Myocardial Sympathetic Innervation Imaging with MIBG in Dementia with Lewy Bodies

Gagandeep Choudhary, MD,[a] and Pradeep Bhambhvani, MD[a]

[a] Division of Molecular Imaging and Therapeutics, Department of Radiology, The University of Alabama at Birmingham, Birmingham, AL

Received Jan 10, 2020; accepted Jan 13, 2020
doi:10.1007/s12350-020-02042-2

See related article, pp. 2151–2163

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease (AD) with significant impact on normal life and activities of daily living. The incidence of DLB increases with advancing age and accounts for 5% of all dementia cases in older population.[1] The diagnosis of DLB is primarily made with clinical and neuropsychological assessment. Patients can present with progressive cognitive decline, deficits in attention, executive function, visuoperception, sleep disorder, parkinsonian symptoms, and autonomic dysfunction. The clinical diagnosis of DLB is challenging as symptoms overlap with other types of dementia and psychiatric illnesses, and many cases are either missed or misdiagnosed, usually as AD.[2] On neuropathology, the hallmark of DLB is alpha-synuclein aggregates forming Lewy bodies and Lewy neuritic plaques, but these are not specific and can be seen in other neurodegenerative conditions like Parkinson's disease and multiple system atrophy.[3,4] DLB is a devastating disorder for which we lack effective therapies which is at least partly due to lack of understanding of underlying molecular mechanisms. Currently available symptomatic treatments only offer modest control of the cognitive and behavioral symptoms. In 2017, the DLB Consortium published their fourth consensus report, with recommendations about the diagnosis and management of probable and possible DLB.[2] In the revised criteria, the SPECT brain dopamine transporter imaging (DAT) for detection of nigrostriatal dopaminergic impairment (reduced uptake in the basal ganglia), and myocardial sympathetic innervation scintigraphy with 123I-metaiodobenzylguanidine (MIBG) to detect norepinephrine transporter deficit (reduced myocardial uptake) are grouped under indicative biomarkers for DLB with increased diagnostic weighting given to MIBG scan. Conventional brain imaging with CT and MRI, SPECT brain perfusion, and 18F-FDG-PET brain metabolism are grouped under supportive biomarkers.[2,4]

123I-metaiodobenzylguanidine (MIBG) is a noradrenaline imaging analogue that binds to postganglionic presynaptic autonomic nerve terminals,[4] and is commonly used to image patients with neuroendocrine tumors. Cardiac MIBG scintigraphy was originally developed to assess myocardial sympathetic innervation in various diseases, including congestive heart failure, ischemic heart disease, coronary artery disease, vasospastic angina pectoris, and cardiomyopathy.[5] Autonomic nervous system failure can also be seen in Lewy body diseases like Parkinson's disease (PD) and DLB.[2] In March 2013, MIBG was approved by the Food and Drug Administration for the assessment of myocardial sympathetic innervation in patients with heart failure and an ejection fraction of $\leq$ 35%.[6] The image acquisition includes an early 10 minutes anterior planar view 15 minutes after injection, and a delayed 10 minutes planar view at 4 hours immediately followed by SPECT acquisition.[7] The delayed planar image is used to calculate the heart-to-mediastinum (H/M) ratio. H/M ratio is the ratio between the count density in the left ventricular region (mean pixel value) and the count density in the mediastinum. Abnormal scans have reduced cardiac uptake as indicated by a low H/M ratio. The SPECT images are reconstructed in a manner similar to that of myocardial perfusion SPECT images.[7,8]

Reprint requests: Pradeep Bhambhvani, MD, Division of Molecular Imaging and Therapeutics, Department of Radiology, The University of Alabama at Birmingham, 619 19th Street South, JT 779, Birmingham, AL 35249; *pbhambhvani@uabmc.edu*

J Nucl Cardiol 2021;28:2164–6.
1071-3581/$34.00

Autonomic dysfunction (e.g., orthostatic hypotension, constipation, urinary incontinence) is one of the supportive clinical diagnostic features in DLB patients.[2] Multiple studies with myocardial MIBG scintigraphy for detecting autonomic cardiac denervation in patients with PD and DLB have been published with variable sensitivity and specificity. DLB and AD share many clinical and pathological features and differentiating between these two is often difficult. But discrimination between DLB and AD is clinically relevant, as there are differences in pharmacological treatment options, for example, adverse effects on cognition and behavior from antipsychotic medications in DLB patients. Moreover, in the future once disease-modifying drugs for AD or other neurodegenerative brain diseases will become available, an early and accurate diagnosis of these dementias will become more important, as these drugs will probably be pathology specific.

Research studies have shown variable results for MIBG cardiac scintigraphy as a diagnostic tool to distinguish DLB from AD.[9,10] While studies have found no correlation of MIBG scintigraphy with the severity or duration of DLB or AD, many other studies have demonstrated reduced myocardial MIBG uptake in DLB compared to AD patients.[11–14] Additionally studies have shown MIBG scintigraphy as a good predictor of the future conversion of possible DLB to probable DLB.[5] It is also superior to brain perfusion SPECT with ^{99m}Tc-ethylcysteinate dimer in detecting the characteristic feature of DLB,[15] and more sensitive than cerebrospinal fluid p-tau in differentiating between DLB and AD.[16] In terms of diagnostic performance, a meta-analysis of 8 studies with 346 patients with dementia, the pooled sensitivity of MIBG scintigraphy for the detection of DLB was 98%, and the pooled specificity for the differential diagnosis of DLB from other dementias was 94%.[17] In another study of 133 patients with clinical diagnosis of probable or possible diagnosis of DLB or AD, overall diagnostic accuracy for differentiating probable DLB from AD was 68.9% sensitivity and 89.1% specificity, and the performance was particularly high in the mild dementia group with sensitivity of 77.4% and a specificity of 93.8%.[18] Cardiac MIBG studies are typically quantified on planar images using the heart-to-mediastinum (H/M) ratio. In the present issue, Roberts G. and colleagues from the UK [19] evaluate regional cardiac MIBG uptake patterns using SPECT in 31 healthy older adults and 32 patients with dementia (15 AD and 17 DLB patients). They observed that non-uniform SPECT myocardial tracer uptake was common and similar in controls, AD, and DLB patients. Thus regional uptake defects were not specific for DLB.[19]

There are many limiting factors to be considered before implementing MIBG scintigraphy in the clinical work up of dementia patients. These include a lack of pathological data in the discrimination of DLB from AD; sharing of clinical and pathological features between DLB and AD; a typically older patient cohort with cardiovascular disease comorbidity which can have reduced cardiac uptake on MIBG scan; polypharmacy in this elderly population with drugs that may interfere with MIBG uptake into the sympathetic nerve terminals; and lack of larger international studies with large patient population.[5] Moreover, in the United States, none of the available nuclear imaging techniques (i.e., DaTscan, FDG-PET, and myocardial MIBG scan) are currently reimbursed by the Centers for Medicare & Medicaid Services (CMS) for diagnosis of DLB, and at present the most commonly performed imaging in suspected cases of DLB is brain CT and MRI.

There is a clear growing interest to include MIBG scintigraphy as an imaging biomarker in DLB and other Lewy body-related disorders, specifically when there is doubt about the diagnosis between DLB and AD.[5] Although the DLB Consortium consensus report [2] has listed MIBG scintigraphy as an indicative biomarker for DLB diagnosis, caution should be exercised in MIBG scan interpretation in light of possible confounding variables as mentioned above and the non-specific pattern of regional myocardial uptake defects on SPECT as noted by Roberts G. and colleagues.[19] Moreover, the use of MIBG scintigraphy for DLB for routine clinical application in the US will be greatly limited until reimbursement improves.

Disclosure

There are no COI with this work.

References

1. Hogan DB, Fiest KM, Roberts JI, Maxwell CJ, Dykeman J, Pringsheim T, et al. The prevalence and incidence of dementia with Lewy bodies: A systematic review. Can J Neurol Sci 2016;43:S83-95.
2. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.
3. Capouch SD, Farlow MR, Brosch JR. A review of dementia with Lewy bodies' impact, diagnostic criteria and treatment. Neurol Ther 2018;7:249-63.
4. Outeiro TF, Koss DJ, Erskine D, Walker L, Kurzawa-Akanbi M, Burn D, et al. Dementia with Lewy bodies: An update and outlook. Mol Neurodegener 2019;14:5.

5. Chung EJ, Kim SJ. (123)I-Metaiodobenzylguanidine myocardial scintigraphy in Lewy body-related disorders: A literature review. J Mov Disord 2015;8:55-66.
6. GE Healthcare AdreView™ Iobenguane I 123 injection prescribing information. http://www3.gehealthcare.com/en/products/categories/nuclear_imaging_agents/adreview. Accessed December 18, 2019.
7. Van Vickle SS, Thompson RC. 123I-MIBG imaging: Patient preparation and technologist's role. J Nucl Med Technol 2015;43:82-6.
8. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 2016;23:606-39.
9. Yoshita M, Taki J, Yokoyama K, Noguchi-Shinohara M, Matsumoto Y, Nakajima K, et al. Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology 2006;66:1850-4.
10. Watanabe H, Ieda T, Katayama T, Takeda A, Aiba I, Doyu M, et al. Cardiac (123)I-meta-iodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: Comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001;70:781-3.
11. Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2001;71:583-8.
12. Hanyu H, Shimizu S, Hirao K, Sakurai H, Iwamoto T, Chikamori T, et al. The role of 123I-metaiodobenzylguanidine myocardial scintigraphy in the diagnosis of Lewy body disease in patients with dementia in a memory clinic. Dement Geriatr Cogn Disord 2006;22:379-84.
13. Oide T, Tokuda T, Momose M, Oguchi K, Nakamura A, Ohara S, et al. Usefulness of [123I]metaiodobenzylguanidine ([123I]MIBG) myocardial scintigraphy in differentiating between Alzheimer's disease and dementia with Lewy bodies. Intern Med 2003;42:686-90.
14. Suzuki M, Kurita A, Hashimoto M, Fukumitsu N, Abo M, Ito Y, et al. Impaired myocardial 123I-metaiodobenzylguanidine uptake in Lewy body disease: Comparison between dementia with Lewy bodies and Parkinson's disease. J Neurol Sci 2006;240:15-9.
15. Tateno M, Kobayashi S, Shirasaka T, Furukawa Y, Fujii K, Morii H, et al. Comparison of the usefulness of brain perfusion SPECT and MIBG myocardial scintigraphy for the diagnosis of dementia with Lewy bodies. Dement Geriatr Cogn Disord 2008;26:453-7.
16. Wada-Isoe K, Kitayama M, Nakaso K, Nakashima K. Diagnostic markers for diagnosing dementia with Lewy bodies: CSF and MIBG cardiac scintigraphy study. J Neurol Sci 2007;260:33-7.
17. Treglia G, Cason E. Diagnostic performance of myocardial innervation imaging using MIBG scintigraphy in differential diagnosis between dementia with lewy bodies and other dementias: A systematic review and a meta-analysis. J Neuroimaging 2012;22:111-7.
18. Yoshita M, Arai H, Arai T, Asada T, Fujishiro H, Hanyu H, et al. Diagnostic accuracy of 123I-meta-iodobenzylguanidine myocardial scintigraphy in dementia with Lewy bodies: A multicenter study. PLoS ONE 2015;10:e0120540.
19. Roberts G, Lloyd JJ, Jefferson E, Kane JPM, Durcan R, Lawley S, et al. Uniformity of cardiac (123)I-MIBG uptake on SPECT images in older adults with normal cognition and patients with dementia. J Nucl Cardiol 2019. https://doi.org/10.1007/s12350-019-01977-5.