somatic anxiety, and retardation were. Further, the scores of "somatic and psychic anxiety (Marcos)" and "somatic anxiety/somatization factor (Pancheri)" increased as the H/M ratio decreased.

Among patients with depression and DLB, some of the patients who were diagnosed with mood disorder at admission and who were thereafter diagnosed with DLB at discharge were previously reported to show severe agitation.[12] In another report on the comparison between PD patients with depression and non-PD patients with depression, inner restlessness and irritability was more common in PD patients with depression than in non-PD patients with depression, whereas a higher proportion of non-PD patients with depression had attempted suicide, experienced delusions, and exhibited a flattening of affect compared to PD patients with depression.[29,30] Therefore, it is not strange that depressive patients with low cardiac MIBG uptake showed severer agitation than those with normal

cardiac MIBG uptake in this study.

Anxiety and apathy are very common in Parkinson disease. The pooled prevalence of anxiety in patients with PD was 30.1%.[31] A higher depression score was associated with severer persistent anxiety in PD.[32] In untreated early-stage PD, 19.0% of the patients were diagnosed as apathetic, and apathy was significantly associated with fatigue.[33] In the diagnosis of DLB, anxiety and apathy are among the supportive clinical features.[34] In elderly patients with depression, those who had somatic complaints such as fatigue may be more likely to have Lewy body pathology.

In PD, somatic scores on the anxiety scale were reported to be associated with autonomic failure.[35] Orthostatic hypotension is closely associated with low cardiac MIBG uptake in DLB.[36,37] Thus, low cardiac MIBG uptake may be closely related to anxiety in Lewy body disease.

Elderly patients with depression show similar remission rates compared to middle-aged patients with depression, but relapse rates appear to be higher. However, patients with Parkinson disease with major depression are reported to be less likely to experience remission.[1,4] In this study, the GAF scores at discharge of the low cardiac MIBG uptake group were lower than

those of the normal cardiac MIBG uptake group. Some depressive patients with low cardiac MIBG uptake may show low therapeutic reactivity, similar to Parkinson disease patients with depression.

This study has several limitations. First, in this study, DAT-SPECT imaging was not performed. When this research was performed, health insurance in Japan did not cover DAT-SPECT. Therefore, we did not evaluate dopaminergic denervation and its relationship with symptoms. Second, needless to say, low cardiac MIBG uptake does not automatically indicate the presence of Lewy body disease. Third, this study included a relatively small number of patients. Therefore, this is an exploratory study, and further study including a larger number of patients is needed. Fourth, low MIBG uptake was reported to be associated with orthostatic hypotension. However, we did not evaluate orthostatic hypotension in this study. Fifth, RBD was not evaluated using an objective assessment method. Therefore, there are more possibilities for patients with potential RBD. Regardless of these shortcomings, this is the first report to show a significant relationship between the H/M ratio of the MIBG test to a few depressive symptoms in elderly patients with depression.

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DISCLOSURE STATEMENT

None.

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