Differentiation of Dementia with Lewy Bodies, Alzheimer's Disease and Vascular Dementia by Cardiac ^{131}I-meta-iodobenzylguanidine (MIBG) Uptake (Preliminary Report)

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Objective : *Differentiation of dementia with Lewy bodies (DLB), vascular dementia (VAD), and Alzheimer's disease (AD) is difficult in clinical practice. Several new techniques have been used for differentiation of various types of dementia. Among these techniques ^{123}I-meta-iodobenzylguanidine (MIBG) uptake was reported to have benefit in distinguishing DLB from AD. The authors study the role of MIBG as a tool for differentiation of DLB, AD and VAD.*
Method : *Patients with dementia were recruited to the study by DSMIIIR criteria. Diagnosis of each dementia type was made by standard clinical criteria. Brain imagings and ^{131}I-MIBG uptake were performed in all the studied patients.*
Results : *Five DLB, 3 AD and 3 VAD patients were clinically diagnosed. The heart/mediastinum (H/M) ratio in 4 out of 5 in DLB was significantly lower than H/M ratio in patients with AD and VAD. AD patients had the highest uptake of MIBG. MIBG uptake of VAD patients was in the range between AD and DLB but the values were close to the AD group.*
Conclusions : *^{131}I -MIBG is helpful in differentiating DLB from AD.*

Keywords : *Dementia with Lewy bodies, Alzheimer's disease, Vascular dementia*

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Recent studies on the treatment of Alzheimer's disease (AD) and vascular dementia (VAD) with cholinesterase inhibitor and memantine showed improvement of clinical outcome and delay of progression of the diseases[1-16]. This has not been confirmed in other types of dementia including dementia of Lewy bodies (DLB). Many demented patients also suffer from psychiatric symptoms such as psychosis which often require antipsychotic treatment. There is evidence that DLB patients are at high risk of developing neuroleptic malignant syndrome[1]. It is, therefore, necessary to carefully consider prescribing neuroleptic drugs in this group of patients.

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Diagnosis of dementia subtypes is often difficult by using clinical data alone. There should be other diagnostic laboratory tests to help such as protein 14-3-3 in Creutzfeldt-Jakob disease (CJD)[17,18]. Sympathetic nerve dysfunction can be detected by ^{123}I-MIBG scintigraphy. It has been used clinically to evaluate myocardial sympathetic nerve damage in both heart diseases and neurological disorders. In 2001, Watanabe et al and Yoshita et al simultaneously reported their studies of ^{123}I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy in the distinction between AD and DLB. They revealed that there was significantly lower ^{123}I-MIBG uptake in DLB patients than that of AD patients[19,20].

In Thailand, Iodine 123 is not available. Therefore, the authors have been using ^{131}I-MIBG instead of ^{123}I-MIBG. The goal of the present study

was to differentiate DLB, VAD and AD by cardiac ^{131}I-MIBG uptake. The method and its preliminary results of ^{131}I-MIBG studies on 11 patients with dementia are as follows.

Patients and Method

Patients

The medical records of sixty one patients with dementia meeting DSMIIIR criteria were reviewed. Only 35 patients were examined and the rest were excluded. Exclusion criteria included head injury, intracranial hemorrhage, brain tumor, normal pressure hydrocephalus, epilepsy, neurosyphilis, hypothyroidism, vitamin B12 or folate deficiency, HIV infection, malignancy, systemic illness with multiple organ involvement, death and refusal to participate in the study. After examination, there were 11 patients who took part in the study. There were four patients with probable DLB, one with possible DLB diagnosed by clinical criteria of the Consortium on DLB International Workshop[21,22]. Three patients were probable AD diagnosed by using both National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's Disease and Related Diseases Association (ADRDA) criteria[23]. Three patients were diagnosed as probable VAD, using NINCDS) and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences (AIRENS) criteria. Thai Minimental Status Examination (MMSE), computerized tomography or magnetic resonance imagings of the brain and blood tests including complete blood count, serology for syphilis, anti-HIV, thyroid function test, blood sugar, blood urea nitrogen and creatinine were performed. All cases did not receive drugs that interfered with the ^{131}I- MIBG uptake such as antidepressant, antipsychotic or sympathomimetic drugs. The present study was approved by Ramathibodi Hospital ethical committee. Informed consent was signed by all participants and caregivers.

Method

Cardiac ^{131}I- MIBG uptake

^{131}I-MIBG was injected intravenously. The images were done as in previous studies[19,20]. Planar images of the thorax in anterior view over 5 minutes with a 180 degree rotation were performed at 30 minutes (early scan) and 4 hours (delayed scan). Uptake of ^{131}I-MIBG was quantified by ratio of ^{131}I-MIBG in the heart to mediastinum (H/M ratio)[19,20].

Non-parametric analysis was used for analysis of the difference of the H/M ratio between each group.

Results

Patients data

Eleven patients with dementia participated in the present study (DLB 5, VAD 3 and AD 3 cases). There were 8 women and 3 men. Ages ranged from 59-76 years. Patients with DLB were older (70-76 years) than other groups (59-68 years). MMSE scores were from 0 to 22. Means of MMSE scores were 6.6 in DLB, 2.3 in AD and 15.6 in VAD. Orthostatic hypotension was detected in 60% of DLB, 50% of AD and none in VAD. AD had a gradually progressive course. Some DLB patients had fluctuation of symptoms and VAD had a stepwise pattern. The mean duration of symptoms were 3.4 years in DLB, 6 years in AD and 1 year in VAD. Recent memory and difficulty learning and retaining new information were affected early in the course of dementia whereas remote memory loss occurred later.

Prominent features in AD patients were language problems such as easily changing the subject during conversation, tangentiality, paraphasia, nominal aphasia and inability to repeat. Motor or sensory aphasia were not documented. One AD patient was left in a mute and bedridden state requiring complete care. Focal neurological signs were not identified.

Parkinsonism was detected in all DLB patients but not in AD or in VAD groups. It was symmetric, consisting of parkinsonian gait with reduced arm swing, en bloc turning, bradykinesia, masked face and cogwheel rigidity without tremor. In DLB, postural instability was observed early in the course of the illness. In DLB, visual hallucination and fluctuation of cognition were observed in 80% and 40% of patients respectively. Visual hallucination was spontaneous and complex and was not related to medication. Among DLB cases, patient No. 5 had the highest values of H/M ratio which was similar to H/M ratio in other dementia group. She had progressive dementia for 6 years and her MMSE score was 6. Her first presentation was recent memory loss, vivid hallucination with normal motor function. She was still able to maintain daily activities during the first few years of her illness. Her motor function had remained intact until the last 2 years when she developed parkinsonism. Subsequently, she became bed-ridden 5 years later. Her natural history was different from those of other DLB patients in terms of late development of parkinsonism.

All VAD cases had dementia symptoms following 1 or 2 major cerebrovascular accidents which were confirmed by CT or MRI brain. Neurological examination revealed facial palsy, spastic dyarthria, spasticity, weakness, brisk tendon reflexes and

extensor plantar response. One patient had emotional instability. Impairment of abstract thinking with frontal and parietal lobe signs were observed in every dementia subgroup.

Cardiac ^{131}I- MIBG uptake

H/M ratio of ^{131}I - MIBG of DLB group in early images were 1.37-1.49 and in late images were 1.12-1.54 in 4 out of 5 cases. There was only one case whose results were 1.8 and 1.71 in early and late images respectively. For AD group, the results were 1.72-1.79 in early images and 1.78-1.8 in late images. In VAD patients, H/M ratio revealed 1.57-1.73 in early images and 1.54-1.92 in late images (Fig. 1, Table 1-3). AD had the highest mean value of MIBG uptake, the second was VAD and the lowest was DLB (Table 4). Thus, there was a significant difference ($p < 0.03$) among the three diseases. The late images had lower H/M ratio than the early images in almost all DLB patients. The difference was greater than that in AD and VAD but without statistical significance. There was also no significant difference ($p = 0.89$) between early and late images regardless of dementia types.

Discussion

Patients were divided into 3 groups, DLB, VAD and AD. AD and VAD are the two most common types of dementia while DLB is rare. In the present series, which is a preliminary report of an ongoing study, there are more DLB patients than other groups, because more AD and VAD patients are still waiting for ^{131}I-MIBG study. The clinical courses of patients are similar to those in previous reports. The mean age of onset in DLB group was higher than those in AD and VAD groups but it was not statistically significant ($p = 0.56$). The mean duration of illness and MMSE scores in VAD were lowest compared to those in AD and DLB. VAD is associated with shorter survival. The majority of patients died from cardiovascular problems.

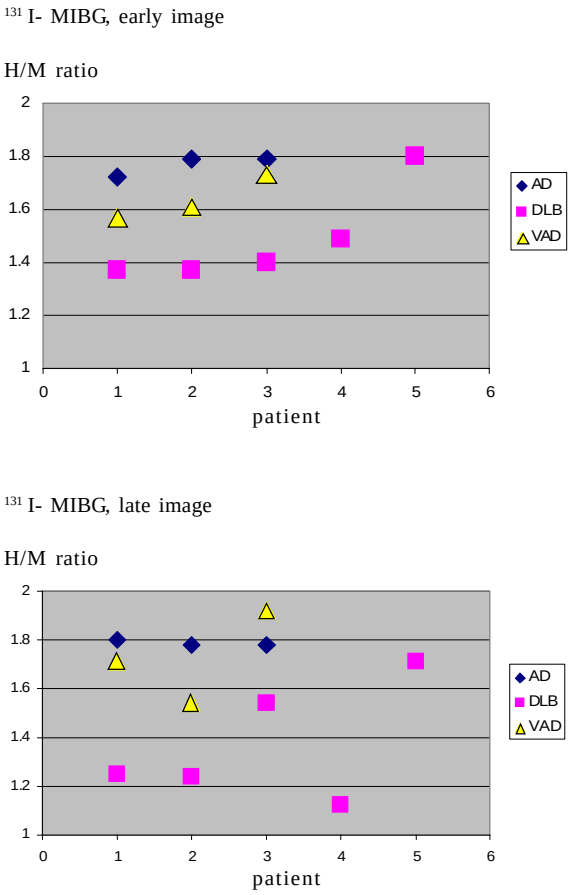

Fig. 1 HM ratio of ^{131} I- MIBG in AD, DLB and VAD patients

DLB has a life expectancy of 7.7+/- 3 years after onset of cognitive symptoms, whilst that in AD was 9.3+/- 3.5 years[24]. Orthostatic hypotension was not specifically identified in DLB patients. This was found in 60% of DLB and 50% of AD cases tested. This finding is also similar to those in previous reports[19]. This clinical sign is, therefore, not useful as a clue for differential diagnosis.

Table 1. DLB patients

Patients case No.	Sex	Age	MMSE	Duration (year)	OH	Parkinsonism	Visual halllucination	Fluctuation of cognition	^{131}I MIBG H/M ratio	
									early	late
1	M	73	9	6	yes	yes	yes	no	1.37	1.25
2	F	76	15	1	no	yes	yes	yes	1.37	1.24
3	M	70	0	2	yes	yes	no	no	1.4	1.54
4	F	74	3	2	yes	yes	yes	yes	1.49	1.12
5	F	73	6	6	no	yes	yes	no	1.8	1.71
mean				3.4					1.486	1.372

MMSE = minimental status examination, OH = orthostatic hypotension

Table 2. AD patients

Patients case No.	Sex	Age	MMSE	Duration (year)	OH	Parkinsonism	^{131}I MIBG H/M ratio	
							early	late
1	F	61	7	4	no	no	1.72	1.8
2	F	67	0	11		no	1.79	1.78
3	F	59	0	3	yes	no	1.79	1.78
mean				6			1.766	1.786

Table 3. VAD patients

Patients case No.	Sex	Age	MMSE	Duration (year)	OH	Parkinsonism	^{131}I MIBG H/M ratio	
							early	late
1	F	62	11	1		no	1.57	1.71
2	M	67	22	4/12	no	no	1.61	1.54
3	F	68	14	2	no	no	1.73	1.92
mean			15.6	1			1.636	1.723

Table 4. Mean value of ^{131}I-MIBG uptake of DLB, AD and VAD in early and late images

	DLB	VAD	AD	Total
Early images	1.486	1.636	1.766	1.6
Late images	1.372	1.723	1.786	1.58
Total	1.429	1.68	1.77	

The results showed that most patients in DLB group had lower uptake of ^{131}I-MIBG than other two groups. These findings were close to the previous studies using ^{123}I-MIBG[19,20]. The H/M ratio (< 1.4) may be used to differentiate DLB from AD. However, it is difficult to distinguish AD from VAD or DLB from VAD as the ratio of AD is pretty close to that of VAD. As in the cases of DLB and VAD, their ratios do not move in a uniform pattern and the number of patients is small.

Metaiodobenzylguanidine (MIBG) is a physiological analogue of noradrenaline. It competes with noradrenaline for neuronal uptake and is taken up by low affinity non-neuronal tissue[25]. The early scan reflects the influx of MIBG into extraneural spaces in the myocardial tissue. The neuronal uptake reaches its peak 3-4 hours after MIBG injection[26]. The delayed scan displays the neuronal uptake more clearly. Therefore, myocardial MIBG uptake was assessed 20 minutes and 3 hours postinjection in the present study. Its low uptake in DLB patients was attributable to the disturbance of postganglionic cardiac sympathetic nerve. Histopathological studies showed that Lewy bodies and Lewy nitrites are present in the cardiac plexuses in incidental Lewy body disease and Parkinson's disease[27]. In patients with DLB, vulnerability of sympathetic ganglionic neurons have also been reported[28].

In the present study, the authors used clinical criteria as a standard diagnosis although histopathology of the brain is the gold standard for diagnosing subtypes of dementia. The specificity of the clinical criteria for probable DLB compared to neuropathological diagnosis is quite high, which ranges from 0.84-1.00[29-32], but its sensitivity is not impressive which ranges from 0.40-0.89[29,31,32]. One can predict that strategy using clinical diagnosis may lead to incorrectly diagnosing DLB as AD. However, the prevalence of DLB is much lower than AD in the general population. Thus, a chance to diagnose DLB incorrectly as AD should be very low.

The difference between H/M ratio of DLB in early and late images was greater than that in AD and VAD but this was not statistically significant. The only patient with DLB who had a high uptake in the early image, the value in the late image was also lower than that in the early image. This result merits further study in more cases. Moreover, the difference of the early and late images was not significant regardless of dementia types. Thus, the duration after ^{131}I-MIBG injection may not be the factor which influenced the results of the analysis.

Admittedly, the number of patients in this preliminary study are too few and the types of dementia were based on clinical diagnosis. Clinical approach together with brain imaging are essential in making the diagnosis in patients with dementia. The present study was the first to utilize ^{131}I-MIBG instead of

^{123}I-MIBG uptake as an additional tool for helping to differentiate DLB from AD. Further studies on a larger number of patients are needed to confirm the present data.

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การแยกภาวะสมองเสื่อมที่มี Lewy bodies โรคอัลซ์ไฮเมอร์ และภาวะสมองเสื่อมจากหลอดเลือดแดงตีบตันด้วยการวัดปริมาณการจับ ^{131}I-meta-iodobenzylguanidine ที่กล้ามเนื้อหัวใจ

ปนิษฐา จินดาหรา, อรรถสิทธิ์เวชชาชีวะ, รวิพรรณ วิทูรพณิชย์, รจนา ศิริศรีโร, ชนิกา ศรีธารา, ธีรธร พูลเกษ

วัตถุประสงค์ *: เนื่องจากการวินิจฉัยแยกภาวะสมองเสื่อมที่มี Lewy bodies โรคอัลซ์ไฮเมอร์ และภาวะสมองเสื่อมจากหลอดเลือดแดงตีบตันยังมีปัญหาอยู่มาก จึงได้มีการพัฒนาการตรวจใหม่ ๆ เพื่อวินิจฉัยโรค มีหลักฐานว่าปริมาณการจับ ^{123}I-meta-iodobenzylguanidine (MIBG) ที่กล้ามเนื้อหัวใจสามารถแยกภาวะสมองเสื่อมที่มี Lewy bodies และโรคอัลซ์ไฮเมอร์ได้ ผู้นิพนธ์จึงได้ศึกษาบทบาทของ MIBG ในการแยกโรคและภาวะทั้งสามนี้*

วิธีการ *: ผู้ป่วยภาวะสมองเสื่อมได้รับการวินิจฉัยตามเกณฑ์ DSMIIIR และการวินิจฉัยภาวะสมองเสื่อมที่มี Lewy bodies โรคอัลซ์ไฮเมอร์ และภาวะสมองเสื่อมจากหลอดเลือดแดงตีบตันใช้เกณฑ์การวินิจฉัยทางคลินิก ผู้ป่วยทุกรายได้ทำ MRI หรือ CT สมอง และตรวจวัดปริมาณการจับ ^{131}I-meta-iodobenzylguanidine*

ผลการศึกษา *: มีผู้ป่วยทั้งหมด 11 คน เป็นภาวะสมองเสื่อมที่มี Lewy bodies 5 คน โรคอัลซ์ไฮเมอร์ 3 คน และภาวะสมองเสื่อมจากหลอดเลือดแดงตีบตัน 3 คน ผล heart/mediastinum (H/M) ratio ของผู้ป่วยสมองเสื่อมที่มี Lewy bodies 4 ใน 5 คนต่ำกว่าผู้ป่วยอัลซ์ไฮเมอร์และสมองเสื่อมจากหลอดเลือดแดงตีบตัน ค่า H/M ของผู้ป่วยอัลซ์ไฮเมอร์มีค่าสูงสุด รองลงมาคือค่าของผู้ป่วยหลอดเลือดแดงตีบตัน*

สรุป *: การตรวจวัดปริมาณการจับ ^{131}I-meta-iodobenzylguanidine สามารถใช้แยกภาวะสมองเสื่อมที่มี Lewy bodies จากโรคอัลซ์ไฮเมอร์ได้*