Editor's comment: The non-motor manifestations of Parkinson's disease (PD) are receiving increased attention in both clinical practice and research. The same is true for the pre-motor features of PD, particularly in the research arena. In this review, Sakakibara and colleagues assess current data on pre-motor PD symptoms and their correlation with 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. They also share some of their own observations and suggest that in the setting of abnormal MIBG some common non-motor PD features such as mild memory disorder, constipation, postural hypotension, and REM sleep disorder may provide a window of opportunity to identify cases of PD in the presymptomatic (non-motor) phase.

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Review

MIBG myocardial scintigraphy in pre-motor Parkinson's disease: A review

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ABSTRACT

Objectives: Detecting very early markers of neurodegeneration that predate the diagnosis of idiopathic Parkinson’s disease (PD) is a crucial research topic for the development of disease-modifying therapeutic interventions. Recently 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy has become widely used for this purpose, since this test shows high sensitivity and specificity in the diagnosis of PD, based on evidence that cardiac sympathetic nerve fibers are affected early and commonly in PD. We reviewed the literature to determine the role of MIBG myocardial scintigraphy for diagnosing pre-motor PD.

Methods: We performed a systematic review of the literature to identify the use of MIBG myocardial scintigraphy in relation to the constellation of pre-motor symptoms in PD.

Results: Mild memory disorder, autonomic failure (constipation and postural hypotension), depression/anxiety, visual hallucination/psychosis (in the elderly), sleep disorder (REM sleep behavior disorder), and impaired olfaction are reported to appear as sole initial symptoms of PD. All clinical features except for impaired olfaction are accompanied by low MIBG uptake, suggestive of very early PD in situ.

Conclusion: Identifying persons with mild memory disorder, constipation/postural hypotension, depression/anxiety, visual hallucination/psychosis (in the elderly), and REM sleep behavior disorder associated with low MIBG uptake may provide a unique opportunity to detect very early PD in situ within a pre-clinical window. Future prospective studies to investigate further the findings of these early cases are warranted.

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1. Introduction

Parkinson's disease (PD) is now considered not only a motor disorder characterized by parkinsonism, but also a systemic illness with several non-motor deficits, including: cognitive impairment (dementia with Lewy bodies [DLB]), depression/anxiety, psychiatric symptoms, autonomic failure, sleep disorder, and impaired olfaction. Although there is a close relationship between the motor disorder and the presence of LB with abnormal α-synuclein aggregation in the substantia nigra pars compacta (SNC), non-motor deficits are mostly independent of the SNC pathology, thereby indicating that different mechanisms converge in the degenerative process. Many non-motor symptoms appear before the motor symptoms, and are referred to as 'pre-motor PD' [1,2]. This has been confirmed by the careful following of patients with these pre-motor symptoms they develop.
the full clinical PD syndrome, and by typical findings at autopsy. Recently, several biomarkers for diagnosing early PD in situ have become available, such as central dopaminergic depletion by positron emission tomography (PET) or single-photon computed tomography (SPECT) [3,4], peripheral noradrenergic depletion by $^{[123]}$I-meta-iodobenzylguanidine [MIBG] myocardial scintigraphy [5,6], $\alpha$-synuclein by brain imaging [7,8] and in the cerebrospinal fluid (CSF) [9,10,], and SNC by ultrasound [11] and magnetic resonance imaging (MRI) [12,13]. However, it is not yet known which biomarker is most closely related to pre-motor PD. In this review, we show, through a review of the literature, that MIBG may be a helpful non-invasive tool in the early detection of a patient with pre-motor PD.

2. Method of MIBG myocardial scintigraphy

$^{[123]}$I-MIBG myocardial scintigraphy was originally developed to assess postganglionic presynaptic cardiac sympathetic nerve endings in heart disease including: congestive heart failure, ischemic heart disease, and cardiomyopathy. Subsequently, cardiac MIBG uptake was demonstrated to be reduced in patients with Lewy body diseases such as PD and DLB and has been reported to be useful for differentiating PD from other parkinsonisms, as well as DLB from diseases such as PD and DLB and has been reported to be useful for uptake was demonstrated to be reduced in patients with Lewy body disease (AD). MIBG scintigraphy is based on evidence that norepinephrine (NE) and MIBG have the same mechanisms for uptake, storage, and release (Fig. 1) [5]. There are 2 types of NE and MIBG uptake. Uptake-1 (neuronal uptake), when the concentration is low, depends on sodium and adenosine triphosphate. Uptake-2 (extraneuronal uptake), which takes place only when the concentration is high, represents simple diffusion. Delayed images are less dependent on uptake-2, and more accurately reflect cardiac sympathetic nerve activity as well as pathology [5,6].

The sensitivity and specificity of MIBG scintigraphy are high (near 90%) [14]. Low HM ratio was obtained in 91.3% of Lewy body diseases (90.0% in PD, 94.1% in DLB, etc.). Normal HM ratio was obtained in 89.1% of disease controls (100% in AD, etc.) [14]. Recently, Tregla et al. [15] and Orimo et al. [16] performed a meta-analysis on the sensitivity and specificity of MIBG scintigraphy. Tregla et al. [15] analyzed 19 studies comprising 1972 patients (1076 patients with PD, 117 patients with other Lewy body diseases and 779 patients with other Non neurological diseases). The pooled sensitivity of MIBG scintigraphy in detecting PD was 88% (95% CI 86–90%); the pooled specificity of MIBG scintigraphy in discriminating between PD and other parkinsonisms was 85% (95% CI 81–88%). The area under the ROC curve was 0.93. Similarly, Orimo et al. [16] analyzed 13 studies comprising 845 patients including 625 PD and 220 other neurodegenerative parkinsonism. The pooled sensitivity to differentiate PD from other neurodegenerative parkinsonisms by a delayed heart-to-mediastinum (HM) ratio was 89.7% and the specificity was 82.6%.

As a factor affecting the HM ratio, patients with mild Hoehn Yahr stage or short-duration disease may have myocardial MIBG abnormality less frequently. However, according to Orimo et al. [16], when PD was limited to early stage (Hoehn-Yahr stage 1 or 2), the pooled sensitivity by delayed H/M ratio was as high as 94.1% and the specificity was 80.2%. PD patients with longer duration may have more frequent myocardial MIBG abnormality. Satoh et al. [17] have estimated the yearly reduction rate of the HM ratio to be 0.02. Another factor might be that dopamine or its precursor DOPA might act as a competitive inhibitor of NE transporter-mediated MIBG uptake. Experimental studies have shown that MIBG uptake is inhibited by NE, more so by dopamine, and to a lesser extent by DOPA and serotonin in neuroblastoma cells that lack dopamine and serotonin uptake systems [18]. In healthy humans and in early-phase PD, levodopa might affect MIBG uptake [19,20].

2.1. Memory disorder

Early differential diagnosis of memory disorder is a challenge for neurologists. In contrast to the focus on early-stage AD [21,22], little is known about early-stage memory disorder in dementia with DLB, a Lewy body disease. Mild cognitive impairment (MCI) is a condition that is described as being not normal for age yet not demented (does not meet criteria (DSM IV, ICD 10) for a dementia syndrome); presence of cognitive decline based on self and/or informant report and progressive impairment on objective cognitive tasks; and essentially preserved basic activities of daily living [23]. In addition, amnestic MCI is diagnosed by the presence of impairment in memory [23]. It is important to identify MCI patients with a higher risk of progression to dementia (10–15% per year), since early treatment might delay disease progression [21,22]. Identifying the causes of MCI is not easy, though individual management depends on the cause. It is now acknowledged that DLB may produce a wide

Fig. 1. Representative cases of $^{[123]}$I-MIBG myocardial scintigraphy. A: normal control (HM ratio 2.84), B: a case of abnormal low accumulation (HM ratio 1.41). MIBG: meta-iodobenzylguanidine. The HM ratio: the heart to mediastinum ratio. The cut-off value of delayed MIBG images (4 h after injection of 111 MBq MIBG, depending on uptake-1 [neuronal uptake], reflecting cardiac sympathetic nerve activity) of the HM ratio was 2.0. A reduced HM ratio indicates peripheral noradrenergic depletion.
spectrum of clinical symptoms, including dementia and spontaneous parkinsonism (the core clinical features), together with depression, sleep disorder, and autonomic disorder [24]. Regarding LB pathology, approximately 8–17% of neurologically normal subjects over 60 years of age have LB on postmortem examination, referred to as incidental LBD [25]. Some pathology-proven LBD patients have shown amnestic MCI before progressing to the core clinical features of DLB (dementia and spontaneous parkinsonism) [26]. However, it is regarded as difficult to diagnose these early-stage DLB patients before they develop the full clinical spectrum.

Using MIBG scintigraphy, Fujishiro et al. recently reported two patients with a clinical diagnosis of amnestic MCI who had low MIBG uptake, without the core clinical features of DLB [27]. One patient, a 75-year-old male, had episodes of RBD, visual hallucination, and spontaneous parkinsonism two years after amnestic MCI was diagnosed. The other patient, a 62-year-old female, developed amnestic MCI, and had occipital hypo-metabolism on a 18F-fluoro-D-glucose PET. Neither patient had diabetes nor a cardiac condition that might affect the MIBG uptake.

During a 3-year period, 254 patients with memory complaints attended our university neurology clinic: 106 men, 148 women; mean age 72.5 years (48–95 years). All patients underwent a neurological examination; cognitive testing including the Mini Mental-State Examination (MMSE; 0–30 scale, normal > 24), the Alzheimer’s Disease Assessment Scale–Cognitive Behavior Section (ADAS–cog; 0–70 scale, normal < 10), the Frontal Assessment Battery (FAB; 0–18 scale, normal > 16), and the Wechsler Memory Scale Revised (WMS-R) if detailed assessment of memory becomes necessary; a brain MRI to check for hippocampal atrophy by VSRAD (Voxel-based Specific Regional analysis system for AD) MRI morphometry software; and 99mTc-L,L-ethylcysteinate dimer (ECD) SPECT. In addition, we performed MIBG scintigraphy with the method described earlier in this paper. The cut-off value of delayed MIBG images of the heart-to-mediastinum (HM) ratio was 2.0. None of the subjects had heart failure or diabetic neuropathy, and none was taking serotonergic or other drugs that might interfere with MIBG scintigraphy. Among the 254 patients, 44 patients were diagnosed with amnestic MCI; and 13 of 44 cases (30%) showed low MIBG uptake. None of the 13 patients had the core clinical features of DLB [28]. The sensitivity and specificity of MIBG scintigraphy were high (around 90%). As described above, low HM ratio was obtained in 91.3% of Lewy body diseases (90.0% in PD, 94.1% in DLB, etc.). Normal HM ratio was obtained in 89.1% of diseases control (100% in AD, etc.). None of the 13 patients had comorbid diseases or were taking drugs that might affect MIBG uptake. Therefore, if we accept reduced MIBG uptake as a biomarker, these patients most probably had LB pathology. The 13 patients had the following clinical characteristics: they were uniformly elderly (mean age 78.9 years, 70–84 years), with an equal sex ratio (7 male, 6 female), and had relatively slow progression (mean duration of memory disorder at presentation, 3.8 years, 1–7 years) and preserved general cognitive function (mean MMSE 24.8, 21–30; mean ADAScog 12.2, 6–20).

In addition to memory impairment, these patients commonly showed slowed frontal executive function by FAB (12.5/18, 8–15) [29,30] and 5 had mild visual hallucinations; therefore, they were regarded as multidomain amnestic MCI. Other than memory disorder, they had various autonomic disorders (nocturia in 7, urinary incontinence in 2, constipation in 2, postural hypotension in one), REM [rapid-eye movement] sleep behavioral disorder (in 3), and occipital hypoperfusion by ECD-SPECT (in 5) [31,32]. These features are rare in AD, but are commonly reported in combination with, or as isolated features of, DLB as described below. This cohort of multidomain amnestic MCI cases may eventually present with early-stage DLB because of the presence of low MIBG uptake. Clinically, many of them have slowed frontal executive function, and some have visual hallucinations and autonomic and sleep disorders, while some do not. Therefore, in cases such as these, MIBG scintigraphy may be particularly helpful in differentiating early-stage DLB from early-stage AD before full clinical features appear.

2.2. Autonomic failure

2.2.1. Constipation

Constipation is a common symptom in the geriatric population. It may occur after loss of dietary fiber consumption and reduction of physical exercise. Rare causes include smooth muscle myopathy, vasculitic neuropathy, amyloidosis, mitochondrial disease, etc [33]. As for PD, the Honolulu Heart Program that followed-up for incidental PD over a 24-year period showed that infrequent bowel movements are associated with an elevated risk of PD [34]. Also, pathology-proven cases with SNC loss an7d LBs have been shown to have been constipated [35]. However, it is regarded as extremely difficult to diagnose such early-stage PD patients on this basis alone. Recently, we examined five such patients [36].

Among 1600 outpatients, only five patients fulfilled our established criteria. The inclusion criteria were: constipation defined as fewer than 3 bowel movements per week, regular laxative use, and/or difficulty defecation, and low HM ratio (<2.0) in the delayed images of MIBG scintigraphy. Among these, we excluded apparent motor disorder indicating PD, apparent neurologic diseases other than PD, apparent gastrointestinal diseases, and drugs that might affect bowel function or MIBG uptake. We administered the quantitative lower-gastrointestinal autonomic test (QL-GAT) to the patients to explore the mechanism of constipation. We also performed polysomnographic, cognitive, autonomic, and imaging tests to the greatest extent possible. Most of the patients were referred from a gastroenterology clinic for elucidation of the neurologic etiologies of their constipation. They were uniformly elderly (mean age, 68 years; range 60–81 years) and male. All patients walked independently. All patients had decreased bowel frequency and difficulty defecating with a mean duration of difficulty of 4.8 years (range 2–10 years).

In addition to a complaint of constipation, these patients showed relatively mild dysfunction by the QL-GAT: namely, case 1, normal; case 2, low resting anal pressure alone; case 3, decreased rectal sensation, decreased rectal contract, anismus, and post-defecation residual; case 4, slowed total colonic transit time (CTT); and case 5, slowed total CTT and post-defecation residual.

Four patients reported REM sleep behavioral disorder (RBD), which started simultaneously with bowel dysfunction in 3 cases, and 2 years after the onset of bowel dysfunction in one. Bladder dysfunction was noted in 4 cases. Transient hallucinations were noted in two. None of the patients had abnormalities as shown on MRI. Three of 4 patients revealed occipital hypoperfusion by SPECT. During the 3 year follow-up period, one patient developed mild muscle rigidity and unilateral postural tremor. These symptoms responded to treatments.

As shown above, ‘constipation and MIBG abnormality’ is clinically different from typical PD, in terms of a lack of motor features, uniformly elderly subjects, and relatively mild bowel dysfunction in the QL-GAT. In contrast, the similarities included RBD, bladder dysfunction [37], occipital hypoperfusion and hallucination. Considering the high sensitivity and specificity of MIBG abnormality for the diagnosis of PD, it seems likely that constipation and MIBG abnormality can be regarded as initial manifestations of PD. Pathological studies have shown degeneration and Lewy neurites in the myenteric plexus in PD [38], which may predate LB in the central nervous system [39]. Although rare, PD can be a cause of constipation in the general geriatric population, and some of these patients might later develop a motor disorder. Clinically, four of five
patients had at least one of the features suggestive of DLB (low frontal executive function, visual hallucination, RBD, bladder dysfunction, and occipital hypoperfusion), one had not. Therefore, in such cases, MIBG scintigraphy may be helpful in alerting the physician to early-stage DLB before full clinical features appear. In addition, in order to manage constipation in the elderly, neurologic observation may be needed as a matter of course.

2.2.2. Postural hypotension

Syncope is not uncommon in the normal population. It is derived from cardiogenic causes (arrhythmias, e.g., paroxysmal atrial fibrillation, long QT syndrome etc. and structural heart diseases, e.g., aortic stenosis etc.) and neurogenic causes (neurally mediated syncope [NMS] and postural hypotension). Among neurogenic causes NMS is the most common [40,41]. NMS, also known as reflex syncope, is a systemic vasodilatation with variable degrees of bradycardia. NMS frequently has a characteristic history that includes premonitory symptoms (yawning, epigastric discomfort, nausea, visual disturbances), and typical appearance (pallor, sweating) and trigger situations (strong emotions, unexpected pain, prolonged standing). NMS is benign, and patients only need to be reassured or recommended to perform regular exercise and maintain their fluid intake.

Postural hypotension is less common than NMS, but leads to a significant burden and morbidity in patients. Postural hypotension is a failure of reflex vasoconstriction in the lower half of body, leading to sustained reduction of systolic blood pressure by at least 20 mmHg, within 3 min of standing or head-up tilt to 60° on a tilt table. Postural hypotension often accompanies numbness of feet (diabetic neuropathy etc.) or gait disturbance with urinary dysfunction (multiple system atrophy, a disease that preferentially affects the spinal sympathetic preganglionic cells). When postural hypotension appears with no other neurological features, usually with evidence of more widespread autonomic failure [42,43], it is called pure autonomic failure (PAF, a disease that affects peripheral sympathetic vasomotor fibers). Although PAF lacks other neurological features in its definition, an over-10-year follow-up showed that some PAF patients developed the full clinical manifestation of DLB [44]. Also, pathology studies of PAF cases showed the presence of alpha-synuclein-positive Lewy neurites in the peripheral sympathetic nerves, suggesting that PAF is an early-stage PD [45]. However, it is regarded as difficult to diagnose such early-stage PD patients on this basis alone.

Yoshida et al. [46] and Kashihara et al. [47] showed reduced MIBG uptake in PAF. Therefore, it seems that PAF is a condition suggesting a future risk of PD. More recently, Goldstein et al. [48] reported a PAF patient with abnormal cardiac uptake of fluorodopamine at a time when brain fluorodopa uptake was normal. Four years later he developed dementia and parkinsonism together with abnormal fluorodopa uptake. In this case, neuroimaging evidence of cardiac noradrenergic denervation and subsequent progressive striatal dopaminergic denervation fit with Braak staging. Bladder and sexual dysfunction are rarely the initial feature of PAF [42]. This is in contrast to multiple system atrophy (MSA), which presents with bladder and sexual dysfunction as sole initial manifestations [49,50]. This is important since some MSA may present with chronic autonomic failure alone without motor features. A recent paper showed that among 29 autopsy-proven MSA cases, two had been clinically misdiagnosed with PAF [51]. Therefore, particularly in such cases, MIBG scintigraphy may help with the differential diagnosis between early-stage DLB and early-stage MSA. In contrast to lesions in the postganglionic sympathetic nerve fibers in PAF [45], preganglionic spinal sympathetic neurons are affected in MSA [51].

2.3. Depression/anxiety

Depression is a common psychiatric illness with a prevalence of around 6% in the general population. It is characterized by feelings of sadness and despair, and causes significant morbidity [52]. Anxiety- and stress-related disorders are also common, with estimated prevalences ranging from 2 to 20% in the general population. These disorders are characterized by excessive worry and irritability associated with symptoms of depression [53]. Depression/anxiety causes not only psychiatric but also physical changes, including insomnia, anorexia, tachycardia, and sexual, bowel and bladder dysfunction [54]. It has recently been recognized that depression/anxiety may precede various neurodegenerative diseases such as AD and PD [55].

Depression is the most common psychiatric disorder in PD. Estimates of the prevalence range, from 2.7 to 76%, with an average prevalence of about 35% [56]. Factors consistently correlated with depression in PD include early-onset PD, advanced stage PD, female gender, anxiety, cognitive impairment, and psychosis [53]. Pathologic degeneration of mesolimbic dopamine, norepinephrine, and serotonergic pathways in conjunction with degeneration of orbital-frontal circuits and subcortical structures, such as the locus coeruleus, dorsal raphe nuclei, and ventral tegmental area, are postulated to be associated with the development of depressive symptoms [57]. Interestingly, Kim et al. found no correlation between serotonergic dysfunction and depressive symptoms in patients with PD, but rather, evidence that the dysfunction of noradrenergic and limbic monoaminergic projections was associated with depression [58]. Several studies have reported that depression may precede the onset of PD [57,58]. However, it is regarded as too difficult to identify such early-stage PD patients, before they develop the motor symptoms. Kobayashi et al. recently described a set of 10 patients with late-onset major depression and 3 patients with late-onset generalized anxiety [36]. The mean ages at onset and at first visit were 66.7 for the 10 late-onset major depression patients and 69.7 years for the 3 patients with generalized anxiety disorders. None of them showed parkinsonian motor features or cognitive decline at the first visit. In addition to depression/anxiety, two patients had repeated episodes of transient amnesia. One had REM sleep behavioral disorder (RBD). Among the 8 cases who underwent SPECT scans, decreased cerebral perfusion was found in the frontal lobe in 5 and the occipital lobe in one. All 13 cases showed reduced MIBG uptake. Eleven of 13 cases later developed symptoms of PD. These findings support the hypothesis that depression constitutes an early manifestation of PD. To the best of our knowledge, no studies have reported the frequency of positive MIBG among older subjects presenting with depression; however, considering the high frequency (8–17%) of incidental LBD at autopsy [25], premotor PD with depression alone might be not rare.

2.4. Visual hallucination/psychosis in the elderly

Psychosis is a common psychiatric symptom characterized by hallucinations and delusions. In community-based samples the estimated prevalence of psychosis in the elderly ranges widely, from 0.2% to 4.75%, and as high as 10–63% in nursing home populations [57,58]. In the elderly, causes may include: schizophrenia, affective illnesses, delirium, substance intoxication, AD, frontotemporal dementia (FTD), and PD. Among these, it is well documented that FTD patients present with behavioral abnormalities and psychosis without cognitive decline in the early stage of the illness [59]. Progressive aphasia without dementia, or semantic dementia, also appears as a clinical manifestation of FTD [60]. Visual hallucinations in the elderly, without dementia or behavioral changes, may occur early in PD/DLB. The biological substrates that
underlie hallucinations and delusions are still not entirely understood. In PD/DLB cases, the mesocortical/mesolimbic areas and basal ganglia (ventral tegmental area and ventral striatum) might be the anatomical substrates [61], and increased visual cortical excitability has also been suggested [62]. Recently, Kobayashi et al. described 4 elderly patients with visual hallucination [36]. Their age at first visit was 79–81 years. In addition to visual hallucinations, all four patients had cognitive difficulties in daily life, and MMSE scores ranging from 20 to 26/30. One of them had constructional apraxia. However, parkinsonian motor signs were completely absent in all four cases. All patients showed occipital hypoperfusion SPECT scan. Two had REM sleep behavior disorder. All four cases showed reduced MIBG uptake. These findings support the hypothesis that visual hallucinations are a future risk for PD.

2.5. Sleep disorder

Parasomnias and sleep-talking are not uncommon in early childhood, but subside in adulthood [63,64]. They also appear in older adults, and rapid eye movement (REM) sleep behavior disorder (RBD) has been extensively studied in this group. Patients with RBD appear to be acting out their dreams while in REM sleep. The behaviors are typically violent, in association with violent dream content, so that the patient or the bed partner may suffer serious harm. The estimated prevalence of sleep disorders in adults is 0.4–0.5% [65], but the frequency is much higher in certain neurodegenerative diseases, particularly PD, DLB, and MSA [66]. The mechanism of RBD?? is still not entirely clear. However, animal models and cases of RBD developing after brainstem lesions (pons pontine tegmentum including locus ceruleus, medulla) have led to the understanding that RBD is caused by a lack of normal REM muscle atonia and a lack of normal suppression of locomotor generators during REM [66].

RBD can occur in the absence of neurologic diseases (the “idiopathic” form), although patients with this form of RBD may ultimately develop full motor signs of PD [67]. Also, an autopsy-proven case with cell loss in the locus ceruleus and the substantia nigra and LB had a history of RBD [68]. However, it is regarded as difficult to diagnose such early-stage PD patients before further symptoms appear. Recently, several reports have described low MIBG uptake in idiopathic RBD patients without parkinsonian motor features [69,70]. Among these, Kashihara et al. [70] reported that cardiac sympathetic denervation is more severe in RBD than in early PD. This suggests that RBD may not simply be a premotor form of PD, but that it may be associated with more widespread changes than are seen in mild PD. In addition, a recent imaging study indicated that cardiac denervation precedes nigrostriatal damage in RBD patients [71]. These findings support the hypothesis that RBD constitutes a future risk for PD.

2.6. Impaired olfaction

A decreased sense of smell can lead to significant impairment of quality of life, including taste disturbance and loss of pleasure from eating with resulting changes in weight and difficulty in avoiding health risks such as spoiled food or not recognizing a natural gas leak. Recent epidemiological reports have shown that when validated smell identification or threshold tests are used, they reveal quite a high prevalence of hyposmia and anosmia in the elderly [72]. Several pathophysiological processes have been postulated for these phenomena, including aging, olfactory receptor gene, toxic exposures/drugs, head trauma, systemic viral infection, autoimmunity, rhinosinusitis, and neurologic diseases such as cerebrovascular disease, AD, and PD [72–75].

In PD, a recent survey showed that the prevalence of hyposmia in PD is 13.4% (669 among 4999 PD cases) [76]. Recent imaging studies showed decreased olfactory bulb volume in PD patients by 3.0-Tesla MRI [77]. It has been well documented that LB pathology first affects the anterior olfactory nucleus and lower brainstem nuclei (Stage 1 according to Braak and colleagues) [78], suggesting that hyposmia is an early symptom/sign in PD. However, it is regarded as difficult to diagnose such early-stage PD patients on this basis alone. At this time there are no studies that have investigated whether hyposmia is related to low MIBG uptake. In contrast, hyposmia has been documented in idiopathic REM sleep behavior disorder (RBD) as described above [79]. Since it is known that some patients with idiopathic RBD may develop the full clinical manifestation of PD, the relationship between hyposmia alone and low MIBG uptake is worth investigating in the future.

Finally, we address the Braak hypothesis and MIBG myocardial scintigraphy. In 2003 Braak et al. [78] reported that the pathological lesions initially occur in the dorsal vagal motor nucleus of the brainstem and olfactory nucleus in the brain. Thereafter, the disease process in the brainstem pursues an ascending course to the mesocortex and the neocortex. This pathological perspective was reproduced by other investigators. Recent studies focusing on incidental Lewy body disease (ILBD) revealed not only brain but also peripheral LB pathology exist, including cardiac sympathetic nerves and those of the conduction system [80–82]. However, a few studies reported peripheral involvement in the absence of LB pathology in the brain, e.g., sympathetic cardiac nerves [83], or sympathetic cardiac nerves and the stellate ganglion [84], it cannot be entirely ruled out that the pathological process may begin in the peripheral autonomic system [85]. In light of the present review, sympathetic cardiac denervation may occur very early with mild memory disorder/psychosis in elderly patients (cortical lesion), constipation (peripheral myenteric plexus), postural hypotension (peripheral vasomotor), depression/anxiety (limbic monoaminergic etc.), and REM sleep behavior disorder (locus ceruleus etc.), before developing a motor disorder [48]. MIBG myocardial scintigraphy may provide a way to detect early PD in situ within a pre-clinical window.

3. Conclusion

Identifying persons with mild memory disorder; constipation/postural hypotension; depression/anxiety; visual hallucination/elderly psychosis; and REM sleep behavior disorder who also show low MIBG uptake may provide a way to detect early PD in situ within a pre-clinical window. Future prospective studies to follow-up these cases will clarify the diagnostic power of MIBG myocardial scintigraphy in detecting pre-motor PD.

Author contributions

Ryuji Sakakibara: study concept and design, acquisition of subjects and/or data, analysis and interpretation of data, and preparation of manuscript.
Masahiko Kishi: acquisition of subjects and/or data.
Yohei Tsuyusaki: acquisition of subjects and/or data.
Fuyuki Tateno: acquisition of subjects and/or data.

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