MRI of nigrosome-1: A potential triage tool for patients with suspected parkinsonism

Sven Haller1,2,3,4 | Anette Davidsson5,6 | Anders Tisel6,7,8 | Miguel Ochoa-Figueroa5,6,8,9 | Charalampos Georgiopoulos6,8,9

1 CIMC – Centre d’Imagerie Médicale de Cornavin, Geneva, Switzerland
2 Department of Surgical Sciences, Radiology, Uppsala University, Uppsala, Sweden
3 Faculty of Medicine, University of Geneva, Geneva, Switzerland
4 Department of Radiology, Beijing Tiantan Hospital/Capital Medical University, Beijing, China
5 Department of Clinical Physiology, Linköping University, Linköping, Sweden
6 Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
7 Department of Medical Radiation Physics, Linköping University, Linköping, Sweden
8 Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden
9 Department of Radiology, Linköping University, Linköping, Sweden

Correspondence
Charalampos Georgiopoulos, Department of Radiology, University Hospital Linköping, S81 85 Linköping, Sweden.
Email: Charalampos.Georgiopoulos@liu.se.

Abstract

Background and Purpose: Susceptibility-weighted imaging (SWI) of nigrosome-1 is an emerging and clinically applicable imaging marker for parkinsonism, which can be derived from routinely performed brain MRI. The purpose of the study was to assess whether SWI can be used as a triage tool for more efficient selection of subsequent Dopamine Transporter Scan (DaTSCAN) single-photon emission computed tomography (SPECT).

Methods: We examined 72 consecutive patients with suspected parkinsonism with both DaTSCAN SPECT and SWI (48 in Philips Ingenia, 24 in GE Signa). Additionally, we examined 24 healthy controls with SWI (14 in Philips Ingenia, 10 in GE Signa). Diagnostic performance of SWI and DaTSCAN SPECT was assessed on the basis of clinical diagnosis, in terms of sensitivity, specificity, and diagnostic accuracy.

Results: A total of 54 parkinsonism patients (69 years ± 9, 32 men), 18 nonparkinsonism patients (69.4 years ± 9, 10 men), and 24 healthy controls (62 years ± 8, 10 men) were recruited. SWI had a specificity of 92% and a sensitivity of 74%, whereas DaTSCAN SPECT had 83% and 94%, respectively. By preselecting patients with abnormal or inconclusive SWI, the diagnostic performance of DaTSCAN SPECT improved (specificity 100%, sensitivity 95%). Scans from Philips were associated with significantly lower image quality compared to GE (p < .001). The experienced rater outperformed the less experienced one in diagnostic accuracy (82% vs. 68%).

Conclusions: SWI can be used as triage tool because normal SWI can in most cases rule out parkinsonism. However, the performance of SWI depends on acquisition parameters and rater’s experience.

KEYWORDS
123I-FP-CIT SPECT, Parkinson’s disease, parkinsonism, magnetic resonance imaging, susceptibility-weighted imaging

INTRODUCTION

The diagnosis of Parkinson’s disease (PD) is usually difficult because the first symptoms may be diffuse, vary from person to person, and resemble symptoms linked to other diseases. As a result, up to 30% of patients are initially misdiagnosed as PD, even in specialized units.1,2 The diagnostic work-up of patients with suspected parkinsonism is, therefore, extensive and includes neuroimaging.3 Single-photon emission computed tomography (SPECT) has been widely used in patients with suspected parkinsonism. SPECT with the radioligand Dopamine J Neuroimaging. 2021;1–6.

wileyonlinelibrary.com/journal/jon
Transporter Scan (DaTSCAN® [ioflupane (123I)]) has a well-established role in the early diagnosis of parkinsonism. 4 Some studies indicate that the uptake pattern of the radioligand can provide useful hints toward PD or atypical parkinsonian syndromes (APS). 5−7

Magnetic Resonance Imaging (MRI) with conventional imaging techniques is helpful to exclude parkinsonism due to other pathologies and to differentiate PD from Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy. 8 Recent advances have allowed the direct assessment of substantia nigra pars compacta (SNpc) by using susceptibility weighted imaging (SWI). 9−11 This technique can visualize nigroisome-1, a lens-shaped area located caudally in the dorsal part of SNpc, where the dopaminergic neuronal loss due to PD is more profound. The healthy nigroisome-1 appears as a hyperintense region in SWI, giving rise to the term "swallow tail sign". In contrast, the swallow tail sign appears to be absent in PD patients, as the nigroisome-1 is hypointense due to loss of neuromelanin. Evaluating nigroisome-1 with SWI appears to have excellent accuracy in PD patients, but its occurrence in healthy subjects is not consistent. 12−14 Nonetheless, SWI is recommended as an essential part of standardized MRI protocol for assessing parkinsonism. 15

In principle, SWI is equivalent to DaTSCAN SPECT. Both techniques are abnormal in both PD and APS. 16,17 However, both techniques are normal in essential tremor and drug-induced parkinsonism and can therefore discriminate PD from those two differential diagnoses. 16,19 Previous studies have supported the efficacy of SWI in the assessment of parkinsonism by showing high concordance rate with DaTSCAN SPECT and high diagnostic accuracy for PD versus healthy controls. 13,20 However, the clinical implementation of SWI remains limited, probably because evaluation of nigroisome-1 is challenging and depends on MRI sequence parameters and rater’s experience. With this study, we wanted to assess whether SWI might be used as an initial screening tool for triaging patients with suspected parkinsonism. Our main hypothesis was that SWI can successfully discriminate patients with parkinsonian syndromes from non-parkinsonian ones and, hence, be used for the preselection of patients for subsequent DaTSCAN SPECT.

METHODS

The local Ethical Review Authority approved the study (registration number 2019–06123). All participants provided written informed consent prior to inclusion.

Participants

We recruited 72 consecutive patients with suspected parkinsonism who visited the department of Nuclear Medicine for DaTSCAN SPECT. The SPECT examination was performed as part of the clinical diagnostic work-up, whereas MRI was performed as part of this research study. All patients underwent SWI either on the same day (53 patients) or within 6 months (19 patients) after DaTSCAN SPECT. Patients with mandibular implants or magnetic/electromagnetic implants (such as pacemakers) were excluded. Clinical diagnosis was decided by the referring neurologist (usually within 6 months after DaTSCAN SPECT, based on clinical examination, laboratory results, neuroimaging, and response to treatment). Thereafter, patients were classified into two groups: (a) parkinsonism and (b) nonparkinsonism (Table 1). Moreover, 24 healthy controls without any neurologic disorders were recruited among patients’ spouses and from advertising at the hospital. To avoid unnecessary exposure to ionizing radiation, healthy controls were only examined with SWI. The performance of SWI and DaTSCAN SPECT was assessed based on clinical diagnosis.

SWI: Acquisition and assessment

MRI data were acquired on two different 3T systems. One group (24 patients, 10 controls) was examined on a SIGNA Architect DV26 (GE Medical Systems, Milwaukee, Wisconsin, US) using a 48-channel phased array head coil and the following parameters: 3-dimensional susceptibility-weighted angiography, axial, field of view (FOV) 200 × 200 × 64.1.4 mm 3, voxel size 0.7 × 0.7 × 1.4 mm 3, asset acceleration = 2, echo time (TE) = 24 ms, and repetition time (TR) = 60 ms. The other group (48 patients, 14 controls) was examined on an Ingenia R5.4 (Philips Healthcare, Best, The Netherlands) using a 12-channel phased array head coil and the following parameters: 3-dimensional fast field echo, axial, FOV 220 × 178 × 130 mm 3, voxel size 0.8 × 0.8 × 1.6 mm 3, Compressed Sensing = 2, TE = 31 ms, and TR = 23 ms.

The swallow tail sign was determined to be a focal oval or linear hyperintense spot within the posterior and caudal part of SNpc. Two neuroradiologists (S.H. with 20 years of experience, and C.G. with 9 years of experience) assessed the images, independently and blinded to diagnosis. One month later, a consensus rating, blinded to diagnosis, was performed. The swallow tail sign was rated on an ordinal scale with four increments: 1, definitely normal; 2, probably normal; 3, probably abnormal; 4, definitely abnormal. For statistical analysis, the results were dichotomized into normal (ratings 1 and 2) and abnormal (ratings 3 and 4). Cases with unilaterally abnormal findings were considered abnormal. Moreover, the two raters estimated the overall image quality for artifacts, with an ordinal scale: 1, very good with little or no artifacts; 2, good with some artifacts; 3, fair with considerable artifacts; 4, poor with significant artifacts, but readable; 5, nondiagnostic scan. All grade 5 scans were excluded from further analysis.

DaTSCAN SPECT: Acquisition and assessment

Data were acquired with a dual-head gamma camera Discovery NM/CT 670 with low-energy, high-resolution collimator (GE Healthcare, Waukesha, USA), 3-4 hours after intravenous injections of 111−185 MBq DaTSCAN. 6 All data were processed with the software DaTQUANT version 4.0 (GE Healthcare). Images were reconstructed using iterative algorithm, ordered subset expectation maximization, two iterations, and 10 subsets. A Butterworth post-filter (cutoff frequency of 0.6 and power 10) and a uniform attenuation were used. Radiotracer binding was calculated for the following volumes of interest: caudate, putamen, striatum, and background. The reconstructed axial images were visually evaluated by a nuclear medicine specialist.
TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Parkinsonism group</th>
<th>Nonparkinsonism group</th>
<th>Healthy controlsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>54</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Age (years)b</td>
<td>Median: 71</td>
<td>Median: 69</td>
<td>Median: 62</td>
</tr>
<tr>
<td></td>
<td>Minimum: 45</td>
<td>Minimum: 44</td>
<td>Minimum: 50</td>
</tr>
<tr>
<td></td>
<td>Maximum: 85</td>
<td>Maximum: 82</td>
<td>Maximum: 73</td>
</tr>
<tr>
<td>Sex</td>
<td>32 M, 22 F</td>
<td>10 M, 8 F</td>
<td>10 M, 14 F</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>PD: 31</td>
<td>Tremor: 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSA-P: 1</td>
<td>Dementia: 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSA-C: 2</td>
<td>MCI: 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LBD: 2</td>
<td>INPH: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBD: 2</td>
<td>Neuralgia: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unspecified APS: 6</td>
<td>Psychogenic pain: 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unspecified parkinsonism: 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aHealthy controls were only examined with SWI.
bHealthy controls were significantly younger compared to patients with parkinsonism (p < .01) and nonparkinsonism (p = .037).

Abbreviations: APS, atypical parkinsonism; CBD, corticobasal degeneration; F, female; INPH, idiopathic normal pressure hydrocephalus; LBD, Lewy body dementia; M, male; MCI, mild cognitive impairment; MSA-C, MSA with predominant cerebellar ataxia; MSA-P, MSA with predominant parkinsonism; PD, Parkinson’s disease.

Performance of SWI

We examined 62 participants on the Philips scanner (37 parkinsonism patients, 11 nonparkinsonism patients, 14 healthy controls) and 34 patients on the GE scanner (17 parkinsonism patients, 7 nonparkinsonism patients, 10 healthy controls). The GE scanner was associated with excellent specificity of 100% but fair sensitivity of 60%, whereas the Philips scanner was associated with moderate specificity of 86% and sensitivity of 82%. Rater 1 (9 years of experience) had an accuracy rate of 68%, whereas rater 2 (20 years of experience) had an accuracy rate of 82% (Table 2). Interrater reliability was moderate, 74% for right SN (65/88, $\kappa = 0.487$, p < .001) and 72% for left SN (63/88, $\kappa = 0.437$, p < .001). After consensus reading, SWI had a high specificity at 92% but relatively moderate sensitivity at 74% (Table 2).

After consensus reading, a total of 15 cases were excluded due to motion-related very poor image quality, among them 3 healthy controls, 11 parkinsonism patients, and 1 nonparkinsonism patient. These cases were excluded from the consensus reading and from the subsequent comparison analysis with DaTSCAN SPECT. Three of the excluded SWI cases were performed on the GE scanner and 12 on the Philips scanner. In terms of image quality, average score was 3.0 (±1.4) for Philips and 2.0 (±1.3) for GE, with Philips being associated with significantly lower image quality compared to GE (p < .001). There were no significant differences among diagnostic groups in terms of image quality. Figure 1 illustrates normal and abnormal cases as acquired with the two different scanners.

Performance of DaTSCAN SPECT

Both raters had a high accuracy rate at 90%-94% (Table 2). Interrater reliability was very good, 93% for right striatum (67/72, $x = 0.834$, p < .001) and 93% for left striatum (67/72, $x = 0.830$, p < .001). After consensus reading, DaTSCAN SPECT had a high sensitivity at 93%,
### Diagnostic performance of SWI and DaTSCAN SPECT

<table>
<thead>
<tr>
<th>Performance</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rater 1</td>
<td>82%</td>
<td>51%</td>
<td>68%</td>
<td>70%</td>
<td>68%</td>
</tr>
<tr>
<td>Rater 2</td>
<td>79%</td>
<td>85%</td>
<td>86%</td>
<td>77%</td>
<td>82%</td>
</tr>
<tr>
<td>Consensus reading</td>
<td>74%</td>
<td>92%</td>
<td>91%</td>
<td>76%</td>
<td>83%</td>
</tr>
<tr>
<td>DaTSCAN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rater 1</td>
<td>94%</td>
<td>78%</td>
<td>93%</td>
<td>82%</td>
<td>90%</td>
</tr>
<tr>
<td>Rater 2</td>
<td>94%</td>
<td>89%</td>
<td>96%</td>
<td>84%</td>
<td>93%</td>
</tr>
<tr>
<td>Consensus reading</td>
<td>93%</td>
<td>83%</td>
<td>94%</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td>Consensus reading (Only abnormal &amp; inconclusive SWI)</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
<td>33%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Inconclusive SWI scans due to motion artifacts were excluded from the analysis, resulting in different number of participants for Rater 1, Rater 2, and consensus reading. Abbreviations: n, number of participants; NPV, negative predictive value; PPV, positive predictive value.

**Concordance and ROC analysis**

The concordance rate between abnormal SWI and ipsilaterally abnormal DaTSCAN SPECT was 77% (46/60) for the right hemisphere and 82% (49/60) for the left hemisphere. McNemar test showed significant discordance in both hemispheres (right hemisphere, \( p = .01 \); left hemisphere, \( p = .01 \)). As cases with unilaterally abnormal scans were considered abnormal, concordance rate for both hemispheres was 77% (46/60), which was significantly discordant according to McNemar test (\( p = .01 \)). Figure 2 illustrates the ROC curves for these two imaging modalities. There was no difference for the area under the curve (.88 for DaTSCAN SPECT, .83 for SWI, \( p > .05 \)).

**False positive and false negative cases**

Among healthy participants, there were three false positive SWI cases, two of which had fair image quality (grade 3) and one had poor image quality (grade 4). All of them were acquired on the Philips scanner. Moreover, we identified 11 false negative SWI cases, with an average image quality score of 2.3 (median grade 2: good image quality). Six of those cases were acquired on the Philips scanner and five on the GE scanner. DaTSCAN SPECT was normal in one of these patients, who was diagnosed with MSA-cerebellar type (C), and abnormal in the remaining 10 patients (7 PD and 3 with undefined parkinsonism). Additionally, we identified four false negative DaTSCAN SPECT cases: 2 patients with MSA-C, 1 with Corticobasal degeneration (CBD), and 1 with undefined parkinsonism. SWI was abnormal in 1 MSA-C patient and the CBD patient. Among nonparkinsonism patients, there were three false positive DaTSCAN SPECT cases: 1 patient with mild cognitive impairment and 2 patients with essential tremor. SWI was
FIGURE 3  Examples of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) scans from the two imaging modalities that were employed in this study. Arrows indicate nigrosome-1 normal in all three cases. Figure 3 summarizes possible combinations of SWI and DaTSCAN uptake in our cohort.

DISCUSSION

This study set out to assess whether SWI can be used as a triage tool in patients with suspected parkinsonism. In contrast to previous studies, apart from a strict comparison between SWI and DaTSCAN SPECT in terms of diagnostic accuracy, we also tried to elucidate a meaningful way to best apply those two complimentary tests in a clinical setting, considering pressure on availability and cost. Our findings indicate that an initial examination with SWI can be beneficial, even though the visual assessment of nigrosome-1 is challenging.

SWI had a high specificity of 92% (after consensus reading), whereas DaTSCAN SPECT had a specificity of 83%. Consequently, if nigrosome-1 appears normal in SWI, then parkinsonism can correctly be ruled out in approximately nine out of 10 cases. Moreover, as 73% (11/15) of the participants who were excluded due to very significant motion artifacts were diagnosed with parkinsonism, poor SWI quality due to motion artifacts could serve as an indicator of parkinsonism. In our cohort, SWI had moderate sensitivity of 74%, which is contrary to a previous meta-analysis that reports high sensitivity of 94%. Moreover, the specificity of DaTSCAN SPECT in our cohort was lower compared to a previous report (83% as opposed to 93%), but similar to a previous study (80%). However, the diagnostic performance of DaTSCAN SPECT can be further improved by the quantitative analysis that is routinely performed alongside the visual assessment. Evaluating the quantitative analysis was beyond the scope of this study.

DaTSCAN SPECT outperformed SWI in terms of sensitivity and overall diagnostic accuracy. After using SWI as a triage tool and focusing only on patients with abnormal or inconclusive SWI, the diagnostic performance of DaTSCAN SPECT was further improved (Table 2). Our findings support the well-established role of DaTSCAN SPECT in detecting parkinsonism and highlight its importance, especially in cases where nigrosome-1 appears to be abnormal in SWI. This combination of findings provides support for performing SWI as an initial triage tool in patients with suspected parkinsonism, with DaTSCAN SPECT further improving the diagnostic outcome in cases where nigrosome-1 is abnormal or cannot be assessed due to motion artifacts.

However, the correct assessment of SWI is highly dependent on acquisition parameters and rater’s experience. Images from the GE scanner performed better in terms of specificity and had significantly better image quality compared to those from the Philips scanner. This can be attributed to the fact the GE employs a multi-echo sequence, resulting in smooth images, whereas Philips uses a single-echo sequence, which produces a more granular appearance of the brain. Similarly, the experienced rater outperformed the less experienced rater in terms of overall diagnostic accuracy (82% as opposed to 68%). The importance of rater’s experience in correctly assessing the nigrosome-1 has also been evident in a previous study.

Rater’s experience and different acquisition parameters between the two MRI vendors can to certain extent explain the significant discordance between SWI and DaTSCAN SPECT in our cohort, which is contrary to the significant concordance rate that was previously reported by Bae et al. The contribution of image quality to correct diagnosis is further emphasized by the three false positive SWI cases (all of them acquired on Philips), where motion artifacts were considerable to significant. However, potential preclinical parkinsonism cannot completely be ruled out in these cases. On the contrary, SWI was normal in three false positive DaTSCAN SPECT cases, strengthening the clinical diagnosis.

There were 2 MSA-C patients within our cohort, both of whom had normal DaTSCAN SPECT, which is in line with previous literature. Only 1 of these patients had normal SWI. One limitation of our study is the short follow-up period, with some patients receiving a clinical diagnosis 3 months after undergoing DaTSCAN SPECT. Subsequently, 6 patients were classified as unspecified APS, and 10 patients as unspecified parkinsonism. Even though misdiagnosis cannot be ruled out, our study has focused on differentiating parkinsonism from nonparkinsonism, and potential misdiagnosis within the group of parkinsonism would not alter our results. Another limitation of this study is that healthy controls were not
examined with DaTSCAN SPECT. According to a previous study, SWI may be a biomarker for premotor stages of PD, but this issue was not addressed in our study. Moreover, the number of participants was not equally distributed between Philips and GE, which may potentially have impacted our results.

The high specificity of SWI indicates that the visual assessment of nigrosome-1 could serve as a triage tool for patients with suspected parkinsonism. Our findings support that patients with normal nigrosome-1 are unlikely to suffer from parkinsonism. Moreover, the diagnostic performance of DaTSCAN SPECT can be further improved, by preselecting patients with abnormal or inconclusive SWI. However, to overcome the challenges of evaluating SWI, neuroimaging centers need to become familiar with the acquisition parameters and image quality of different MRI vendors.

ACKNOWLEDGMENT AND DISCLOSURE

The authors would like to thank the staff at the department of Nuclear Medicine for facilitating all MRI examinations in conjunction to DaTSCAN SPECT, and Charlotte Brage, research coordinator at the Department of Radiology, for her administrative help. The authors declare no conflict of interest.

ORCID

Charalampos Georgiopoulos https://orcid.org/0000-0001-8850-3742

REFERENCES
