The Role of I-131 MIBG Cardiac Scintigraphy in Diagnosing Dementia with Lewy Bodies : A Case Report

Matthew Stephen L. Jatico, MD, Eduardo Erasto S. Ongkeko, MD

Division of Nuclear Medicine and PET Center , St. Luke's Medical Center - Bonifacio Global City
E-mail address: msljatico@stlukes.com.ph

ABSTRACT

The objective of this case report is to highlight the role of Iodine-131 metaiodobenzylguanidine (MIBG) cardiac scintigraphy in discriminating Dementia with Lewy Bodies (DLB) from other neurodegenerative diseases such as Alzheimer's Disease. This patient is a known case of Parkinson's disease and has been treated as such since 2011. However, the patient also concurrently deals with visual hallucinations and because of this, the patient's attending neurologist wanted to rule in the diagnosis of DLB rather than AD. Hence, an I-131 MIBG cardiac scan was requested in order to support the diagnosis of DLB. The use of I-131 MIBG cardiac scintigraphy as a diagnostic tool for diagnosing Lewy Body Dementia is not prevalent and to our knowledge, this was the first time in the country that this procedure was done (December 9, 2019).

INTRODUCTION

Dementia with Lewy Bodies (DLB) and Parkinson's Disease with Dementia (PDD) each fall under the umbrella diagnosis of Lewy Body Dementia. Although these two diseases have similarities in their clinical, morphological, and neurochemical characteristics, these types of dementias are actually two distinct entities. The distinction between the two diagnoses is based on the onset of cognitive symptoms (dementia) and motor symptoms (parkinsonism). In DLB, dementia precedes parkinsonism while in PDD, there is appearance of motor symptoms prior to the onset of the cognitive symptoms. These two types of dementias share the same framework and are defined morphologically by the presence of α-synuclein/Lewy bodies plus β-amyloid and tau pathologies. However, it is still important to differentiate the two from each other.

Alzheimer's Disease (AD) on the other hand, is the most common age-related neurodegenerative disorder and is characterized clinically by progressive neuronal loss which results in memory loss and dementia. A definite diagnosis can be made at autopsy and rarely by brain biopsy. Histopathology of these brain samples show the characteristic neurofibrillary tangles and amyloid plaques.

CASE REPORT

Patient Information

This is a case of an 81-year old male who had been diagnosed with Parkinson's disease since 2011. The patient was diagnosed clinically and through a Parkinson's Disease Profile done on July 22, 2011, it was determined that he is responsive to Carbidopa/Levodopa and Domperidone. In the interim, the patient started to have deterioration in memory and was treated with Rivastigmine for dementia. Brain PET/CT was then requested and done on August 8, 2017 however, it did not show any metabolic abnormality in the brain. In July 2019, patient had an unwitnessed fall in the bathroom and was found to have complete subcapital and intertrochanteric right femoral fractures. Patient was eventually admitted and during his stay, it was found that he had a subacute infarct in the right parietal lobe. Patient was then started on cerebrolysis. According to the patient's wife, he had increased sleeping time or hypersomnia with reported cognitive changes (episodes

of agitation, poor attention span, and confusion) after the initiation of cerebrolysis. Patient then had another Brain PET/CT done on October 15, 2019 with findings of mild to moderately hypometabolic frontal lobes, moderate to severely hypometabolic parietal lobes more severe in the posterior parietal cortices, moderately hypometabolic temporal lobes, and hypometabolic posterior cingulate cortex which are suggestive of Alzheimer's dementia. However, the patient was also noted to have visual hallucinations not associated with agitation. A cardiac I-131 MIBG scan was then done in order to determine whether the patient's declining neurodegenerative condition was due to Dementia with Lewy Bodies.

Methods

This study was approved by the institution ethical review board of St. Luke's Medical Center-Global City. Patient's consent for the procedure and for this study were obtained.

Before the scintigraphy was done, it was necessary to establish an appropriate withdrawal period for interfering drugs, taking into account their biological half - lives and the recommended withdrawal time. The patient's drugs that may have an effect on the scintigraphy were discontinued. Patient was then advised to take Lugol's solution (potassium iodide saturated solution) – 3 drops three times a day, two days prior to the administration of I-131 and to continue this for 6 days after.

For the scintigraphic method of myocardial innervation imaging, I-131 MIBG was intravenously administered at rest with a total dose of 70.3 MBq (1.9 mCi). Early (15 minutes after tracer injection) and delayed (4 hours after tracer injection) anterior planar images of the chest were then obtained using a high energy collimator with a large field of view camera for adequate evaluation of cardiac sympathetic function. Anterior planar imaging of the chest at 30 minutes was also done for quality control (see Figure 1).

Regions of interest (ROIs) were then drawn over the heart and mediastinum to derive the count-based quantitative parameters as shown in Figure 2. The regions of interest (ROIs) drawn over the heart and mediastinum in this report were based on the ROIs done in the study by Yang et al in 2016 [7].
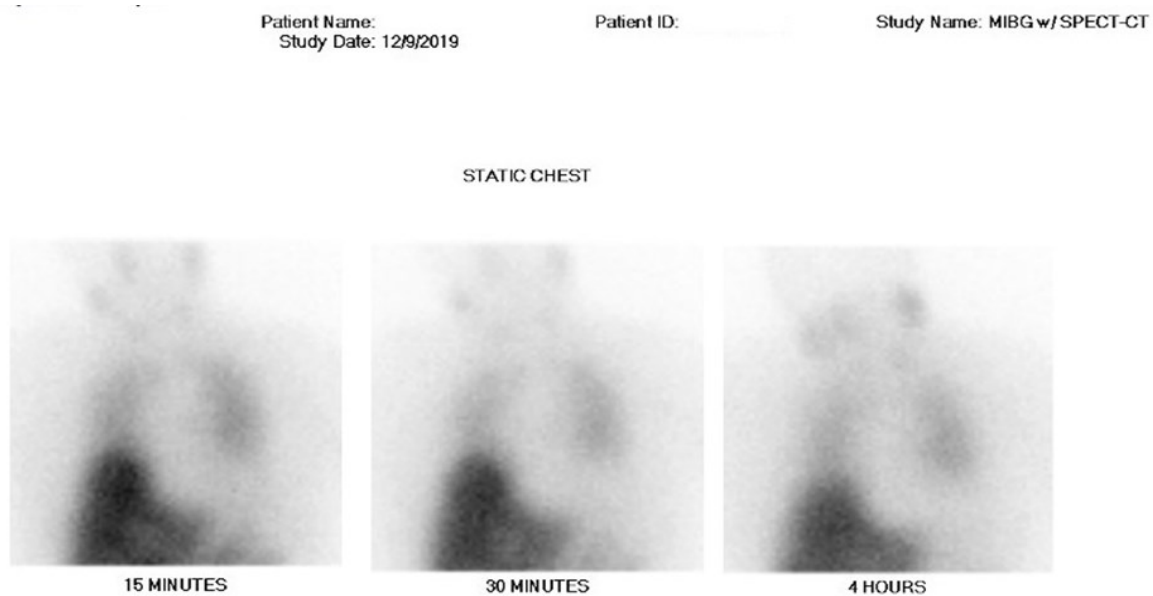

Patient Name:
Study Date: 12/9/2019

Patient ID:

Study Name: MIBG w/ SPECT-CT

STATIC CHEST

15 MINUTES   30 MINUTES   4 HOURS

FIGURE 1. Anterior static images of the chest acquired at 15 minutes (early), 30 minutes (quality control), and 4 hours (delayed) after IV administration of I-131 MIBG
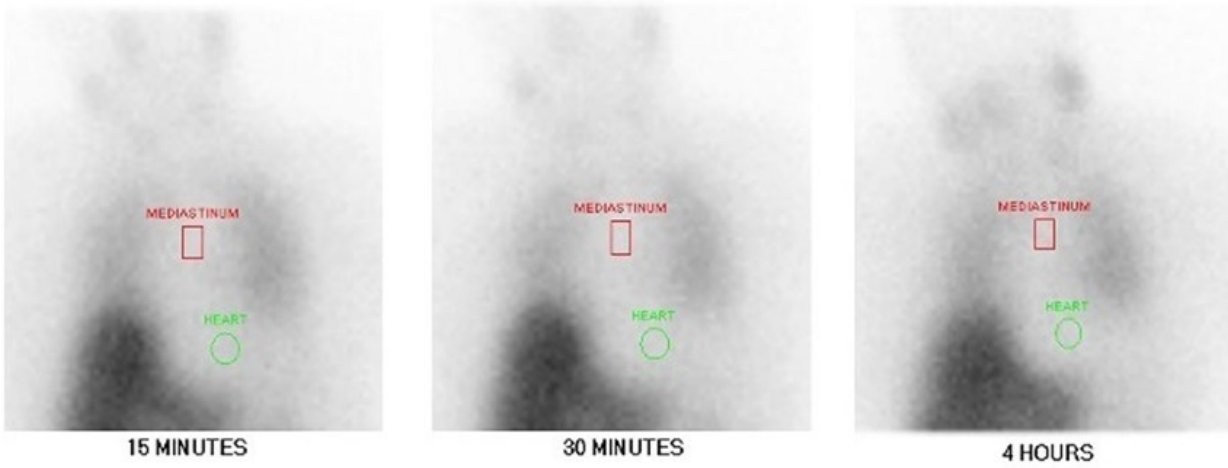
STATIC CHEST WITH ROI

FIGURE 2. Anterior static images of the chest acquired at 15 minutes, 30 minutes and 4 hours with ROIs drawn over the heart and mediastinum
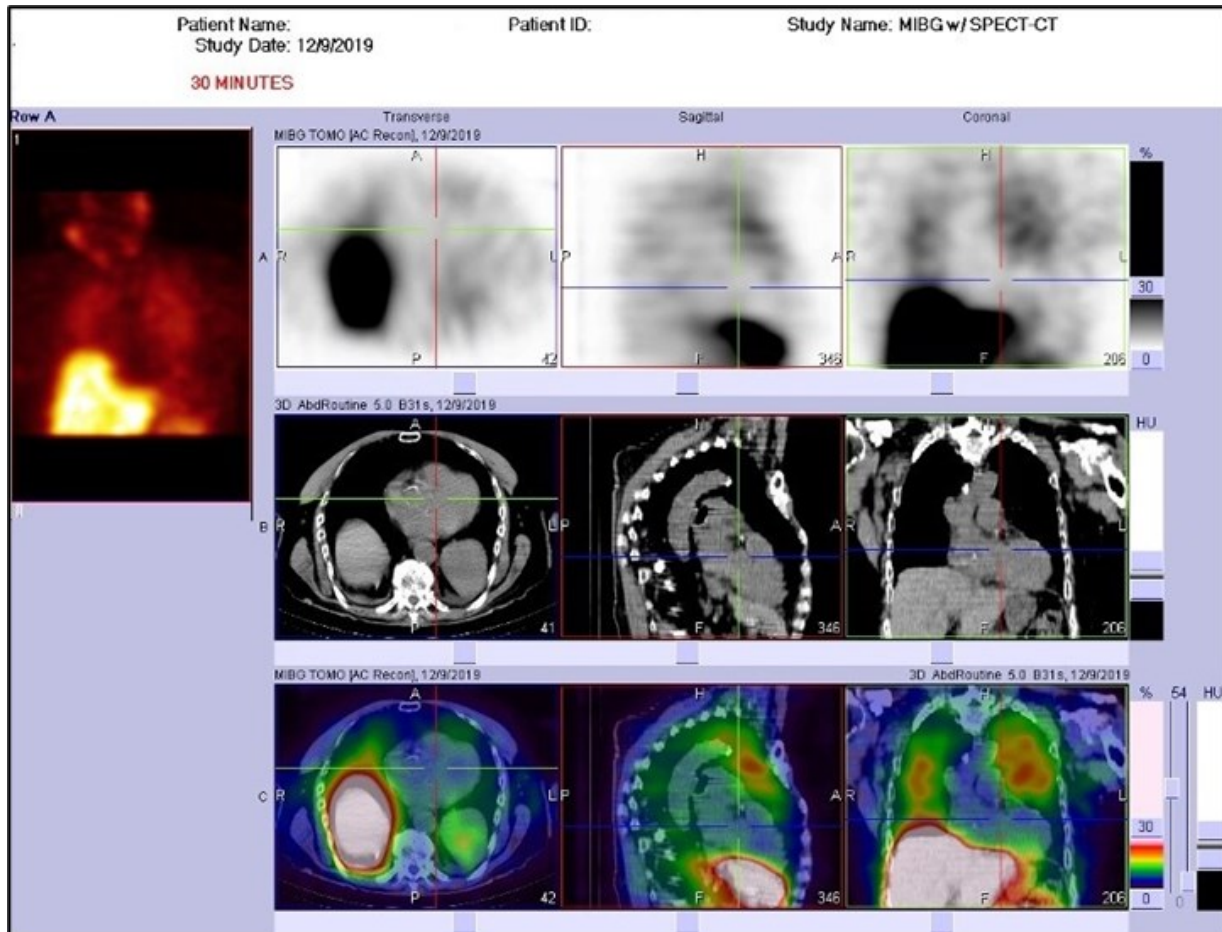

FIGURE 3. SPECT-CT image of the heart at 30 minutes (quality control)

SPECT-CT of the chest was also done to evaluate the three-dimensional myocardial uptake pattern with anatomical guidance from the low dose CT as seen in Figures 3 — 6. This was done 30 minutes (quality control) and 4 hours after tracer injection.

Average counts per pixel of the heart and mediastinum were used from their respective ROIs in order to compute for the Heart to Mediastinum ratios (HMRs). The mediastinum was used as a reference because it contains few sympathetic nerves. The HMRs were then computed using the counts garnered from the 15th minute (Early) and 4th hour (Delayed) planar images using formulas based on the study by Yang et al in 2016 [7]. The following formulas were then used:

$$15^{th} \text{ minute HMR} = \frac{HC \text{ (Early)}}{MC \text{ (Early)}}$$

$$4^{th} \text{ hour HMR} = \frac{HC \text{ (Delayed)}}{MC \text{ (Delayed)}}$$

HC: Heart counts

MC: Mediastinum counts

The following are the average counts per pixel in the heart and mediastinum of the patient used for his HMRs:

	HEART	MEDIASTINUM
15 MINUTES	221.65	183.53
4 HOURS	158.96	159.27

$$15^{th} \text{ minute HMR} = \frac{221.65}{183.53} = \mathbf{1.21}$$

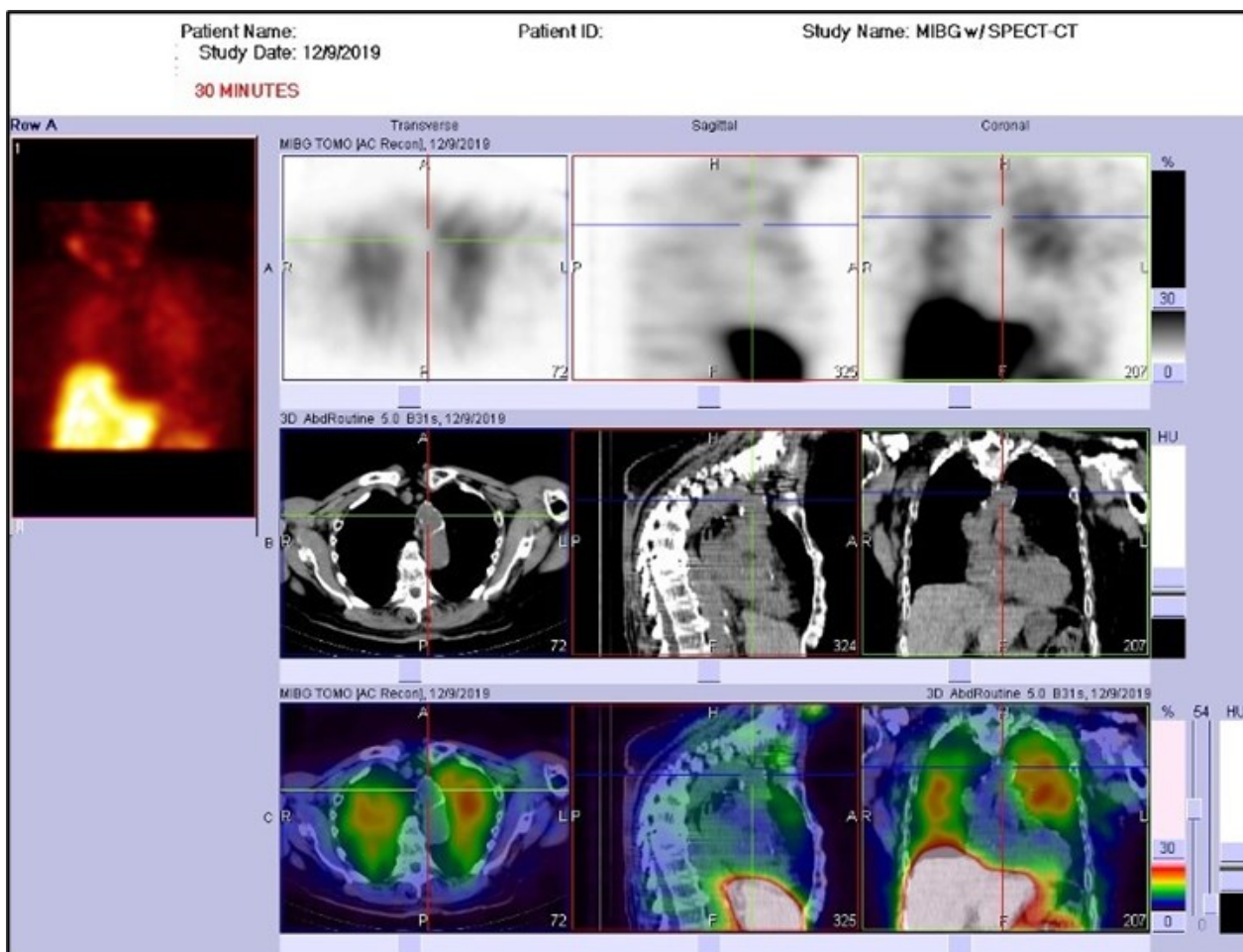$$4^{th} \text{ hour HMR} = \frac{158.96}{159.27} = \mathbf{1.00}$$

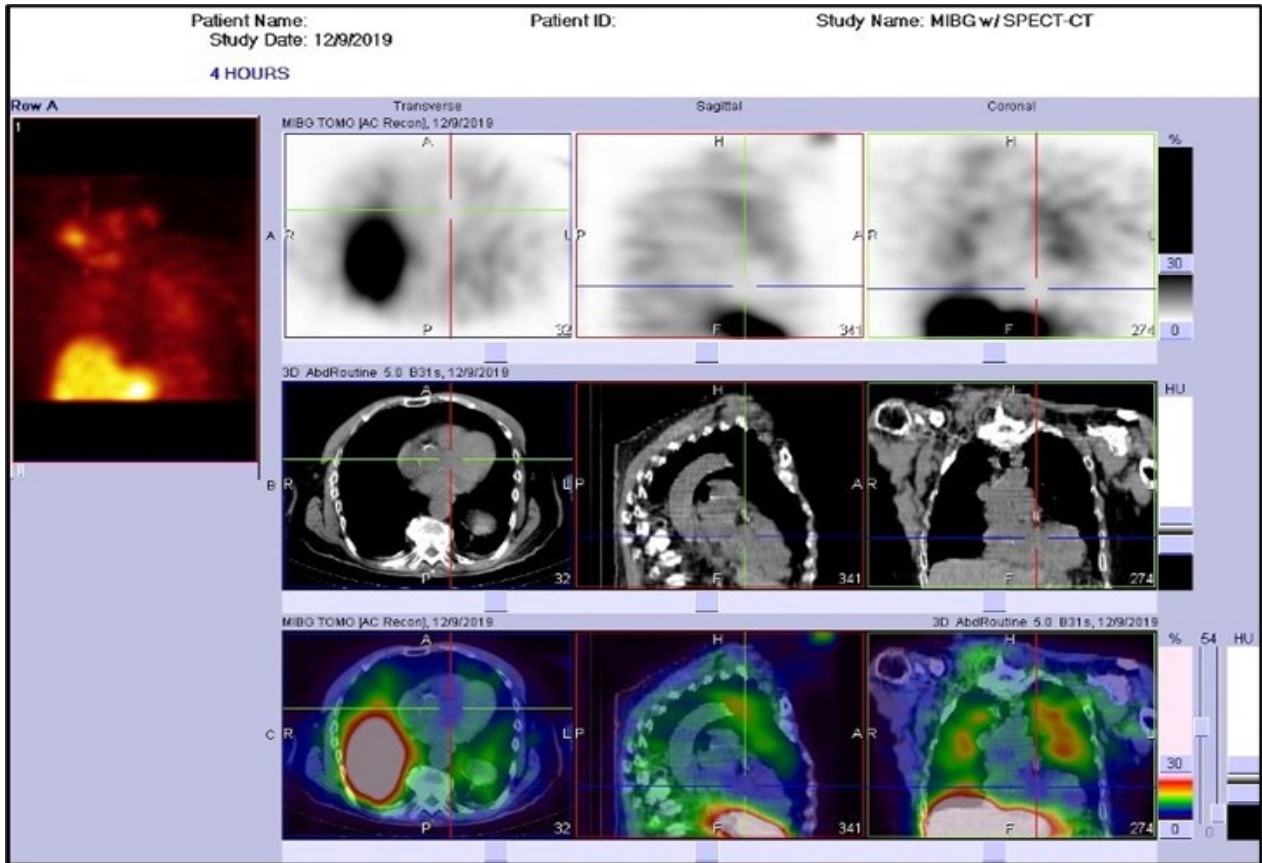**FIGURE 4.** SPECT-CT image of the mediastinum at 30 minutes (quality control)

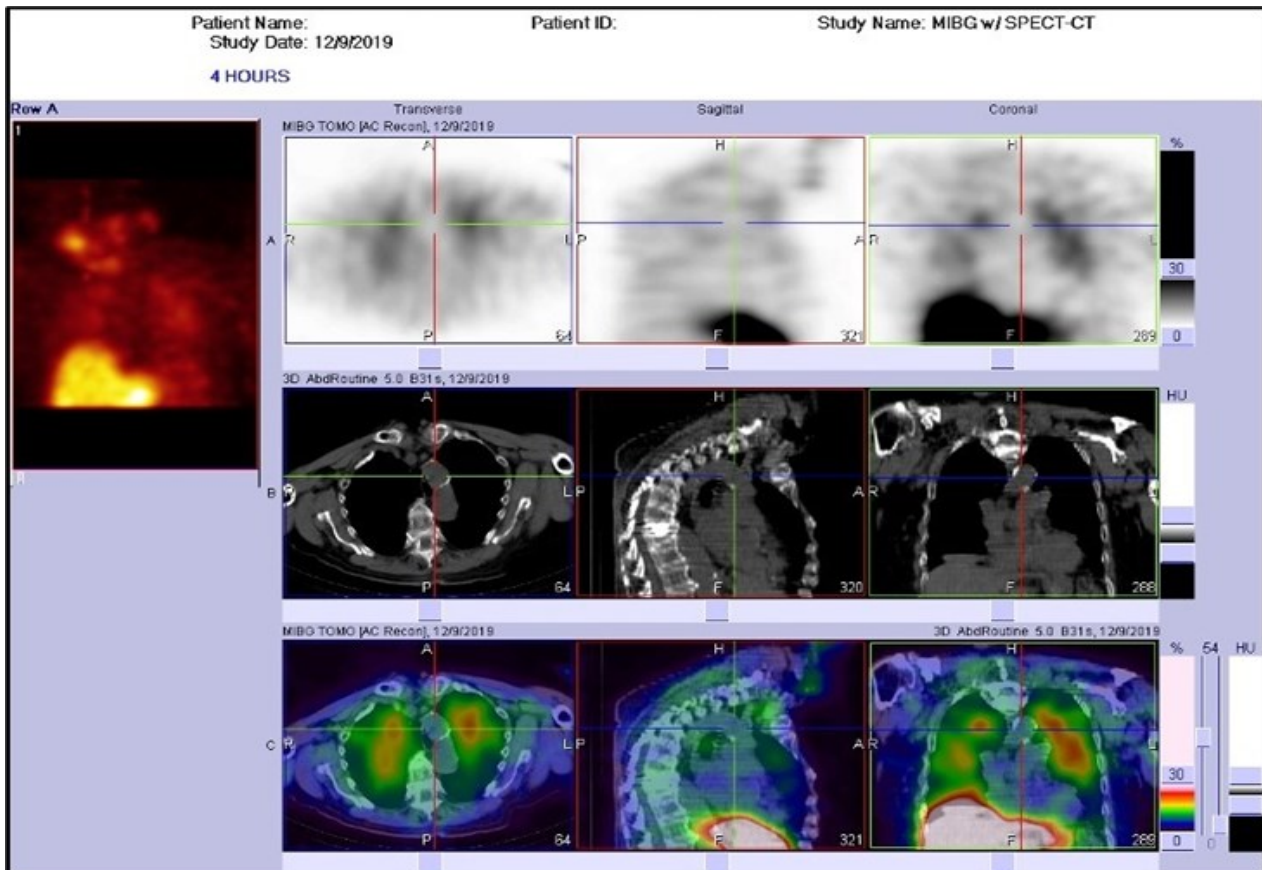**FIGURE 5.** SPECT-CT image of the heart at 4 hours

FIGURE 6. SPECT-CT image of the mediastinum at 4 hours

The washout ratio (WOR) of MIBG indicated the activity tone of the presynaptic sympathetic nerves. The WOR was then calculated based on the formula in the study by Yang et al in 2016:

WOR =

$$\frac{[HC(early)\text{-}MC(early)] - [HC(Delayed)\text{–}MC(Delayed)]}{[HC(early) \text{ - } MC(early)[}$$

x 100

The following is the WOR of the patient:

WOR = $\frac{[221.65 - 183.5] - [158.96 - 159.27]}{[221.65 - 183.5]}$ x 100

= **99.2 %**

A WOR of 30% or more is compatible with both PD and DLB. WOR is expected to be near zero in healthy control patients or even negative in some cases.

The following are reported normative values extrapolated from the studies by Yang et al (2016), Yoshita et al (2006), and Slaets et al (2015)[7, 9, 10] in comparison to the patient's HMR.

Heart to Mediastinum Ratio (HMR):

	EARLY HMR (15 MINUTES)	DELAYED HMR (4 hours)
Patient	**1.21**	**1.00**
Normal	>2.2	> 2.2
Parkinson's Disease	1.7	1.5
Dementia with Lewy Bodies	<1.3	<1.3

The following are the scan findings and conclusion of this study:

Scan findings:

The heart exhibited decreased MIBG uptake, both in early and delayed images as well as on SPECT-CT images.

The mediastinum also exhibited relatively decreased MIBG uptake, an expected finding in Parkinson's Disease and Dementia with Lewy Bodies.

The calculated WOR for this patient is 99.2%.

Incidental note of cardiomegaly was also seen on low-dose CT.

Conclusion:

Decreased cardiac MIBG activity, with Heart to Mediastinum Ratio of 1.21 (early) and 1.00 (delayed) and Washout Rate of 99.2%. This is compatible with impaired sympathetic nervous system and is suggestive of Dementia with Lewy Bodies.

DISCUSSION

Alzheimer's disease

Alzheimer's disease is a progressive lingering neurodegenerative disorder that is distinguished by three primary groups of symptoms. The first group is cognitive dysfunction, which includes memory loss, language difficulties, and executive dysfunction. The second group comprises of psychiatric symptoms and behavioral disturbances which are collectively termed as non-cognitive symptoms. The last group comprises of difficulties with performing activities of daily living. These symptoms of Alzheimer's disease progress from mild symptoms of memory loss to very severe dementia [1].

The beginning of mental changes in patients with AD is usually so subtle that neither patient or the patient's family can exactly determine the timeframe when the onset of these mental changes started. In most instances, these changes only come to the attention of the patient several months or years after the decline had already began. The major symptom of AD is gradual development of forgetfulness [2].

Histopathologic diagnosis of AD can definitively be made at autopsy or by performing brain biopsy, which is rarely done. These pathological samples show characteristic neurofibrillary tangles and amyloid plaques [3].

There are 3 criteria usually used in diagnosing Alzheimer's Disease and these are the shown in Figure 7 [4].

Imaging modalities such as Brain F-18 FDG PET in patients with AD usually shows bilateral hypometabolism in the posterior cingulate and superior posterior parietal cortex. Even if classic examples of AD are often symmetric, it is usually rather asymmetric, especially in its early stages. It may progress to involve the frontal cortices, although involvement of the parietal and temporal lobes is usually more profound [5].

Dementia with Lewy Bodies

On the other hand, Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia after Alzheimer's disease. Given the overlap in clinical symptoms between DLB and other causes of dementia such as Parkinson's disease and Alzheimer's disease, making a correct diagnosis is often a daunting task.

The exact cause of DLB is unknown however, there is widespread deposits of abnormal clumps of protein that form in the neurons of the diseased brain and these are called Lewy Bodies.

	NINCDS-ADRDA	DSM-IV	ICD-10
Cognitive deficits	Memory decline and impairment in at least one other cognitive domain	Memory decline and at least one of aphasia, apraxia, agnosia, executive dysfunction	Memory decline and deterioration in judgement and thinking
Confirmation	MMSE or similar, and neuropsychological testing	–	–
Functional impairment	–	Impairment of social or occupational functioning	Impairment of activities of daily living
Course	Progressive worsening	Gradual onset and continuing decline	Gradual onset and slow deterioration
Exclusions	Age at onset < 40 or > 90*	Substance abuse or other major mental disorder	Sudden onset or focal neurological signs

FIGURE 7. Criteria for diagnosing Alzheimer's Disease

Cognitive domains are most commonly affected in patients with DLB. These include deficits in attention, executive function, and visual-spatial skill. Patients with DLB often have impairment with short-term memory, a reflection of a problem with retrieval of stored information. Over time, the patient's cognitive impairment progresses and spreads to involve other cognitive domains. Once this impairment has become sufficiently severe to impair social or occupational function (basic activities of daily living), they now reach the criteria for a diagnosis of dementia [6].

Recurrent, complex visual hallucinations are frequently seen in patients with DLB and the presence of these hallucinations at an early stage is diagnostically useful. These visual hallucinations tend to be well formed and animated in patients with DLB.

There is also fluctuation of attention and alertness, leading to increased episodes of staring, frequent daytime drowsiness, and naps during the day. It is important to note however that these episodes are hard to quantify.

Parkinsonism often develops concurrently or subsequently to these cognitive problems and is beneficial in diagnosing DLB. These motor signs are often symmetrical and usually present with bradykinesia and gait impairment rather than resting tremors. However, the variance of these motor signs is high.

REM sleep behavior disorder is also commonly seen in patients with DLB. It is a type of parasomnia that is manifested as a recurrent enactment of dreams which includes movements that mimic the dream content. This is also associated with the absence of atonia in normal REM sleep.

Another common feature in patients with DLB is autonomic impairment. Constipation is the most commonly encountered problem and becomes vexing if not treated right away. Most patients with DLB also have orthostatic hypotension and its complications such as syncope and history of repeated falls. Denervation of cardiac sympathetic ganglia is prevalent and is appreciated using MIBG cardiac scans.

The consensus criteria for a clinical diagnosis of DLB is based on the revised criteria for the clinical diagnosis of probable and possible Dementia with Lewy bodies by the Dementia with Lewy Bodies Consortium done in 2015 and is seen in Table 1. Dementia or the presence of progressive cognitive decline of sufficient magnitude involving attention, executive function, and visual-spatial skills is required for the diagnosis of DLB. The core features of these criteria include the following:

1) Fluctuations in attention and alertness

2) Recurrent visual hallucinations that are well formed and detailed

3) REM sleep behavior disorder

4) Parkinsonian motor signs or Parkinsonism

Supportive features include; severe sensitivity to anti-psychotic agents, postural instability, repeated falls, syncope or other transient episodes of unresponsiveness, severe autonomic dysfunction, hypersomnia, hyposmia, hallucinations in other modalities, systematized delusions, apathy, anxiety, and depression.

A diagnosis of clinically probable DLB requires:

a) At least two or more core clinical features with or without the presence of indicative biomarkers, or;

b) One core feature but with one or more indicative biomarkers

A diagnosis of clinically possible DLB requires:

a) One core feature present with no indicative biomarker, or;

b) One or more indicative biomarkers but no core clinical features present

TABLE 1. Revised criteria for the clinical diagnosis of probable or possible Dementia with Lewy Bodies [6]

Core clinical features:
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically well formed and detailed
REM sleep behavior disorder, which may precede cognitive decline
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia, rest tremor, or rigidity
Indicative biomarkers:
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET
Abnormal (low uptake) I-123 or I-131 MIBG myocardial scintigraphy

I-131 MIBG cardiac scintigraphy

Metaiodobenzylguanidine (MIBG) is a norepinephrine analogue which competes with norepinephrine (NE) for the same cellular transporter mechanisms in postganglionic sympathetic neurons and is actively taken up by sympathetic nerve terminals. Since MIBG and NE have the same mechanisms for uptake, storage, and release, radiolabeling of MIBG with I-131 enables the visualization and quantification of cardiac postganglionic sympathetic innervation in vivo. Cardiac MIBG uptake in the early image (15 minutes) mainly reflects the density of the presynaptic cardiac sympathetic nerve endings. MIBG is mainly stored in NE vesicles, and is quickly washed out in non-neuronal uptake and almost disap-pears after the delayed images (4 hours)7. In contrast, MIBG clearance in neuronal uptake is low, therefore the delayed image also reflects the presynaptic functional tone of the cardiac sympathetic nerves, which is more accurate for the evaluation of the sympathetic nervous system. The delayed H/M ratio combines information on neuronal function from uptake to release through the storage vesicles at the nerve terminals [8].

Autonomic failure is a late complication of DLB. It is known that cardiac uptake of MIBG was decreased in patients with DLB. Histopathologically, Lewy neurites were detected in the cardiac plexus in patients who were incidentally found to have DLB. It was also reported that cardiac sympathetic nerves were dramatically depleted in most of patients with DLB. These pathologic findings indeed support that decreased cardiac uptake of MIBG is seen in patients with DLB. The reduced uptake of MIBG to the myocardium indicates that the capacity of MIBG to enter the neuronal tissue is weakened [9]. Further, it indicates that the ability of the sympathetic nerves to store MIBG or the amount of sympathetic nerves in the myocardium is reduced in patients with DLB. On the other hand, an increased WOR in DLB patients may represent a MIBG retention failure, an increase in the turnover rate, or a decrease in uptake suggestive of reduction of sympathetic nerves, inability of sympathetic nerves to store MIBG and reflects the postganglionic cardiac sympathetic denervation [10].

This case demonstrates the use of I-131MIBG scintigraphy as an indicative biomarker in the diagnosis of DLB. As seen in the patient's scan, he had a decreased heart to mediastinum ratio of 1.21 (early) and 1.00 (delayed), which is consistent with the HMR of a patient with DLB. The patient's washout ratio of 99.2% is also compatible with DLB.

Based on the clinical presentation of the patient and the scintigraphic features seen in this case, a diagnosis leaning more towards to probable Dementia with Lewy Bodies rather than Alzheimer's Disease was deemed more appropriate for the patient.

Limitations

The reported normative values for the heart to mediastinum ratios and washout out ratios were extrapolated from the references stated below, each involving sample sizes of less than 100 patients each. There were also no normative values for HMR and WOR computed for patients Alzheimer's Disease in this scintigraphic report. Absolute values for these diseases mentioned in this report have not yet been fully determined and there has been no consensus yet regarding these values.

CONCLUSION

Cardiac I-131 MIBG scintigraphy is an indicative biomarker in the clinical diagnosis of Dementia with Lewy bodies and its use serves as a diagnostic tool in differentiating DLB from other neurodegenerative diseases such as Alzheimer's disease.

This case demonstrates the use of I-131MIBG scintigraphy as an indicative biomarker in the diagnosis of DLB. As seen in the patient's scan, he had a decreased heart to mediastinum ratio of 1.21 (early) and 1.00 (delayed), which is consistent with the HMR of a patient with DLB. The patient's washout ratio of 99.2% is also compatible with DLB.

REFERENCES

1. Burns A, Iliffe S. Alzheimer's disease. Bmj. 2009;338 (Feb05 1). doi:10.1136/bmj.b158.

2. Klein JP, Ropper AH, Samuels MA. Degenerative Diseases of the Nervous System. In: Adams and Victor's Principles of Neurology. S.l.: s.n.; 2014:1064-1065.

3. Mayer M. Dementia. In: On Call Neurology (Third Edition). W.B. Saunders; 2007:401.

4. Storey, Elsdon & Kinsella, Glynda & Slavin, Melissa. (2001). The neuropsychological diagnosis of Alzheimer's disease. Journal of Alzheimer's disease : JAD. 3. 261-285. 10.3233/JAD-2001-3302.

5. Ziessman HA, O'Malley JP, Thrall JH, Fahey FH. Clinical applications for cerebral perfusion imaging . In: Nuclear Medicine. Philadelphia, PA: Elsevier Saunders; 2014:357.

6. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100. doi:10.1212/WNL.0000000000004058.

7. Yang T, Wang L, Li Y, Cheng M, Jiao J, Wang Q, Guo H. 131I -MIBG myocardial scintigraphy for differentiation of Parkinson's disease from multiple system atrophy or essential tremor in Chinese population. J Neurol Sci. 2017 Feb 15;373:48-51. doi: 10.1016/j.jns.2016.12.006. Epub 2016 Dec 7. PMID: 28131225.

8. Chung EJ, Kim SJ. (123)I-Metaiodobenzylguanidine Myocardial Scintigraphy in Lewy Body-Related Disorders: A Literature Review. J Mov Disord. 2015;8(2):55-66. doi:10.14802/jmd.15015.

9. Yoshita M, Taki J, Yokoyama K, Noguchi-Shinohara M, Matsumoto Y, Nakajima K, Yamada M. Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology. 2006 Jun 27;66(12):1850-4. doi: 10.1212/01.wnl.0000219640.59984.a7. PMID: 16801649.

10. Slaets S, Van Acker F, Versijpt J, et al. Diagnostic value of MIBG cardiac scintigraphy for differential dementia diagnosis. Int J Geriatr Psychiatry 2015;30(8):864-869.