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Research Article

Reduced Cardiac 123I-MIBG Scintigraphy and Olfactory Impairment in Idiopathic REM Sleep Behavior Disorder

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ABSTRACT

Cardiac 123I-MIBG scintigraphy (cMIBG) and an olfactory function test using the Odor Stick Identification Test for Japanese (OSIT-J) were performed for 46 patients with idiopathic REM behavior disorder (iRBD). The H/M ratio on cMIBG of iRBD patients was classified according to the Hoehn-Yahr's (H-Y) stages of Parkinson's disease (PD) as follows: early images, normal range, 11(23.9%); H-YI, 3 (6.5%); H-YII, 5 (10.9%); ≥ H-YIII, 27 (58.7%); and delayed images, normal range, 9 (19.6%); H-YI, 3 (6.5%); H-YII, 1 (2.2%); ≥ H-YIII, 33 (71.7%). The OSIT-J scores decreased in 76.2% of iRBD patients, and 20.5% of Normal subjects. The OSIT-J scores in iRBD patients were strongly correlated with the H/M ratio on early and delayed cMIBG images ($p<0.001$, Pearson correlation coefficient). PD progresses from H-Y stage I to V, with the H/M ratio on cMIBG decreasing as the H-Y stage progresses.The H/M ratio in iRBD patients decreased to PD H-Y III/IV or dementia with Lewy bodies (DLB) levels in 71.7% of patients.Thus, in many cases, iRBDs is a precursor of DLBs but not of PDs. Although olfactory dysfunction has no disease specificity, it is a simple and useful screening test that can be applied before cMIBG for patients with iRBD.

Keywords: iRBD; Olfactory impairment; DLB; Cardiac MIBG scinchigraphy; Parkinson

INTRODUCTION

In this commentary, we described the clinical significance of cMIBG and olfactory impairment as a predicative biomarker for the conversion from iRBD to α - synucleinopathies, particularly dementia with Lewy bodies (DLB).

MATERIALS AND METHODS

Forty-six patients with iRBD were selected based on the medical records and enrolled in this study (Table 1).

Table 1: Demographic data of the iRBD patients.

				cMIBG Early		Delayed		Washout rate %	DaT					
Case	Age	Sex	MMSE	H/M ratio	Level	H/M ratio	Level			PSG	OSIT-J score	RBD period*	Follow up period*	Conversion to DLB*
1	43	M	30	2.7	N	2.8	N	41.2	N	RWA(+)	7	10	2	-
2	45	M	30	3.36	N	3.35	N	22.7	N	NE	10	20	not	-
3	48	M	29	3	N	3.26	N	38.5	N	RWA+abn-beh	12	2	not	-

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4	54	M	28	2.14	#	1.42	###	59.1	N	RWA+abn-bih	10	7	1	-
5	57	F	30	1.61	###	1.29	###	52.2	N	RWA+abn-bih	10	3	1	-
6	61	M	29	1.89	###	1.45	###	59.9	N	RWA(-)	9	1	2	-
7	63	M	30	1.57	###	1.26	###	52.9	Dec	RWA(+)	8	7	1	-
8	65	M	30	1.89	###	1.74	###	47.8	NE	NE	NE	3	not	-
9	65	M	28	1.82	###	1.35	###	48.8	N	RWA+abn-beh	1	25	1	-
10	66	F	29	1.82	###	1.51	###	50.8	N	RWA+abn-bih	5	17	1	-
11	66	M	30	1.67	###	1.43	###	43.7	Dec	RWA+abn-bih	4	5	1	-
12	66	M	28	2.3	#	2	#	39.8	N	RWA(+)	4	1	1	-
13	66	M	29	2.22	#	1.48	###	58.4	N	RWA+abn-bih	7	2	1	-
14	66	F	29	3.36	N	3.23	N	37.8	N	RWA(+)	12	10	2	-
15	68	M	30	1.54	###	1.22	###	54.1	N	RWA(-)	4	11	not	-
16	68	M	29	1.54	###	1.22	###	54.1	NE	RWS(-)	4	10	not	-
17	68	M	29	2.03	##	1.52	###	50.1	NE	NE	3	4	not	-
18	69	M	30	1.95	##	1.34	###	60	N	RWA(+)	6	6	6	-
19	69	M	28	2.7	N	2.2	N	44.7	N	RWA+abn-bih	2	8	2	2
20	69	M	30	1.78	###	1.46	###	54.2	Dec	RWA+abn-bih	6	7	0.5	-
21	70	M	30	1.57	###	1.17	###	48	Dec	RWA(+)	NE	15	2	2
22	70	M	29	1.95	##	1.31	###	59.7	N	RWA+abn-bih	7	7	5	1
23	70	F	28	2	##	1.62	##	52.9	N	RWA(+)	4	21	1.5	-
24	70	M	29	1.57	###	1.2	###	54.9	N	RWA+abn-bih	3	8	not	-
25	70	F	30	1.64	###	1.11	###	55.1	Dec	RWA+abn-bih	5	20	1	-
26	70	M	30	1.86	###	1.63	###	50.4	N	RWA+abn-beh	2	3	not	-
27	71	F	30	1.97	##	1.43	###	54.3	N	RWA+abn-bih	5	30	1.5	-
28	72	M	29	1.57	###	1.14	###	47.4	NE	RWA+abn-beh	1	10	6	4
29	72	F	28	1.44	###	1.15	###	54.2	N	RWA(+)	6	2	2	-
30	73	F	29	1.71	###	1.26	###	54.6	N	RWA(+)	0	7	6	4
31	73	F	28	1.9	###	1.37	###	52.8	N	RWA(+)	4	10	2	-
32	74	M	30	1.89	###	1.5	###	49.9	N	RWA+abn-bih	3	4	1	-
33	74	M	29	2.57	N	2.81	N	34.2	NE	RWS(-)	NE	5	1	-

34	75	F	30	2.52	N	2.17	#	50.8	N	RWA+abn-beh	5	3	5	-
35	76	M	29	1.55	###	1.18	###	59.5	Dec	RWA(+)	2	3	0.5	0.5
36	76	F	30	2.43	N	1.93	#	49.5	NE	RWA(-)	6	11	10	2
37	76	F	29	1.92	###	1.46	###	51.8	N	RWA+abn-beh	NE	30	2	-
38	76	M	28	1.56	###	1.19	###	53.5	NE	RWS(-)	0	40	1	-
39	78	F	30	2.53	N	2.41	N	37.6	NE	RWA(+)	8	2	1	-
40	79	M	29	1.58	###	1.29	###	44.7	Dec	RWA(-)	2	5	5	-
41	79	M	29	1.67	###	1.19	###	58.2	Dec	RWA(+)	0	11	2	2
42	79	F	29	2.83	N	2.95	N	37.6	N	RWA(+)	9	1.5	1.5	-
43	80	M	29	3.05	N	2.63	N	37	N	RWA+abn-bih	12	3	not	-
44	82	F	30	1.52	###	1.06	###	53.4	N	RWA+abn-beh	4	7	7	6
45	82	M	27	1.4	###	1.13	###	56.5	N	RWA+abn-bih	2	5	5	-
46	82	M	29	1.68	###	1.17	###	53.7	NE	NE	2	1	1	0.5

cMIBG Level: 95%CI of PD: #;PD1, ##;PD2, ###;PD3 or PD4; N: normal, Dec: deceased, NE: not examined; PSG : polysomnography, RWA: REM sleep withot atonia, abn-beh: abnormal behavior; Dat: Dat scan;*: years

The clinical diagnosis of iRBD was made with the presence of clinical history of sleep-related complex motor behaviors or REM sleep complex vocal behaviors[1]. Polysomnography (PSG), an olfactory test using the Odor Stick Identification Test for Japanese (OSIT-J), dopamine transporter (DaT) single-photon emission computed tomography (SPECT), cMIBG and brain SPECT were conducted in patients with iRBD [2].

The OSIT-J developed in Daiichi Yakuhin Sangyo Co. Tokyo, Japan was used for the test of olfactory function. The OSIT-J consists with 12 kinds of odor sticks. The subjects were asked to select an odor from a list of 4 odors that were rubbed on the medicine wrapping paper of each odor stick. The maximum score was 12.

RESULTS

The demographic data of the iRBD patients were shown in Table 1. The cMIBG cut-off values were as follows: early H/M ratio, 2.36; delayed H/M ratio, 2.19; and washout rate; 40.3%. The H/M ratio on cMIBG for iRBD patients was classified according to the Hoehn-Yahr's (H-Y) stages of Parkinson's disease as follows: early images, normal range, 11 (23.9%); H-YI, 3 (6.5%); H-YII, 5 (10.9%); ≥ H-YIII, 27 (58.7%); delayed images, normal range, 9 (19.6%); H-YI, 3 (6.5%); H-YII, 1 (2.2%); ≥ H-YIII, 33 (71.7%). A DaT scan was performed for 37 (80.4%) iRBD patients, in 8 cases (21.6%) decreased accumulation was observed.

The polysomnography was performed for 42 patients, 35 (83.3%) showed REM sleep without atonia (RWA) and/or abnormal behaviors, and 2 of 7 patients without RWA were unable to sleep during the examination.

Forty-two iRBD patients and 44 normal subjects (male, n=13; female, n=31; age 69.8 ± 8.2 years) performed the OSIT-J test. The OSIT-J scores of the normal subjects and iRBD patients were 9.25 ± 2.21 and 5.14 ± 3.38, respectively ($p<0.001$, Kruskal-Wallis, Dunn's test). Since the lower limit of the 99% confidence interval in normal subjects was 8.13, the cut-off value of the OSIT-J was set to 8. With a cut-off value 8, abnormalities were observed in 32 (76.2%) iRBD patients and 9 (20.5%) normal subjects.

The sensitivity and specificity for differentiating iRBD patients from normal subjects were 76.2 % and 79.5%, respectively. The correlation between the H/M ratio on cMIBG and the OSIT-J scores was examined, and the ratios on both early image and delayed images were strongly correlated with the OSIT-J scores($r=0.6475$, $p<0.001$, $r=0.6378$, $p<0.001$, respectively, Pearson's correlation coefficient) (Figure 1).

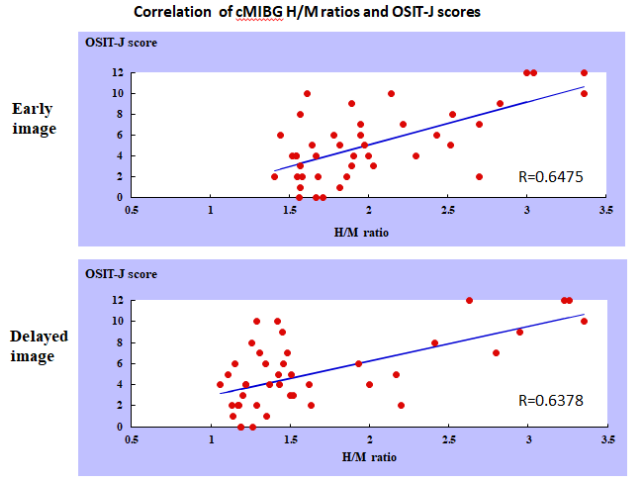

Figure 1: The correlation between the H/M ratio on cMIBG and the OSIT-J scores. The H/M ratio and OSIT-J score were showed strongly correlated on both early and delayed cMIBG images

The duration of iRBD symptoms, (j.e., vivid, often frightening dreams associated with simple or complex motor behavior during REM sleep) ranged from 1 to 40 years. The follow-up period was as short as 0.5-6 years, but 10 out of 37 patients converted to DLB. In 8 of the 10 cases, H/M on cMIBG was equivalent to PD3/4 level, and 2 cases developed mild Parkinson's symptoms. The remaining 1 case showed normal H/M ratio and 1 case showed an H/M ratios equivalent to PD 1.

DISCUSSION

In this study, we focused on the H/M ratio on cMIBG in patients with iRBD and estimated the possibility of conversion from iRBD to DLB and PD.

Schenk et al. reported that >80.8% (21/26) of patients with iRBD eventually developed synucleinopathies, including PD(n=13), DLB (n=3), MSA (n=2), Alzheimer's disease (2) and unspecified dementia (n=2) [2,3]. Postuma BR et al. have reported 1280 cases of conversion from iRBD to neurodegenerative diseases in a multicenter study, but it is difficult to compare their results with our results, because cMIBG test is not commonly performed in Western countries [4]. The most notable finding in this study was that among the iRBD patients in this study, the H/M ratio on cMIBG images had already decreased to the level of PD stage 3 or 4 or DLB on 58.7% of early images and 71.9% of delayed images.The results of this study are similar to previous reports [5,6].

Regarding the findings from the cMIBG study, >10 years will be needed to draw any definitive conclusions as to whether or not the H/M ratios is applicable for predicting conversion from iRBD to synucleinopathies. However, the results of the present study indicate that the H/M ratios showed a marked decrease to the level of PD3/PD4 or DLB at the time of the first examination has some clinical significance. PD is a progressive neurodegenerative disease and despite the diversity of its symptoms and signs, the severity of PD is classified according to the H &Y stage from I to V, and progresses according to that stage. The values of the H/M ratio decreased in the order of the H &Y stages in PD, while, the H/M ratios in 71.9% of the iRBD patients decreased to the level of the PD3/PD4 and/or DLB patients in this study. Since PD does not start at the PD3 or PD4 level, we can assume that the iRBD patients with a marked decrease in their H/M ratios might have a risk of developing DLB in the future, but that they would not develop PD. A normal H/M ratio or a mildly decreased H/M ratio in iRBD patients might be a risk factor of developing PD or DLB, or continuing iRBD (Figure 2).

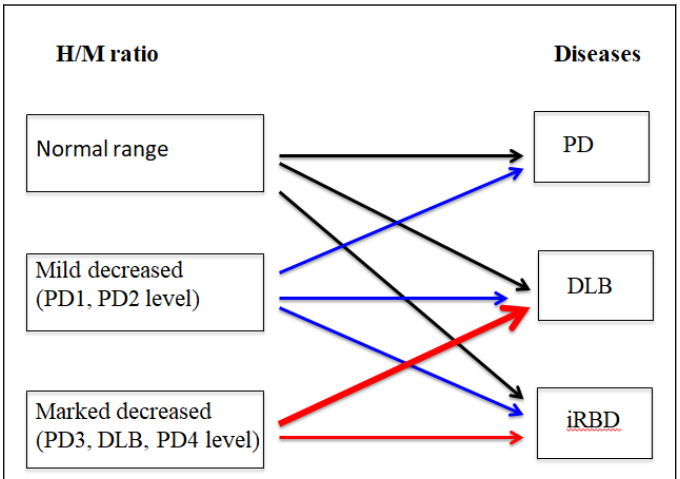

Figure 2: Proposed patterns of conversion from iRBD to α-synucleinopathies, particularly to DLB (red arrow).

The results of cMIBG study may be a useful indicator for selecting candidates for disease modification trials among iRBD patients as pointed out in the previous paper.

Olfactory dysfunction is known to be a frequent and early feature of PD, DLB, and Alzheimer's disease, often preceding the motor or cognitive symptoms by several years [7-10]. Fantini et al. tested 54 consecutive PSG-confirmed iRBD patients and 54 age-and gender-matched control subjects with the Brief University of Pennsylvania Smell Identification Test [7]. They found that 61.1% of iRBD patients and 16.6% of controls, had an abnormal olfactory function. In this study in the OSIT-J yielded similar results with their results (i.e., a decreased olfactory function in 76.2% of iRBD patients and 20.5% of normal subjects).

CONCLUSION

The olfactory dysfunction showed a strong correlation with the cMIBG H/M ratio. Olfactory dysfunction itself has no disease specificity; however, it is a simple test that can be applied as a screening test before cMIBG for patients with RBD.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Ethics Committee of the Nagasaki Kita hospital.

CONFLICT OF INTEREST STATEMENT

All authors declare that this study was conducted in the absence of any commercial or financialrelationships that could be construed as a potential conflict of interest.

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