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NEUROIMAGING IN PARKINSONISM

A study with magnetic resonance and spectroscopy as tools in the differential diagnosis

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Abstract – The differential diagnosis of Parkinsonism based on clinical features, sometimes may be difficult. Diagnostic tests in these cases might be useful, especially magnetic resonance imaging, a noninvasive exam, not as expensive as positron emission tomography, and provides a good basis for anatomical analysis. The magnetic resonance spectroscopy analyzes cerebral metabolism, yielding inconsistent results in parkinsonian disorders. We selected 40 individuals for magnetic resonance imaging and spectroscopy analysis, 12 with Parkinson's disease, 11 with progressive supranuclear palsy, 7 with multiple system atrophy (parkinsonian type), and 10 individuals without any psychiatric or neurological disorders (controls). Clinical scales included Hoenh and Yahr, unified Parkinson's disease rating scale and mini mental status examination. The results showed that patients with Parkinson's disease and controls presented the same aspects on neuroimaging, with few or absence of abnormalities, and supranuclear progressive palsy and multiple system atrophy showed abnormalities, some of which statistically significant. Thus, magnetic resonance imaging and spectroscopy could be useful as a tool in differential diagnosis of Parkinsonism.

KEY WORDS: Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, magnetic resonance, spectroscopy.

Neuroimagem no parkinsonismo: estudo com ressonância magnética e espectroscopia por ressonância como ferramentas no diagnóstico diferencial

Resumo – O diagnóstico diferencial do parkinsonismo baseado em parâmetros clínicos pode ser difícil. Alguns exames complementares podem ser úteis, especialmente a ressonância magnética, um método não invasivo, de menor custo quando comparado a tomografia por emissão de pósitrons, proporcionando uma análise anatômica satisfatória. A ressonância por espectroscopia analisa o metabolismo cerebral, com resultados variáveis na literatura no estudo das síndromes parkinsonianas. Selecionamos 40 indivíduos para realização de ressonância magnética e espectroscopia, sendo 12 com doença de Parkinson, 11 com paralisia supranuclear progressiva, 7 com atrofia de múltiplos sistemas tipo parkinsoniana e 10 indivíduos sem manifestações neurológicas ou psiquiátricas (grupo controle). As escalas clínicas analisadas foram a de Hoenh e Yahr, unified Parkinson's disease rating scale e o mini-exame do estado mental. Os resultados encontrados revelaram que pacientes com doença de Parkinson e controle apresentavam em geral o mesmo aspecto por imagem enquanto os grupos paralisia supranuclear progressiva e atrofia de múltiplos sistemas com anormalidades, havendo significância estatística em algumas variáveis. A ressonância magnética e a espectroscopia podem ser úteis no diagnóstico diferencial do parkinsonismo.

PALAVRAS-CHAVE: Parkinsonismo, doença de Parkinson, paralisia supranuclear progressiva, atrofia de múltiplos sistemas, ressonância magnética, espectroscopia.

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The Parkinsonian syndrome or parkinsonism (PK) correspond to clinical signs of rigidity, bradykinesia, tremor, and postural instability, and the presence of two of them is required to define probable PK, and one of these two signs must be tremor or rigidity. The PK is classified as primary, secondary, atypical or plus, and hereditary[1,2]. The accurate diagnosis may be difficult based upon clinical signs, especially at early stages, and in some cases only after the performance of neuropathological studies it could be possible to define the diagnosis[3-7]. It is important to determine this due to the different prognosis, pharmacotherapy, and epidemiological analysis[8,9].

Magnetic resonance imaging (MRI) and spectroscopy by MRI (MRS) are noninvasive tools helping the physician to establish a more accurate diagnosis. MRI offers an adequate analysis of abnormalities in the basal nuclei, midbrain, *pons, medulla*, and *cerebellum*, which are impaired in atypical PK[10-23].

We selected patients with diagnosis of PK and analyzed the usefulness of neuroimaging (MRI and MRS) in the differential diagnosis of this condition.

METHOD

We designed a prospective, case-control, double-blind, 24 months study. The MRI was performed in a GE machine, 1.5 Tesla Sigma Horizon model, the sequences analyzed were T 1, T 2, *flair*, diffusion, axial-oblique in T 2 in Fast Spin-Echo (FSE) and Proton Density (PD) and T 2 in Spin-Echo (SE). In addition to 5 mm slices, we included 3 mm slices in the lentiform nucleus. The MRS was single voxel (8 cc), PRESS technique (TR/TE=1500/50) bilaterally in lentiform nucleus, midbrain, white matter of frontal lobe and hippocampus.

Informed consent was obtained from all patients or their immediate relatives, and the study was approved by the Ethics Committee of the institutions involved.

Forty individuals were included in this study (age range: 50 to 85 years), 30 with Parkinsonian syndrome and 10 without any neurological or psychiatric disorders. Four patients were excluded, two due to cerebrovascular disease showed in MRI, and two related to technical problems during MRI.

All individuals were examined by the same neurologist, and 26 patients met the criteria for probable Parkinson's disease (PD) [n=10], (Gelb et al.[24]), progressive supranuclear palsy (PSP) [n=10], (Tolosa et al.[25]), and multiple system atrophy-parkinsonian type (MSA-P) [n=6], (Gilman et al.[26]). For clinical assessment, the scales adopted were Hoehn-Yahr stage[27], unified Parkinson's disease rating scale (UPDRS) Part III[28] and mini-mental status examination (MMSE)[29]. The patients performed the Tilt Table test for evaluation of dysautonomia.

The indication for MRI was the same for all individuals: "parkinsonism", so that the radiologist did not know the actual diagnosis.

The variables in MRI were: anteroposterior diameter of the *medulla, pons,* midbrain and fourth ventricle, transverse diameter of lateral and third ventricles, presence of cerebral and/or cerebellar atrophy, and signal abnormalities in white matter, lentiform, midbrain, *pons* and *medulla*, linear posterolateral hypersignal in lentiform nucleus, and transverse signal in the *pons*.

MRS was performed bilaterally on white matter of frontal lobe, lentiform nucleus, midbrain and hippocampus. We used the N-acetyl aspartate/creatine (NAA/Cr) and N-acetyl aspartate/choline (NAA/Cho) relation. The value adopted was the mean of both white matter from the frontal lobe and the hippocampus, and the contralateral relation of the most affected side on the lentiform and midbrain, and when there was symmetry, the mean was obtained.

Statistical analysis

For quantitative variables the statistical analysis adopted was Student's t-test or the Mann-Whitney test, and for qualitative the X2, Fisher and Mantel Haenszel. There was statistical significance when p value was <0.05.

RESULTS

The clinical variables that did not show differences statistically significant among the three groups were: age, disease duration, and sex (Table 1).

Table 1. Demographic and clinical characteristics by patient group.

Characteristics	PD	MSA-P	PSP	Control subjects
N	10	6	10	10
Age (yr)	64±10.4	73.3±13.2	70.3±7.2	63.4±10.3
Disease duration (yr)	8.5±3.5	8±2	6.6±3.1	NA
Number of men	6	4	5	6
MMSE	26	24	20	30
Hoehn and Yahr stage	3	5	4	NA
UPDRS – Part III	21	49	33	NA

Mean values ± Standard Deviation (SD) are given for age and disease duration; Mean values are given for MMSE, Hoehn-Yahr stage and UPDRS; PD, Parkinson disease; MSA-P, multiple system atrophy; PSP, progressive supranuclear palsy; NA, not applicable.

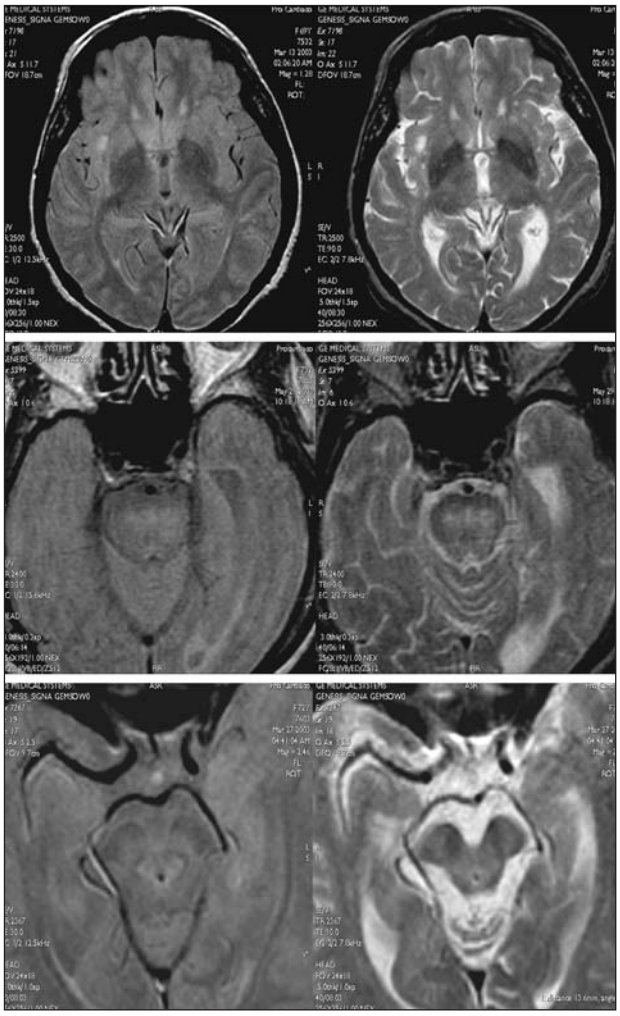

Fig 1. Hyposignal in the lentiform nucleus (found in 67% of MSA-P group), and hypersignal in the pons (found in 33% of MSA-P group) and the midbrain on T2, flair or DP sequences (found in 70% of PSP group).

Dysautonomia was documented in 20% of PD and 100% of MSA-P.

In the motor scales (UPDRS and Hoehn and Yahr), the results showed higher scores in PSP and MSA-P than in PD. There was statistical significance in PD *versus* MSA-P (Hoehn Yahr p=0.021 and UPDRS p=0.029), and a trend to statistical significance in PD and PSP (Hoehn and Yahr, and UPDRS p=0.08).

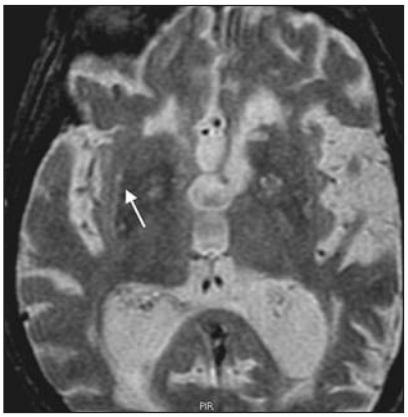

Fig 2. Posterolateral linear hypersignal in the lentiform nucleus, with asymmetric symptoms, T2 sequence (found in 50% in MSA-P group).

Patients with PSP presented lower scores in MMSE, followed by MSA-P and PD, and there was statistical significance in the three groups comparing to controls (PD p=0.046; MSA-P p=0.002, and PSP p=0.0004) (Table 1).

Image variables demonstrated cerebral atrophy in all cases of PSP and MSA-P, having statistical significance in PD *versus* PSP (p=0.001), PD *versus* MSA-P (p=0.006), controls *versus* PSP (p=0.011), and controls *versus* MSA-P (0.043). Cerebellar atrophy was more common in MSA-P and PSP, with statistical significance in PD *versus* MSA-P (p=0.043), controls *versus* PSP (p=0.034) and controls *versus* MSA-P (p=0.010). We observed a higher prevalence of white matter alterations in atypical PK with no statistical significance. Signal change in the lentiform nucleus was observed more commonly in MSA-P and PSP, but no statistical significance was documented (Figs 1–3).

The posterolinear increased signal in the lentiform nucleus was demonstrated only in the MSA-P and PSP groups, presenting statistical significance when compar-

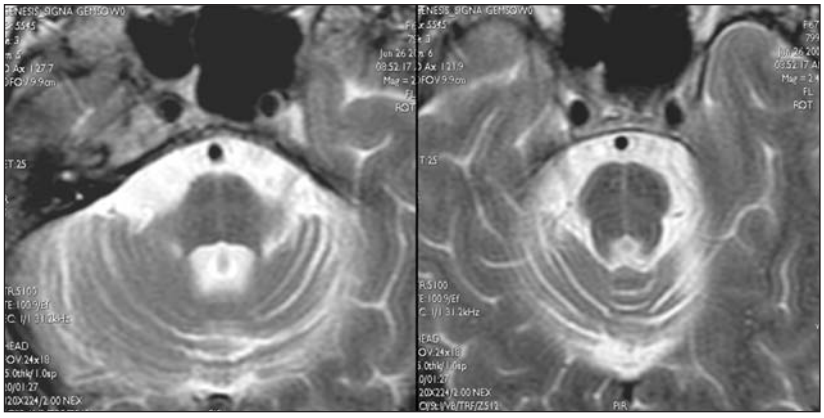

Fig 3. Transverse signal ("hot cross bun sign") in the pons, T2 sequence (found in 33% of MAS-P group).

Table 2. Magnetic resonance variables (quantitative).

	Mean values (mm)±SD			
	PD	MSA-P	PSP	Control subjects
Posteroanterior diameter of the midbrain	17±1.06	15±1.54	14±2.32	17±1.32
Posteroanterior diameter of the pons	22±2.22	20±2.51	19±1.75	23±1.71
Posteroanterior diameter of the medulla	13±1.81	12±1.23	12±1.7	14±1.17
Transverse diameter of the lateral ventricles	32±7.47	37±7.6	39±5.7	33±4.85
Transverse diameter of the third ventricle	3±3.71	5±3.24	8±2.21	4±3.38
Posteroanterior diameter of the fourth ventricle	9±0.93	10±1.59	10±2.29	9±1.82

PD, Parkinson disease; MSA-P, multiple system atrophy; PSP, progressive supranuclear palsy.

Table 3. Spectroscopy variables.

Variables		PD (N=10)	PSP (N=10)	MSA (N=6)	Control subjects (N=10)
NAA/Cr lentiform nucleus	Mean	1.46	1.31	1.4	1.45
NAA/Cr midbrain	Mean	1.77	1.5	1.74	1.65
NAA/Cr frontal lobe	Mean	1.51	1.47	1.53	1.56
NAA/Cr Hippocampus	Mean	1.36	1.2	1.33	1.42
NAA/Chol lentiform nucleus	Mean	1.64	1.43	1.55	1.56
NAA/Chol midbrains	Mean	1.53	1.34	1.69	1.56
NAA/Chol frontal lobe	Mean	1.71	1.57	1.55	1.62
NAA/Chol Hippocampus	Mean	1.4	1.41	1.42	1.5

Naa, N-Acetyl aspartate; Cr, creatine; Col, choline; Naa/Cr in the lentiform nucleus, PD *versus* PSP controls (p=0.049) and PSP *versus* controls (p=0.036); Naa/Cr in the hippocampus, PSP *versus* control (p=0.0007); Naa/Col in the midbrain, PSP versus MSA (p=0.028) and PSP *versus* control (p=0.046).

ing PD *versus* MSA-P (p=0.03), and controls *versus* MSA-P (p=0.03).

Signal changes in the midbrain were more commonly observed in PSP, and in MSA-P in the *pons*, with statistical significance in midbrain (p=0.0015).

The quantitative variables detailed in Table 2 demonstrated that some measurement of brainstem and ventricular system had statistical significance to differentiate atypical PK and PD/control group. The measurements that revealed statistic significance according to region and groups were:

Midbrain – PD *versus* PSP (p=0.002), PD *versus* MSA-P (p=0.012), controls *versus* PSP (p=0.002) and controls *versus* MSA-P (0.010).

Pons – DP *versus* PSP (p=0.012), PSP *versus* controls (p=0.007) and MSA-P *versus* controls (p=0.01).

Medulla – DP *versus* MSA-P (p=0.041), PSP *versus* controls (p=0.008) and MSA-P *versus* controls (p=0.001).

Lateral ventricles – PD *versus* PSP (p=0.041) and controls *versus* PSP (p=0.045).

Third ventricle – DP *versus* PSP (p=0.015) and PSP *versus* controls (p=0.009).

Fourth ventricle – DP *versus* PSP (p=0.037) and DP *versus* MSA-P (p=0.024).

The values of MRS are related in Table 3 and some reduction showed statistical significance:

NAA/Cr in the lentiform nucleus – PD *versus* PSP (p=0.049) and PSP *versus* controls (p=0.036).

NAA/Cr in the hippocampus – PSP *versus* control (p=0.0007).

NAA/Cho in the midbrain – PSP *versus* MSA (p=0.028) and PSP *versus* control (p=0.046).

DISCUSSION

The increase of life expectancy results in a raise of degenerative disorders. PD is one of the most common neurodegenerative disease (followed by Alzheimer disease), as epidemiological studies show in the literature[30]. Parkinsonian signs may be seen in different medical conditions, having variable course, treatment and prognosis so it is important to determine an accurate diagnosis as soon as possible[8,9]. Based only in clinical data, especially in the early stages of the disease, physicians may not establish a correct diagnosis[3-7].

The accuracy of clinical diagnosis of PK is variable, in PD ranging from 76% to 90%, and in others PK the accuracy is even lower[3-7]. One study conducted in a movement disorders specialized center, showed that the positive predic-

tive value of PD was 98.6%, and to atypical parkinsonism 71.4%, confirming that the diagnosis of atypical PK, even in specialized centers, is sometimes difficult to establish[7].

Some diagnostic tests could be useful for the differential diagnosis of PK, and MRI is one of the most important[10-23]. Our objective was to determine the usefulness of MRI and MRS in a PK group, based on well known imaging aspects according to the subtype of PK, assessing which variables had statistic significance in these groups.

We included the three PK that most frequently lead to misdiagnosis: PD, MSA-P, and PSP, all compared to control group. The criteria used to clinical diagnosis was the most specific, as showed in the literature[24-26].

We used three clinical scales: motor part of UPDRS, Hoehn and Yahr and MMSE[27-29]. These scales showed increased motor impairment (higher scores in UPDRS and Hoehn-Yahr) in the MSA-P, followed by PSP, and increased cognitive impairment (lower scores of MMSE) in PSP, followed by MSA-P. We did not observe a correlation between the duration of the symptoms with MRS abnormalities, but with the clinical diagnosis of patient.

MRI variables demonstrated that some are helpful to differentiated PK syndromes, as the presence of cerebral and cerebellar atrophy and signal enhancement of some encephalic structures (lentiform nucleus, midbrain and *pons*), more common in atypical PK.

The decreased signal enhancement in the lentiform nucleus may be observed in normal aging, so in our study we only considered it as "abnormal" if the hypointensity was moderate to severe[15,31]. Our data showed that moderate to severe decrease hypointensity in lentiform nucleus was observed more frequently in MSA and PSP, with no difference between PD and control groups and when it was associated with posterolateral linear hypersignal in putamen, suggested the diagnosis of atypical PK (more frequently in MSA group).

The most useful measurement of encephalic diameter in our study was the midbrain, as it had been shown by Warmutth et al.[18]. Values below 15 mm in the midbrain suggested PSP or MSA-P, with lower values seen in PSP.

Some values of MRS had statistical significance, the most useful were from the lentiform nucleus, hippocampus, and midbrain, depending on the diagnosis, indicating a severe neuronal impairment (neuronal death). There are few studies in which the brainstem is evaluated by MRS, due to technical difficulties (bone proximity). In our study we demonstrated that it is feasible, but we had to repeat the exam, in some cases several times, to achieve a consistent chart. The study done by Watanabe et al.[23] demonstrated the usefulness of MRS of the *pons* in MSA patients. As the midbrain is the most affected area in PSP, we analyzed it by MRS. We have found NAA/Cho decrease in midbrain of PSP group with statistical significance, indicating neuronal loss.

Based on our data we concluded that: **(1)** Patients with PSP and MSA-P presented increased motor and cognitive impairment in the scales used, correlating with decrease in NAA/Cr in lentiform nucleus and NAA/Cho in midbrain in the PSP group; **(2)** Cerebral and cerebellar atrophy were more prevalent and severe in PSP and MSA-P groups; **(3)** Linear hypersignal in the lateral portion of the putamen, hypersignal in midbrain and in pons, all suggest the diagnosis of PSP or MSA-P; **(4)** Midbrain or pons atrophy suggests atypical parkinsonism, the former PSP, and the latter MSA-P; **(5)** Comparing the two methods, MRI and MRS, the former had better applicability.

Our study showed that anatomical analysis through MRI and MRS of some areas could be useful in the differential diagnosis of PD and atypical PK, helping physicians to establish a more accurate diagnosis of PK.

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