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Clinical Utility of (123) I-MIBG Scintigraphy in Suspected Dementia with Lewy Bodies

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Abstract

A Clinical diagnosis of Lewy Body Dementia (LBD) has low sensitivity (positive predictive values of 34% to 47%). Although Dopamine Active Transporter (DaT) brain scintigraphy is generally useful in suspected LBD, it has a diagnostic sensitivity of only 85%. A normal scan may, therefore, present a dilemma. ^{123}I-MIBG Myocardial Scintigraphy (MIBG) may support diagnosis, but the diagnostic cut-off values are poorly defined. Here, we describe the presentation of an assessment of a patient with cognitive impairment and psychotic symptoms and discuss the role of investigations aimed at supporting the diagnosis of LBD in clinical practice.

Abbreviations

ACE-III: Addenbrooke's Cognitive Examination-III
AD: Alzheimer's Disease
CT: Computed Tomography Brain Scan
DaT: Dopamine Active Transporter Brain Scintigraphy
H/M ratio: Heart-To-Mediastinum Ratio
LBD: Lewy Body Dementia
MIBG: ^{123}I-Metaiodobenzylguanidine Myocardial Scintigraphy
sMMSE: Standardised Mini Mental State Examination

Case Presentation

The family of a 76-year-old retired psychiatric nurse who lived alone raised concerns about her cognitive decline over 4 years, which had progressively deteriorated in the past 1 year–2 years. Over the previous year, she also developed poor sleep (1 hour–2 hours per night because of waking several times), had frequent falls, experienced hallucinations that were worse at night, irritability, and physical and verbal aggression. She demonstrated fluctuating confusion, including repetitive purposeless behavior, repetitive conversation, concentration difficulties in watching films, short-term memory deficits, mathematical difficulties, loss of possessions, lack of language fluency, and difficulties in dressing. She displayed reduced road safety, had episodes when she left the house undressed, and made executive errors while cooking. The patient experienced visual and auditory hallucinations concerning an imaginary crying baby, seen soothing an imaginary baby and wandering around the house during the night looking for the 'baby,' and would not leave the house because of worries about the welfare of the 'baby.' She once called emergency services, saying that her granddaughter was locked in a cupboard. In her family history, her grandmother had memory difficulties in her 70s. Her medical history included chronic kidney disease stage 3, osteoarthritis, lumbago with sciatica, essential hypertension, gout,

and colonic polyp. Her regular medications were propranolol 40 mg od, omeprazole 20 mg od, allopurinol 300 mg od, amlodipine 10 mg od, co-codamol 10 mg/500 mg od, and salbutamol 100 mcg/dose inhaler. Her as-needed medications were tramadol 50 mg od and zolmitriptan 2.5 mg od.

She was mobile with a Zimmer frame, indoors and outdoors. She was dependent on her daily activities and support from her carers and family. She was commenced on sertraline 100 mg od. Promethazine 25 mg PRN, zopiclone 3.75 mg PRN, and amitriptyline 25 mg od were tried unsuccessfully for her sleeping difficulties.

The standardized Mini-Mental State Examination (sMMSE) score was 28/30 on cognitive assessments. Addenbrooke's cognitive examination-III (ACE-III) score was 58/100 in 2023, with evident deficits in fluency, memory, and visuospatial skills.

Five months later, her cognitive assessment scores were sMMSE 23/30 and ACE-III 53/100. She at this point reported right hand stiffness and tremors.

Her Computed Tomography (CT) brain scan showed mild involutional change and mild chronic small vessel ischaemic change in the periventricular subcortical deep white matter bilaterally (Medial Temporal Atrophy score of 1, Koedem score of 1, and Fazecasscore of 1). DaT scan showed normal tracer accumulation throughout the basal ganglia. MIBG scintigraphy was performed, which showed faint myocardial uptake only with a heart-to-mediastinum (H/M) ratio of 1.3 at both 15 minutes and 3 hours post-injection and no lung uptake. It was reported as abnormal. A diagnosis of probable LBD was made according to ICD 10 diagnostic guidelines (also in keeping with the 4th consensus for LBD diagnosis by McKeith et al. 2017 [3]).

She was commenced on memantine and melatonin titrated up to 10 mg per day, which reduced her agitation and allowed her to attend structured social activities. Memantine was started in favour of rivastigmine for its favourable effects on behavioural and psychological symptoms. She has now commenced on rivastigmine.

Discussion

Although our patient's clinical presentation was consistent with LBD, she had a normal DaT scan, which, therefore, had to be interrogated further for accuracy. MIBG was planned.

Clinical diagnosis of LBD in this case was challenged by the clinical overlap between delirium, psychotic disorders, Parkinson's disease, and Alzheimer's Disease (AD). Increasingly, it is observed that there is a significant pathological overlap between AD and LBD [4]. In an autopsy study of 1,920 patients, over 33% diagnosed with AD had concurrent LBD neuropathology, and 32% to 54% of patients diagnosed with LBD had AD pathology [1].

DaT imaging changes clinical management in approximately half of patients and results in altered diagnosis in one-third, regardless of time from symptom onset to scan results [5]. However, in our patient, DaT scan was within normal limits. DaT has been found to have a pooled sensitivity of 86.5% and specificity of 93.6% [2]. We considered the possibility of a false negative in our patient. One reason for false negatives in the DaT scan is that the normal range for age on quantification is not well defined. The mean age at onset of DLB is 75 years, so our patient's age (76) was within the normal range of onset for LBD [6]. An autopsy study of 55 patients by Thomas (2017) has shown that a DAT scan might also produce false negatives in the early stage of the disease [7]. Hence, in equivocal scan results or results that are discrepant with their clinical diagnosis, follow-up scans can quantify the rate of decline. Due to these limitations, a second test, such as MIBG scintigraphy, can be helpful. In this case, it was a superior test, allowing a diagnosis to be made and treatment started without waiting 12 months–18 months for a repeat DaT scan.

MIBG has a 71%–72% sensitivity and specificity of 81%–93% for distinguishing LBD from AD and is, therefore, not typically the first line [8,9]. A decrease in myocardial MIBG uptake in LBD reflects the degeneration of the cardiac muscle sympathetic innervation. Myocardial MIBG accumulation is quantified as the heart-to-mediastinum (H/M) ratio. The accuracy of this index is affected by the cut-off scores to distinguish between abnormal and normal scans. The authors noted that several recent MIBG scans in their nuclear medicine department for movement disorders had shown definite but faint myocardial uptake and borderline heart-to-mediastinum ratios. Variations in the H/M ratio exist between controls and people with LBD and normal and cut-off values to differentiate LBD from other neurodegenerative diseases that do not cause sympathetic autonomic dysfunction are poorly defined in the literature and vary between studies [10]. Our patient's H/M value of 1.3 was below what is considered normal in the literature. In the study of Sakamoto et al. (2016) of 453 patients, which identified that MIBG could accurately differentiate between LBD and non-LBD, the cut-off value for differentiating LBD from non-LBD was < 2.2 for the early H/M ratio, and < 2.1 for delayed H/M ratio [8]. The authors identified that early ratios, which relate to the functioning of the presynaptic nerve terminals, were not significantly different from delayed ratios, which reflect the sympathetic neuronal function, and that early ratios were sufficient [8]. Another measure, washout rate, was not significantly different between LBD and non-LBD groups [8]. When the early H/M ratio was < 2.0, 92% of patients had LBD; lowering the cut-off increases the specificity. In the study of Matsubara et al. (2022) of 56 patients at autopsy, further lowering the cut-off for the delayed H/M ratio to 1.8 increased specificity without reducing sensitivity [11]. The early ratio shows higher specificity than the delayed ratio, and the delayed ratio had higher sensitivity compared to the early ratio [11]. In this study, the washout rate showed sensitivity and specificity of 80.0% and 84.6% respectively, using a cut-off of 34% [11]. In the study of Sakamoto et al. (2018), which used

cut-off values of 2.1 and 2.0 for the early and delayed H/M ratios, respectively, the washout rate was significantly different in the LBD and non-LBD groups, even among patients with normal early H/M ratios [12].

The absence of lung uptake in our patient may reflect reduced endothelial uptake of amines. A retrospective study comparing lung uptake with myocardial uptake would be helpful, as the diagnostic relevance of this observation is uncertain.

We considered the possibility that MIBG was falsely positive. It should be noted that certain medications may affect myocardial MIBG accumulation, including tricyclic antidepressants, which may cause a false positive result. Our patient had been prescribed amitriptyline since at least 1997 for chronic pain, at doses ranging from 10 mg to 50 mg od. The patient had already discontinued amitriptyline nine weeks before the scan. Since the plasma elimination half-life of amitriptyline in the elderly is 31 hours, we excluded the prolonged effects of amitriptyline [13]. Cardiac conditions such as heart failure and diabetes can also result in false positive outcomes in MIBG. Our patient did not have cardiac disease or diabetes. False positive rates increase with age, as H/M ratios decrease with aging; however, as already noted, our patient's age was near the mean onset for LBD [14]. Although our scan was positive, it has been suggested that early-stage LBD may have a higher false negative rate with MIBG, which is also the case in DAT scan [8]. Negative results should be interpreted with caution in patients with suspected concomitant Alzheimer's pathology as false negatives can occur due to accumulation of α-synuclein and denervation in the heart, especially as the dementia progresses [11,15]. MIBG cardiac scintigraphy does not distinguish between LBD and PD, but these were clinically distinguishable in our patient. We considered the possibility that our patient was presenting with a primary psychotic disorder or other form of dementia. Our patient had fluctuating cognitive impairment and persistent visual hallucinations, which, according to consensus criteria for clinical diagnosis, amount to 2 of the three core symptoms and indicate probable LBD [16]. Consensus clinical criteria have been found to have high specificity (> 0.8) but have lower sensitivity (0.22–0.83) [6]. The presence of the fluctuating cognitive impairment indicates a cognitive rather than psychotic disorder. There was an absence of stroke disease or other physical illness to account for the clinical picture. We considered the possibility of intermittent delirium, but the duration did not support this diagnosis. Given the presence of mild chronic small vessel ischaemic disease on the CT head, a mixed picture of vascular dementia was considered. However, these vascular changes are common in LBD, and the Fazecas score was not suggestive of vascular dementia [17].

A larger scale comparison of DAT scan and MIBG and validation of each scan in certain patient populations would aid the formation of clinical guidelines. Patients with comorbidities hypertension, diabetes mellitus, cardiovascular disease, thyroid disease, and hyperlipidemia were excluded from many MIBG studies [18]. However, an autopsy study demonstrated good specificity when patients with cardiac disease and diabetes (including peripheral neuropathies but excluding diabetic polyneuropathy) were included [11]. Interpretation of MIBG is affected by certain medications such as antidepressants tricyclics and serotonin noradrenaline reuptake inhibitors, as well as calcium channel blockers, labetalol, reserpine, amiodarone, and phenylephrine [19]. The recommendation to withhold or withdraw certain antidepressants, such as tricyclics, prior to MIBG may limit the clinical utility in some patients. DAT scan is generally the superior choice in terms of sensitivity and specificity. However, in terms of a broader diagnostic framework, MIBG might have value in cases of suspected falsely negative DAT scan due to its high specificity, particularly in suspected early disease, although early disease can cause false negatives for both scan modalities [7,11]. It can also be used to differentiate LBD from other diseases with parkinsonism, such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration, in which DAT scan might be ineffective [11]. It should be noted that patients with advanced age can cause false positive results in both DAT scan and MIBG. The alternative option is to repeat DAT scan after a time interval. Autopsy studies have suggested that repeating MIBG after a time interval might be less useful, particularly in patients with dementia-onset disease [11].

Conclusions

In our patient, ^{123}I-Metaiodobenzylguanidine Myocardial Scintigraphy supported the clinical diagnosis and affected treatment choice. A better understanding of the clinical utility of MIBG and the protocols around the investigation would improve the use of nuclear imaging in investigating suspected Lewy Body Dementia. MIBG appears to have clinical utility in validating suspected false negative results in Dopamine Active Transporter scans, especially given the high specificity in differentiating LBD from other neurodegenerative diseases, in particular where movement disorders are present, and dementia is in the mild stage.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Informed consent was obtained for this publication.

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