Cardiac ^{123}I-MIBG scintigraphy: A window into the brain in Parkinsonism?

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Parkinson's disease (PD) and other forms of neurodegenerative parkinsonism are multisystem disorders affecting several components of the central and peripheral nervous system.[1,2] ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) is a false adrenergic neurotransmitter analog of norepinephrine, and cardiac ^{123}I-MIBG scintigraphy can be used to evaluate noradrenergic postganglionic cardiac innervation. The use of cardiac ^{123}I-MIBG scintigraphy has been established in the differential diagnosis of Lewy body diseases (PD and dementia with Lewy bodies). This is because patients with Lewy body diseases display a significantly lower myocardial ^{123}I-MIBG uptake in comparison to healthy controls and individuals with other parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration.[3,4] However, the role of cardiac ^{123}I-MIBG scintigraphy in parkinsonism is not limited to diagnosis. This imaging technique could also help detect early markers of neurodegeneration that predate the clinical diagnosis of PD, which is a prerequisite step in the development of disease-modifying therapies.[5] A recent study by Takahashi et al showed a strong quantitative correlation between cardiac ^{123}I-MIBG uptake and corresponding sympathetic axon loss in the cardiac tissue samples of 23 patients with autopsy-confirmed Lewy body diseases.[6] This study confirmed the potential use of cardiac ^{123}I-MIBG scintigraphy as a biomarker of cardiac sympathetic axon loss and Lewy body pathology. Moreover, cardiac ^{123}I-MIBG scintigraphy may have significant clinical implications. Changes in ^{123}I-MIBG uptake over time may help to characterize patients with PD, identify clinical phenotypes, and aid in predicting prognosis.[7] Finally, cardiac ^{123}I-MIBG scintigraphy may be used as a pathophysiological indicator in PD and related disorders. For the past 20 years, genetic research has led to the identification of several monogenic forms of PD and of numerous genetic risk factors, yet little is known about the cardiac autonomic innervation in these patients.[8]

In the current issue of the Journal of Nuclear Cardiology, De Rosa et al report the cardiac ^{123}I-MIBG scintigraphy results of 10 patients with parkin mutations (6 patients with single parkin mutations (HET) and 4 with two mutations (PARK2)), 8 patients with idiopathic PD, and 10 control subjects. The results showed that PARK2 patients did not differ from controls with respect to any parameter (early and late heart-to-mediastinum (H/M) ratios and washout rates (WR)), whereas HET patients had significantly lower early H/M ratios in comparison to controls (Figures 1, 2). As reported by the authors, it is noteworthy that 3 out of 6 HET patients had reduced both early and late H/M ratios and the WR were increased in 2 of the 3 patients. As expected, 7 out of 8 patients with idiopathic PD showed significant cardiac sympathetic denervation. Even though the number of PARK2 patients included in this study was limited, De Rosa et al confirmed that cardiac sympathetic innervation in PARK2 mutation carriers does not differ from controls. This is in accord with another recent study in which the authors observed that there was less sympathetic denervation in 8 PARK2 mutation carriers than in 13 idiopathic PD patients (late H/M uptake ratio: 1.52 ± 0.35 in PARK2 mutation carriers versus 1.32 ± 0.25 in PD patients; $P < 0.05$).[9] One of the

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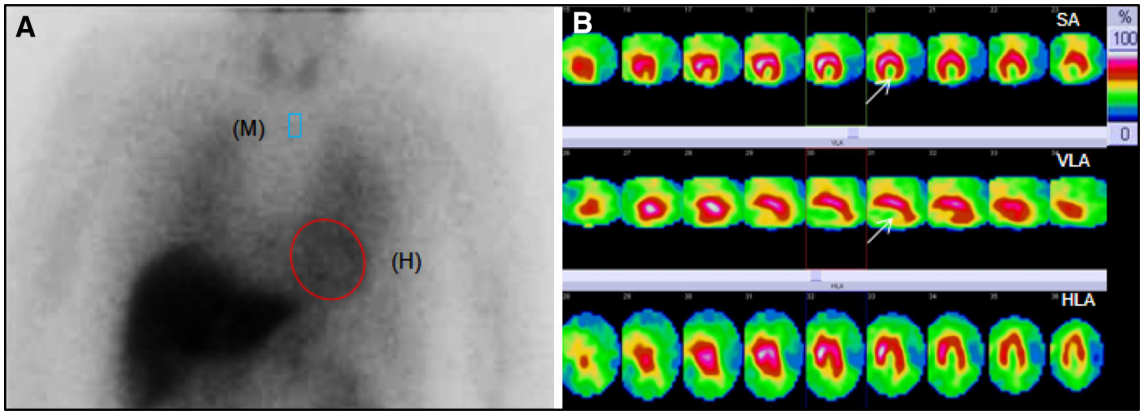

Figure 1. Cardiac planar and ^{123}I-MIBG SPECT imaging in a patient (70 years old) with parkinsonism being a PARK2. The HMR is in the normal range for this age (1.65). The SPECT shows an absence of MIBG uptake in the inferior LV region.

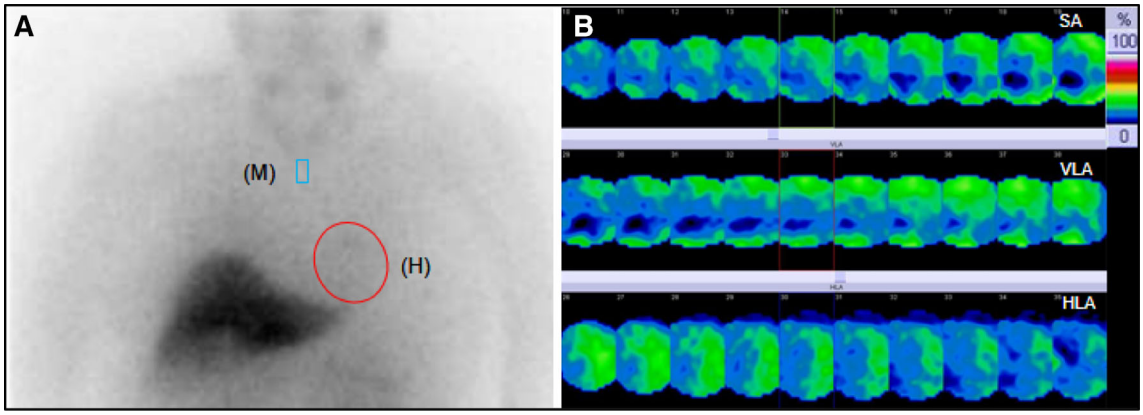

Figure 2. Cardiac planar and ^{123}I-MIBG SPECT imaging in a patient (65 years old) with parkinsonism being a Parkinson Disease. The HMR is very low 1.2 and the SPECT does not show any cardiac uptake in all LV regions.

original findings of the De Rosa et al study is the fact that there seems to be a degenerative process of postganglionic myocardial sympathetic fibers in some patients with single parkin mutations (4 out of 6), while postganglionic myocardial sympathetic innervation is normal in others (2 out of 6 with normal early and late H/M and normal WR).

This study by De Rosa et al also confirms that cardiac ^{123}I-MIBG scintigraphy enables the study of the extracranial Lewy body type-degeneration in Lewy body diseases. Indeed, the majority of PD patients with mutations in the PARK2 gene do not exhibit the classical neuropathological markers of PD and the presence of Lewy body in PARK2 is uncommon and seemingly associated with later onset of disease, similar to idiopathic PD.[9,10] The absence of cardiac sympathetic denervation in PARK2 has been supported by postmortem examination of cardiac tissues revealing that TH-immunoreactive nerve fibers in the epicardium were preserved in 3 patients with PARK2.[11] Interestingly, ^{123}I-MIBG uptake was abnormal in 4 out of 6 patients with single parkin mutations, which may suggest that these patients have cerebral and extracranial Lewy body pathology. Lewy bodies have been reported in PD patients with heterozygous parkin mutations[12] and several explanations have been proposed for the inconsistent presence of Lewy bodies in parkin diseases: incidental Lewy bodies in older patients, a lack of the mechanisms necessary to clear protein accumulation, and residual ligase activity associated with the partial loss of parkin ubiquitin E3 ligase function.[10] De Rosa et al speculate that a single parkin gene mutation in the setting of abnormal ^{123}I-MIBG uptake may be a susceptibility factor for idiopathic PD. On the other hand, the authors suggest that the HET cases with normal myocardial scintigraphy might carry mutations within

the promoter on the second allele, not identified by the molecular genetic techniques, or might carry additional mutations in genes that interact with parkin in common biological processes. This group of patients may be more similar to PARK2 patients.

In summary, we believe that cardiac ^{123}I-MIBG scintigraphy is a window into the brain in patients with parkinsonism and provides valuable information about the pathology and the pathophysiology of different parkinsonian disorders. We share the authors' point of view that further knowledge of the genetic makeup of PD will allow better understanding of the pathophysiology and help design specific treatments that alter the course of the disease. Future studies using cardiac ^{123}I-MIBG SPECT imaging will provide valuable information to evaluate myocardial function and detect cardiac neuronal architecture with higher diagnostic performance than planar images[13,14] according to the recommendations of the European Cardiovascular Committee.[15] Further prospective studies in a larger group of patients with parkin mutations and other genetic forms of PD are required to confirm the findings of De Rosa et al.

References

1. Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386:896-912.
2. Stamelou M, Bhatia KP. Atypical parkinsonism: Diagnosis and treatment. Neurol Clin 2015;33:39-56.
3. Orimo S, Suzuki M, Inaba A, Mizusawa H. 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: A systematic review and meta-analysis. Parkinsonism Relat Disord 2012;18:494-500.
4. Lamotte G, Morello R, Lebasnier A, Agostini D, Defer GL. Accuracy and cutoff values of delayed heart to mediastinum ratio with I-metaiodobenzylguanidine cardiac scintigraphy for Lewy body disease diagnoses. BMC Neurol 2015;15:83.
5. Sakakibara R, Tateno F, Kishi M, Tsuyusaki Y, Terada H, Inaoka T. MIBG myocardial scintigraphy in pre-motor Parkinson's disease: A review. Parkinsonism Relat Disord 2014;20:267-73.
6. Takahashi M, Ikemura M, Oka T, Uchihara T, Wakabayashi K, Kakita A, et al. Quantitative correlation between cardiac MIBG uptake and remaining axons in the cardiac sympathetic nerve in Lewy body disease. J Neurol Neurosurg Psychiatry 2015;86:939-44.
7. Tsujikawa K, Hasegawa Y, Yokoi S, Yasui K, Nanbu I, Yanagi T, et al. Chronological changes of 123I-MIBG myocardial scintigraphy and clinical features of Parkinson's disease. J Neurol Neurosurg Psychiatry 2015;86(9):945-51.
8. Spatola M, Wider C. Genetics of Parkinson's disease: The yield. Parkinsonism Relat Disord 2014;20:S35-8.
9. Tijero B, Gabilondo I, Lezcano E, Teran-Villagra N, Llorens V, Ruiz-Martinez J, et al. Autonomic involvement in Parkinsonian carriers of PARK2 gene mutations. Parkinsonism Relat Disord 2015;21:717-22.
10. Doherty KM, Silveira-Moriyama L, Parkkinen L, Healy DG, Farrell M, Mencacci NE, et al. Parkin disease: A clinicopathologic entity? JAMA Neurol 2013;70:571-9.
11. Orimo S, Amino T, Yokochi M, Kojo T, Uchihara T, Takahashi A, et al. Preserved cardiac sympathetic nerve accounts for normal cardiac uptake of MIBG in PARK2. Mov Disord 2005;20:1350-3.
12. Sharp ME, Marder KS, Cote L, Clark LN, Nichols WC, Vonsattel JP, et al. Parkinson's disease with Lewy bodies associated with a heterozygous PARKIN dosage mutation. Mov Disord 2014;29:566-8.
13. Oh JK, Choi EK, Song IU, Kim JS, Chung YA. Comparison of I-123 MIBG planar imaging and SPECT for the detection of decreased heart uptake in Parkinson disease. J Neural Transm (Vienna) 2015;122:1421-7.
14. Lebasnier A, Lamotte G, Manrique A, Peyronnet D, Bouvard G, Defer G, et al. Potential diagnostic value of regional myocardial adrenergic imaging using (123)I-MIBG SPECT to identify patients with Lewy body diseases. Eur J Nucl Med Mol Imaging 2015;42:1043-51.
15. Flotats A, Carrió I, Agostini D, Le Guludec D, Marcassa C, Schäfers M, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2010;37:1802-12.