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# Neuroradiological Study (Nigrosome and Neuromelanin) in Parkinson's Disease *versus* Secondary Parkinsonism - Diagnostic Accuracy

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## Abstract

**Objective:** Evaluate the accuracy, sensitivity, specificity and predictive values of magnetic resonance imaging (MRI) 3 tesla (3T) in the differential diagnosis between patients with Parkinson's disease (PD) and secondary parkinsonism.

**Methods:** Patients with parkinsonian syndromes, essential tremor or restless legs syndrome were submitted to 3T MRI device with a 32 channel head matrix coil to obtain oblique axial neuromelanin (NML) sensitive T1 weighted images. HR – SWI weighted sequence images were reviewed in multiple planes using 3D assessed for absence or presence of nigrosome (NG) 1 hyperintensity (the swallow tail sign). Two blinded neuroradiologists for the clinical features analyzed the MRIs. The measures of accuracy were calculated with 95% confidence intervals. To verify the reproducibility between the methods, the Cohen's kappa coefficient was used.

**Results:** Sixty–three patients, including patients with PD, atypical parkinsonism, secondary parkinsonism, essential tremor, and restless legs syndrome, were evaluated. The combined study of NG and NML had a sensitivity of 96.97% (95% CI 84.24% to 99.92%), specificity of 93.33% (95% CI 77.93% to 99.18%), positive predictive value of 94.12% (95% CI 80.73% to 98.39%), negative predictive value of 96.55% (95% CI 80.21% to 99.49%) and accuracy of 95.24% (95% CI 86.71% to 99.01%).

**Conclusion:** The 3T MRI is a good diagnostic method, with high sensitivity, specificity, and accuracy to differentiate PD and atypical parkinsonism from secondary forms of parkinsonism. It must help to make the right diagnosis and treatment, even at the beginning of the disease, changing the prognosis of the disease.

***Keywords:*** *MRI; Parkinson's disease; Parkinsonism; Nigrosome; Neuromelanin*

***Abbrevations:*** *PSP: Progressive Supranuclear Palsy; MSA: Multiple System Atrophy; LBD: Lewy body dementia; CBD: Corticobasal Degeneration; SP: Secondary Parkinsonism; NML: Neuromelanin; NG: Nigrosome*

## Introduction

Parkinsonism is a hypokinetic syndrome characterized by resting tremor, muscular rigidity, bradykinesia or akinesia, and postural instability. Although Parkinson disease (PD) is the most frequent cause of parkinsonism, there are a number of other entities that mimic the clinical presentation of PD [1,2].

All the parkinsonian syndromes, should be considered while making the differential diagnosis, inclunding those classified as atypical parkinsonian, like progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD) and Lewy body dementia (LBD) [3,4], and those that are considered as secondary parkinsonism (SP), referring about cases of parkinsonism that have a specific known cause, such as drug-induced, metabolic disorders, cerebrovascular disease, hydrocephalus and infections [5].

The considerable overlap of signs and symptoms between atypical parkinsonian syndromes, PD, secondary parkinsonisms, and heredodegenerative disorders makes clinical diagnosis a challenge. Diagnosis is mainly based on observable symptoms. There is not an established role for neuroimaging, and neuropathology is still considered the gold standard for definitive diagnosis [4,1]. Since the main neuropathological feature in PD and atypical parkinsonism is the degeneration

of the nigrostriatal dopaminergic pathway, with the loss of dopaminergic neurons containing neuromelanine (NML) and the loss of nigrosome (NG), we searched for the efficacy of magnetic resonance imaging (MRI) 3 tesla (3T), analyzing nigrosome 1 and neuromelanin, to differentiate PD and atypical parkinsonism from the other forms of parkinsonism. [6-8].

### Data Availability Statement

Our group has full responsibility for the data's analyses and interpretation and the conduct of the research. We also have full access to all data and the right to publish any and all data separated and apart from any sponsor. Any anonymized data will be shared if requested by any qualified investigator. A regional review board has approved the use of humans, and we had written informed patient consent to perform this study. All authors and contributors have agreed to conditions noted on the Authorship Agreement Form. We received consent forms from all participant and the approval from an ethical standards committee [9-11].

## Methods

### Study design

Retrospective study by medical records analysis.

### Patients

This research was performed in the Hospital Beneficência Portuguesa of São Paulo, where the data was collected during 2015. Patients were eligible for inclusion if they had any parkinsonian syndrome, essential tremor or restless legs syndrome. They were diagnosed based on clinical, laboratory and, image criteria. Exclusion criteria were the impossibility of performing MRI. Each patient was submitted to MRI and a structured anamnesis and physical examination conducted by a neurologist.

### Image analysis

Images were performed using a 3T MRI device (Siemens Skyra, VE11C, A Tim System, Siemens Healthcare Sector, Erlangen, Germany) with a 32 channel head matrix coil to obtain oblique axial neuromelanin sensitive T1 weighted images, using fast spin – echo sequence, repetition time, 550 ms; echo time, 9,7 ms; flip angle, 90 ; echo train length, 2; number of excitations, 8; matrix size, 314 x 512; field of view, 220 mm; voxel size 0,2 x0,2 x2,5 mm; number of slices, 20; slice thickness, 2.5 mm; interslice gap, 1 mm; acquisition time, 5:48 min (Figure 1), and HR--SWI weighted sequence with 3D acquisition using a gradient echo-planar imaging sequence FEEPI, TR/TE 48/30, echo train length 5, flip angle 18 deg, number of slices: 48, voxel size 0,3 x 0,3 x 0,7 mm, scan duration: 5 minutes 23 seconds, only magnitude image used for interpretation. The orientation of the axial slices was individually aligned parallel to the splenium and genu line of the corpus callosum. The magnitude images were reviewed in multiple planes using 3D assessed for absence or presence of nigrosome-1 hyperintensity (the swallowtail sign) (Figure 2). The two neuroradiologists performing the MRI analysis were blinded for the clinical features [11-14].

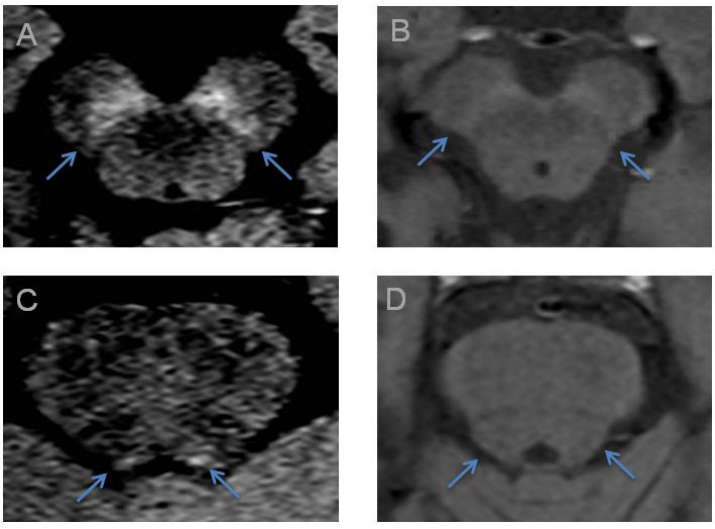



**Figure 1:** MRI T1 spin-echo axial sequences to study neuromelanin
(A) Neuromelanin sign on the substantia nigra pars compacta in a normal patient. (B) Absent of neuromelanin sign on the substantia nigra pars compacta in PD's patient. (C) Neuromelanin sign on the locus coeruleus in a normal patient . (D) Absent of neuromelanin sign on the locus coeruleus in a PD's. patient.

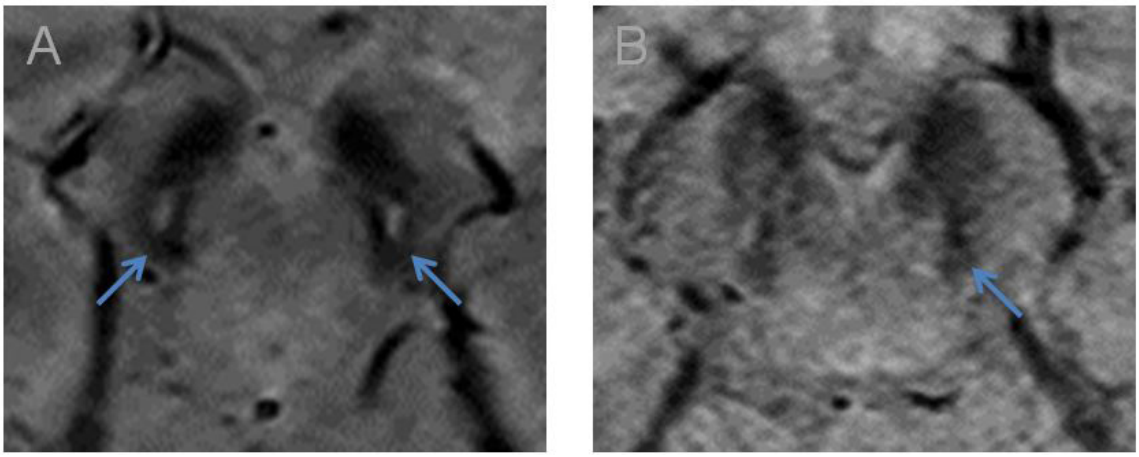



**Figure 2:** MRI SWI axial sequences to study nigrosome 1
(A) Swallow tail sign (substantia nigra) of a normal patient. (B) PD'S- absent of the swallow tail sign on the left.

Axial T1 and T2 weighted images, axial FLAIR, and diffusion as well as sagittal T1 weighted images of the entire brain were also obtained to enable the visual assessment and linear measurement of morphological changes as well as to exclude other neurological disorders or coexisting lesions that would interfere with further assessment. All the examinations were analyzed in a PACS system.

### Statistical analysis

The data was described considering the mean, standard deviation, minimum, maximum, and quartiles for the quantitative variables and frequency tables for the qualitative variables.

In order to verify the discrimination of NG, NML and the panel (abnormal NG and /or abnormal NML) for the diagnosis of PD (primary or atypical parkinsonism *versus* SP or essential tremor or SPI), the sensitivity, specificity, positive and negative predictive value and accuracy were calculated with their respective 95% confidence intervals. To verify the reproducibility between the methods, the Cohen's kappa coefficient was used.

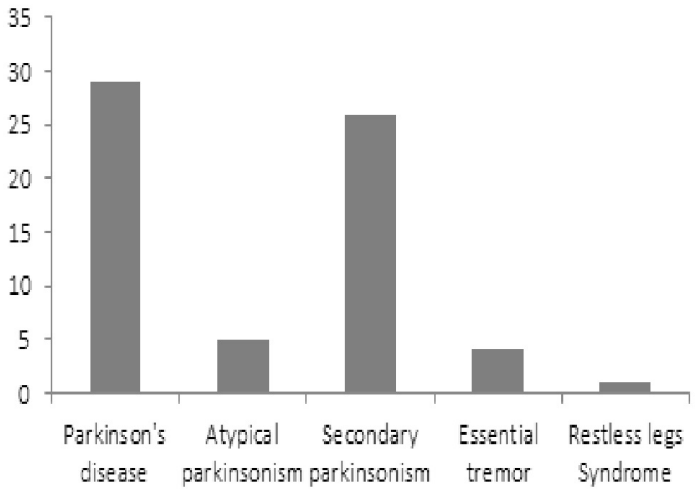
In all studies, a significance of 0.05 was considered, and the data was analyzed using SPSS v25 Software.

## Results

### Participants

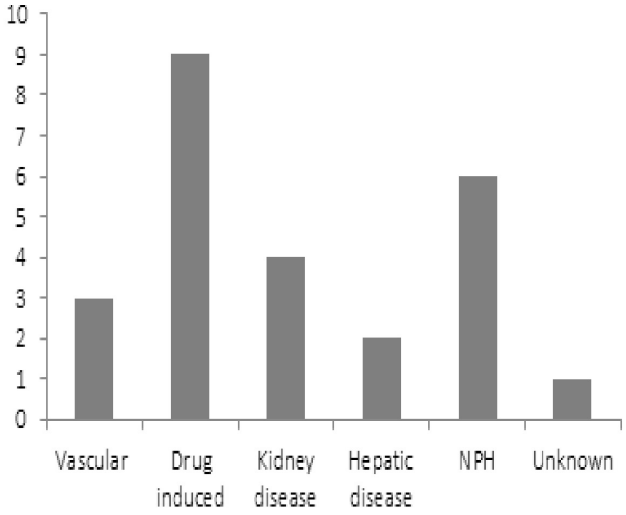
In this research, sixty-three patients with different types of movement disorders were evaluated. There were thirty – three were women, and thirty men, and the average age was 71 years old (SD: 15).

The average time of illness was 2,74 years (SD: 3,60). Based on clinical, laboratory and, imaging criteria, they were classified into groups. Group 1 of PD had twenty – nine patients. The second group was made up of four patients with atypical parkinsonism. Group 3 had twenty – five patients with SP. The fourth group was made up of four patients with essential tremor, and finally, we also evaluated one patient with restless legs syndrome (Graphic 1) [15].

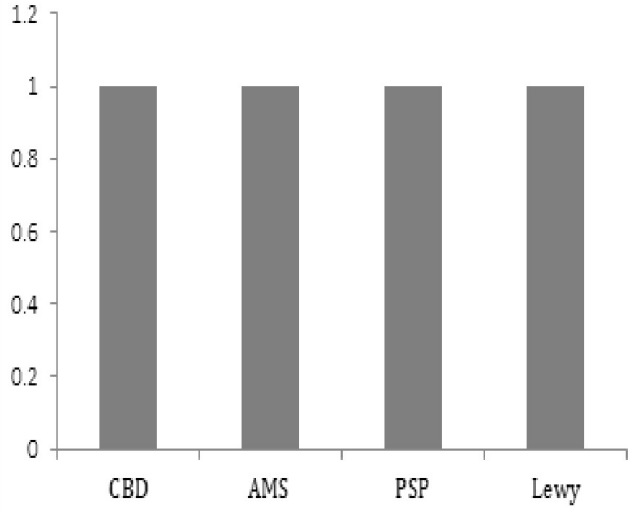



**Graphic 1:** Participants

Among the secondary parkinsonism there was nine patients diagnosed with drug-induced parkinsonism, six had normal pressure hydrocephalus, four had dialysis dependent kidney failure, three were diagnosed with vascular parkinsonism, two had hepatic encephalopathy and one an undetermined diagnosis. From the patients with drug induced parkinsonism, five had done chronic use of neurolepts, two had used lithium, and two had used calcium channel blockers (Graphic 2). The group of patients with atypical parkinsonism was composed of one patient with CBD, one with MSA, parkinsonian type, one with PSP and one LBD (Graphic 3) [16].




**Graphic 2:** Secondary Parkinsonism




**Graphic 3:** Atypical Parkinsonism

## Test results

Nineteen patients from group 1 and 4 patients from group 2 had both NG and NML signs changed in brain MRI. Seven patients from group 1 had abnormality just on the NG sign and three just on the NML sign. Those signs were typical in groups 3, 4, and 5, with two exceptions on group 3. The first was a patient with vascular parkinsonism and MRI showing diffuse lacunar ischemic events, including a large area of the substantia nigra pars compacta, justifying the alteration of NG and NML signals. The second exception was a 13 years old patient with pyramidal and extrapyramidal syndromes, who was inserted into group 3 for having an unknown cause of parkinsonism, in spite of extensive diagnostic research. She obtained an excellent response to dopaminergic agonist, showing that she should have a degeneration of the nigrostriatal pathway.

By the statistical analysis it was estimated that NG alone study in MRI has the sensitivity of 93,94% ( 95% CI 79.77% to 99.26%) , specificity of 93.33% (95% CI 77.93% to 99.18%), positive predictive value of 93.94% ( 95% CI 80.20% to 98.34%), negative predictive value of 93.33% (95% CI 78.46% to 98.18%) and accuracy of 93.65% ( 95% CI 84.53% to 98.24%). (Table 1) [17].

| Statistic | Value | 95% CI |
|---|---|---|
| Sensitivity | 93.94% | 79.77% to 99.26% |
| Specificity | 93.33 % | 77.93% to 99.18% |
| Positive Predictive Value | 93.94% | 80.20% to 98.34% |
| Negative Predictive Value | 93.33 % | 78.46% to 98.18% |
| Accuracy | 93.65% | 84.53% to 98.24% |

**Table 1:** Nigrosome measures of diagnostic accuracy

The NML alone study in MRI has the sensitivity of 72.73% ( 95% CI 54.48% to 86.70%), specificity of 93.33% (95% CI 77.93% to 99.18%), positive predictive value of 92.31% ( 95% CI 75.58% to 97.90%), negative predictive value of 75.68% (95% CI 63.87% to 84.56%) and accuracy of 82.54% (95% CI 70.90% to 90.95%) (Table 2).

| Statistic | Value | 95% CI |
|---|---|---|
| Sensitivity | 72.73% | 54.48% to 86.70% |
| Specificity | 93.33 % | 77.93% to 99.18% |
| Positive Predictive Value | 92.31% | 75.58% to 97.90% |
| Negative Predictive Value | 75.68 % | 63.87% to 84.56% |
| Accuracy | 82.54% | 70.90% to 90.95% |

**Table 2:** Neuromelanin measures of diagnostic accuracy

The combined study of NG and NML has the best values, showing sensitivity of 96.97% ( 95% CI 84.24% to 99.92%), specificity of 93.33% (95% CI 77.93% to 99.18%), positive predictive value of 94.12% ( 95% CI 80.73% to 98.39%), negative predictive value of 96.55% (95% CI 80.21% to 99.49%) and accuracy of 95.24% (95% CI 86.71% to 99.01%) (Table 3).

| Statistic | Value | 95% CI |
|---|---|---|
| Sensitivity | 96.97% | 84.24% to 99.92% |
| Specificity | 93.33 % | 77.93% to 99.18% |
| Positive Predictive Value | 94.12% | 80.73% to 98.39% |
| Negative Predictive Value | 96.55 % | 80.21% to 99.49% |
| Accuracy | 95.24% | 86.71% to 99.01% |

**Table 3:** Nigrosome plus neuromelanin measures of diagnostic accuracy

## Discussion

Until today, a definitive diagnosis of PD is only possible by anatomopathological exam post mortem [6]. Its main neuropathological feature is the loss of dopaminergic nigrostriatal neurons, whose cells bodies are in the substantia nigra pars compacta. These neurons contain NML, which degenerate to a greater extent in PD than dopaminergic neurons not containing NM [5]. NG represent small clusters of dopaminergic cells. The largest one is labeled as nigrosome 1, which contains the biggest proportion of neurons most commonly affected by PD. Changes within nigrosome 1 can be demonstrated with high resolution T2*/SWI (HR – SWI) weighted magnetic MRI of 7T [9]. An abnormal NM deposition also can be seen with specific sequences in MRI. In this research, we used 3T MRI to study NG and NM in patients with different kinds of parkinsonism.

## Conclusion

It was found that the 3T MRI is a good diagnostic method, with high sensitivity, specificity, and accuracy to differentiate PD and atypical parkinsonism patients - diseases that there is a loss of normal nigrostriatal pathway - from patients with secondary forms of parkinsonism, which have a normal nigrostriatal pathway. It's possible because the nigrostriatal pathway's integrity the can be reflected in some MRI sequences. Since some participants patients had recent begin of the symptoms, we suggest that 3T MRI studying NG and NML should be applied in every patient with parkinsonian syndromes, helping to make a right diagnosis, even in the beginning of the disease.

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