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ARTICLE

Cardiac ^{123}I-MIBG uptake in *de novo* Brazilian patients with Parkinson's disease without clinically defined dysautonomia

Cintilografia Miocárdica com ^{123}I-MIBG em pacientes brasileiros com doença de Parkinson recentemente diagnosticada sem disautonomia clinicamente manifesta

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ABSTRACT

Myocardial scintigraphy with meta-iodo-benzyl-guanidine (^{123}I cMIBG) has been studied in Parkinson's disease (PD), especially in Asian countries, but not in Latin America. Most of these studies include individuals with PD associated to a defined dysautonomia. Our goal is to report the cardiac sympathetic neurotransmission in *de novo* Brazilian patients with sporadic PD, without clinically defined dysautonomia. We evaluated retrospectively a series of 21 consecutive cases with PD without symptoms or signs of dysautonomia assessed by the standard bedside tests. This number was reduced to 14 with the application of exclusion criteria. ^{123}I cMIBG SPECT up-take was low or absent in all of them and the heart/mediastinum ratio was low in 12 of 14. We concluded that ^{123}I cMIBG has been able to identify cardiac sympathetic neurotransmission disorder in Brazilian *de novo* PD patients without clinically defined dysautonomia.

Keywords: Parkinson's disease, dysautonomia, denervation, radionuclide imaging, 3-Iodobenzylguanidine.

RESUMO

A cintilografia miocárdica com meta-iodo-benzil-guanidina (^{123}I cMIBG) foi estudada na doença de Parkinson (DP), especialmente nos países asiáticos, mas não na América Latina. A quase totalidade desses estudos inclui indivíduos com DP com disautonomia definida. Nosso objetivo é relatar a neurotransmissão simpática cardíaca em doentes brasileiros com DP *de novo* esporádica, sem disautonomia clinicamente definida. Foi avaliada retrospectivamente uma série de 21 casos consecutivos com DP sem sintomas ou sinais de disautonomia observáveis pelos testes de beira-de-leito. Com a aplicação dos critérios de exclusão, este número foi reduzido para 14. A captação do ^{123}I MIBG pelo SPECT foi baixa ou ausente em todos os pacientese; a relação coração / mediastino foi baixa em 12 dos 14. Concluímos que a ^{123}c MIBG é capaz de identificar alteração da neurotransmissão simpática cardíaca em doentes com DP de novo sem disautonomia clinicamente definida.

Palavras-chave: doença de Parkinson, disautonomia, denervação, cintilografia, 3-Iodobenzilguanidina.

Parkinson's disease (PD) is classified as a movement disorder. The movement disorders can be defined as neurological syndromes in which excess or decrease of voluntary and automatic movements unrelated to weakness or spasticity[1]. Most researchers use the criteria of the PD Society Brain Bank of London for the diagnosis of PD[2]: bradykinesia associated with rest and/or rigidity and, later on, with disease progression, to postural instability. The classification, the concept, the diagnostic criteria and even the title of the original work of James Parkinson about the disease, "An Essay on the Shaking Palsy", emphasize the motor disturbances in PD. However, non-motor symptoms (NMS) occur frequently in PD. They might arise several times during the development of the disease, including the preceding motor signs (premotor phase)[3]. In this earlier period autonomic symptoms (intestinal constipation), sensory

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(hyposmia), sleep-related (rapid eye movement behavior disorder) and mood (depression) are described[4]. To support these clinical observations findings, it is theorized that Parkinson's disease (PD) results from a sequence of anomalies that start in the non-motor areas of the bulb and/or parasympathetic peripheral nervous system[5]. Although they may be overlooked by healthcare professionals and patients, NMS cause disability and loss of life quality[6]. Vivid dreams, dementia, diplopia and nocturia are examples of the many NMS arising along the PD[7]. Among the several types of autonomic disturbances described as NMS, a cardiac sympathetic denervation is reported[8]. In recent years, cardiac scintigraphy, with meta-iodo-benzyl-guanidine (cMIBG) labeled with iodine-131 (^{131}I) or iodine-123 (^{123}I) have been used in PD for the evaluation of noradrenergic activity of myocardium. This method provides a functional analysis of the sympathetic postganglionic pathway evaluating in vivo the noradrenergic neurotransmission of heart[9]. Unlike cardiac scintigraphy with meta-iodo-benzyl-guanidine (cMIBG) ^{131}I or ^{123}I, other methods that estimate the cardiac sympathetic neurotransmission are difficult to implement, expensive and very invasive[10]. Since 1995, just over a hundred original articles related to the use of ^{131}I or ^{123}I cMIBG in PD individuals have been published[11]. However, despite the restrained elegance in the development of a great deal of these studies, they included PD individuals affected with comorbidities that cause cardiac autonomic dysfunction, such as diabetes mellitus and metabolic syndrome[12]. In some instances the exclusion of patients using drugs that act on noradrenergic neurotransmission is not considered. There are few in vivo studies regarding the sensitivity of cMIBG in detecting a dysfunction and/or injury of the autonomic nervous system in PD early stages. Furthermore, there are very few studies focusing the existence of dysautonomia without signs and symptoms of it in PD individuals[13].

Most research on cMIBG in PD was performed in Japan. Goldstein et al.[14] and Nakajima et al.[15] emphasized the need for more studies about this topic in different other parts of Asia and Europe. To our knowledge this issue had not been addressed in Latin America[11].

Our goal is to report ^{123}I cMIBG cardiac sympathetic neurotransmission in Brazilian patients recently diagnosed with sporadic PD without clinically defined dysautonomia.

METHOD

Subjects

We evaluated retrospectively a consecutive series of 21 PD cases followed between January 2008 and January 2010, who met the following inclusion criteria: (a) PD diagnosed according to the PD Society Brain Bank of London criteria[2]; (b) no licit or illicit drug intake 12 months preceding ^{123}I cMIBG; (c) no previous use of anti-parkinsonian drugs or n-methyl-D-aspartate blockers of memantine type; (d) no previous neurosurgical treatment; (e) appearance of motor signs (bradykinesia, rigidity, tremor, postural instability) after 55 years old or more; (f) motor manifestations of PD appearing only one to three year before ^{123}I cMIBG; (g) being native Brazilian, son and grandson of Brazilian (native); (h) having no PD ascendants; (i) have normal Ewing's tests (heart rate variability, assessed by R-R interval of the electrocardiogram graphing during deep inspiration; cardiac response to Valsalva maneuver; Test ratio 30/15 - immediate response of heart rate when getting up; response of blood pressure response to standing up; blood pressure in response to sutained handgrip)[16]; (j) no orthostatic hypotension (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology criteria (1996))[17]; (k) normal rest electrocardiogram, two-dimensional transthoracic Doppler echocardiography, ambulatory blood pressure monitoring and heart Holter; (l) no complaints suggesting salivation, swallowing, sweating, urination and bowel movements involvement; (m) not suffer from intolerance to cold and/or heat, erectile dysfunction, problems with ejaculation or vaginal lubrication, pre-syncope or syncope.

All PD patients were followed in the Movement Disorders Section at *Hospital Universitário Antonio Pedro, Universidade Federal Fluminense*.

Seven individuals were removed due to following exclusion criteria: (a) history of any cardiovascular disease; (b) transplanted individuals; (c) diabetes mellitus, metabolic syndrome, glucose intolerance, diabetes "insipidus", adrenal insufficiency, anemia, dehydration, gastrostomy, ileostomy, renal failure, azotemia, salt wasting nephropathy, hepatic dysfunction, thyroid dysfunction, alcoholism, AIDS, vagotomy, spinal cord transection, transverse myelitis, Guillain-Barre syndrome, Chagas disease, focal or generalized seizures, postural tachycardia syndrome, orthostatic hypotension, dysautonomia congenital, hereditary or acquired dysautonomia, verified by history, clinical examination and/or complementary tests; (d) participants that during the interval between the clinical evaluation and ^{123}I-cMIBG had used antidepressants, reserpine, guanethidine, phenylephrine, pseudoepinefrina, phenylpropanolamine, antipsychotics, calcium channel blockers, clonidine, alpha-methyldopa, minoxidina, moxonidine, barbiturates, anesthetics, bethanidine, alpha blockers, amphetamine, adrenaline releasers, tyramine, beta-adrenergic receptor stimulants, antiarrhythmics, anticholinergics, botulinum toxin, mimics cholinergic or angiotensin inhibitors B; (e) the participant has undergone treatments exposed to occupational and environmental toxins (thallium, lead, arsenic, mercury, carbon monoxide, carbamate, organophosphate and other pesticides); (f) dementia related to PD[18] or with other dementia and/or psychotic and/or hallucinations and/or delusion and/or dellirium; (g) claustrophobia; (h) malignant tumors and/or paraneoplastic syndromes; (i) history of sleep apnea or snoring and/or excessive daytime sleepiness, restless legs syndrome.

Our sample was then composed of 14 individuals with PD who underwent ^{123}I cMIBG.

Myocardial scintigraphy, scales, tests and cut-off values

^{123}I cMIBG was performed in a gamma camera SPECT, provided by digital scanner and low energy high-resolution double collimator (each phototype set to 159 keV). Radiopharmaceutical volume was to 5mCi or 185 MBq ^{123}I MIBG. We calculated the heart/mediastinum (H/M r) ratios scintigraphy uptake in the early stages (e) in 20 minutes, and late (d), 4 hours after intravenous infusion of ^{123}I MIBG, and the washout rate (WR). We consider as normal values for the H/M r (e) when $\geq$1.8 and (d) $\geq$1.7, and for WR $\leq$27%[19,20]. The Hoehn and Yahr scales[21] and the UPDRS[22] (sections I, II, III) were applied. Regarding the five Ewing tests, we adopted as the normal value zero or one scores (0 to 10)[16].

Statistics and ethics

The statistical analysis was performed applying the Chi-square test with Yates in the software SPSS 13.0 for Windows®. Significance level was considered with α=0.05 ($p<0.05$, with a margin of error of 5%). The study was approved by the Ethics Committee at *Hospital Universitário Antonio Pedro, Universidade Federal Fluminense*.

RESULTS

Clinical aspects of this series and results related to ^{123}I cMIBG are summarized in Table.

We observed small H/M r indexes (<1.8 (e) and <1.7 (d)), abnormal in 85.71% of patients (12 out of 14 participants). Both H/M r (e) and (d) was modified in 11 individuals. In one case, only the value of H/M r (e) was abnormal (<1.8). In ten volunteers, we noticed the tendency to have higher rates of H/M r (e) (1.50±0.29). The other four patients presented values of H/M r (d) (1.76±0.12) exceeding the H/M r (e). However, this later difference of reasonshad no statistical significance (p=0.68). The WR was abnormal in 71.43% (10 of 14 participants).

We checked visually the diffuse reduction of cardiac uptake on SPECT in all 14 subjects, evenly in nine cases and uneven in five (Figure 1). In two of them, myocardial scintigraphy with technetium-99m was performed with normal results. The reduction in cardiac uptake in four subjects was so pronounced that prevented the formation of planar topography tomographic images of the heart.

In attempting to correlate the values of H/M r, WR, gender, age of onset of motor symptoms, time of onset of motor symptoms and UPDRS scores, we did not notice, due to the dispersion of data, statistically significant differences and/or clinically relevant. However, we noticed a tendency of changing the values of H/M r with the worsening of PD. We found normal results for both H/M st in two volunteers with stage 1 Hoehn-Yahr. Furthermore, as the disease became more severe (stages 2 and 3), the values became low, especially H/M r (d) (H/M r (e) p=0.054, H/M r (d), $p<0.05$).

None of the 14 participants expressed any kind of side effect related to the method. Few experienced light discomfort during the examination: two people complained of tolerable cold sensation (low temperature of the examination room) and three, two claimants due to the cold, complained of minor pain or discomfort resulting from venous puncture.

DISCUSSION

In our 14 cases, the longer the time of onset of motor symptoms, greater was the frequency of abnormal values of both H/W r, without, however, having statistical significance for these results. The correlation between the time of onset of motor manifestations of PD and the values of H/M r, provided one more information about our series of cases: in the patients with only normal levels of H/M r (cases 1 and 9), the motor symptoms emerged 13 and 14 months before scintigraphy. Different reasons are speculated as causing changes in the rates of H/M r (e) and H/M r (d). It is possible that the H/M r (e) matches the information on the density of postsynaptic adrenergic receptors and integrity of the presynaptic terminal (sympathetic neurons). But the value of H/M r (d) refers to the pre-synaptic neuron function that includes release, capture and storage of adrenaline[23]. The late rate decreasing more than the early one, seems to be related to the initial phase of the cardiac sympathetic alteration caused by the PD, in which, during the progression of neuronal pathological process, the dysfunction would precede the estrutural destruction for a while[24]. The tendency to higher rates of H/M r (e) than the H/M r (d) observed by us (10 patients) had no statistical significance in our sample (p=0.68) and also unable to correlate it to the time of onset of motor symptoms.

There are conflicting reports in the literature concerning the moment in wich PD start changes in ^{123}I cMIBG[25,26]. These studies, unlike ours, solely considered the H/M r and WR, making no mention about the visual analysis of SPECT planar images. We infer that there was a noradrenergic transmission disturbance by sympathetic denervation despite not being able to be quantified in values. Through immunohistochemical examination, it was proved the existence of cardiac sympathetic oved the existence of cardiac

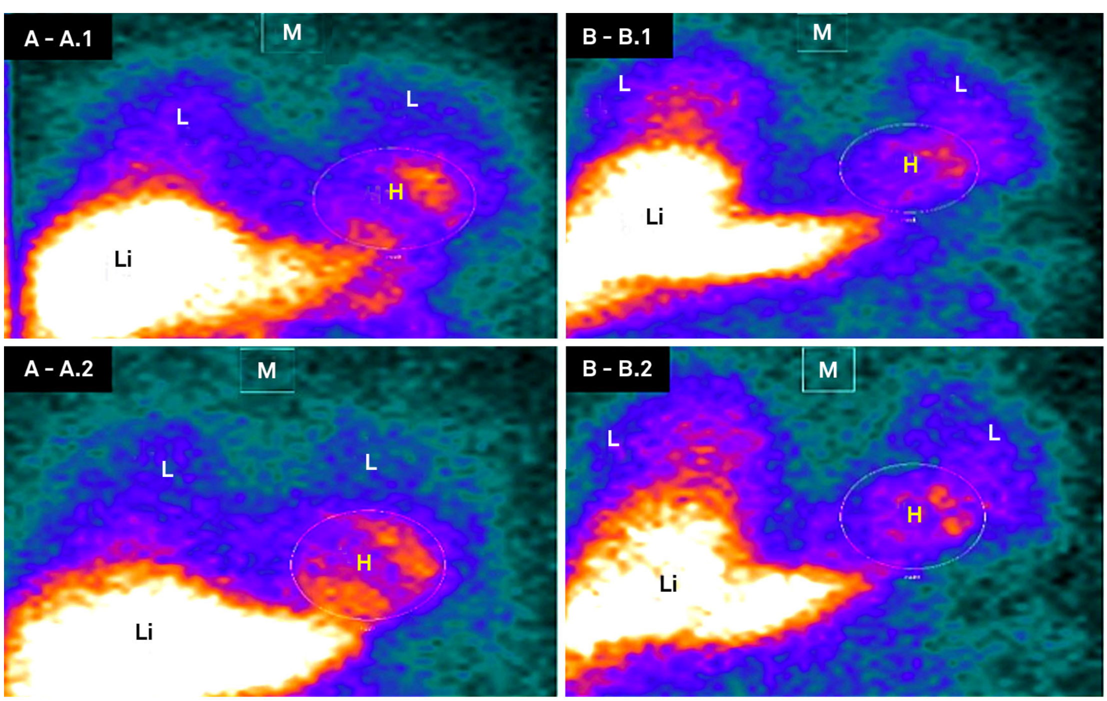
Table. The characteristics of the study group. Cardiac ^{123}I MIBG up take in *de novo* Brazilian patients with Parkinson's disease without clinically defined dysautonomia (n=14 cases).

Case	G	IISM	TD	H/M r		WR	HY	UPDRS
		years*	months*	(e)	(d)	%		I, II and III
1	F	55	13	2.20	1.90	27	1	15
2	M	68	25	1.28	1.10	29	2	40
3	M	73	16	1.54	1.52	18	3	44
4	F	61	28	1.59	1.60	31	2	38
5	F	62	29	1.51	1.40	30	2	45
6	M	64	32	1.39	1.17	34	3	51
7	M	62	26	1.78	1.69	23	3	34
8	M	56	12	1.30	1.27	35	1	17
9	M	70	14	1.81	1.91	13	1	18
10	M	55	30	1.54	1.82	32	3	50
11	F	57	17	1.75	1.66	30	1	19
12	F	58	25	1.34	1.25	43	2	42
13	F	58	28	1.27	1.16	51	2	38
14	F	62	23	1.19	1.12	58	2	23

*age at which the participant was submitted to cardiac MIBG (IISM: age of participant at the beginning of motor symptoms; TD: time duration of symptoms enginese lapsed until the completion of cardiac MIBG); G: gender; F: female; M: male; H/M r: heart to mediastinum (H/M) ratios (e) early - and delayed (normal >1.8) - (d) (normal >1.7)); WR: washout rate (normal ≤27%); HY: Hoehn and Yahr scale, UPDRS: Unified Parkinson Disease Rating Scale (sections I, II and III).

sympathetic denervation in the very early stages of PD, including the initial periods of motor involvement (stage I of Hoehn-Yahr) and premotor (phases 1 and 2 of Braak)[27].

We suppose that our restricitve inclusion and exclusion criteria resulted in a small number of cases, providing to the study a homogeneous group without the influence of other factors causing dysautonomia, than the PD itself. We chose to examine only individuals who did not use anti-PD drugs. Furthermore, although some authors consider not to exist any influence of the anti-PD drugs on the results of ^{123}I cMIBG , it was observed that selegiline increases the serum levels of norepinephrine[28]. Likewise, it was conjectured to have levodopa implication in changing the indexes and images concerning this exam[29]. Therefore, in our series it was possible to verified cardiac sympathetic denervation determined exclusively by PD. This was possible



Early (A.1 and A.2 – 20 minutes) and late (B.1 and B.2 – four hours) planar 123| meta-iodobenzylguanidine myocardial scintigraphy. H: heart; L: long; Li: liver; M: mediastinum. A: normal cardic up take (esential tremor; B: reduced cardic uptake (Parkinson's disease – case 10).

Figure. ^{123}I Myocardial scintigraphy with meta-iodo-benzyl-guanidine: planar tomographic images of the heart topography.

due to the observation of altered indexes of H/M r (85.71% of cases) and WR (71.43% of cases) as well as the diffuse reduction of cardiac uptake in 100% of participants. In our 14 cases the absence of risks resulting from the use of ^{123}I-cMIBG reinforce the knowledge that scintigraphy is highly secure diagnostic tool.

In conclusion, the ^{123}I cMIBG was able to identify cardiac sympathetic neurotransmission impairment in PD patients. This abnormality was observed in *de novo* Brazilian sporadic PD patients without signs of clinically defined dysautonomia.

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