Diagnostic Reliability of I-123 Ioflupane SPECT Imaging (DaTscan) in Movement Disorders

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BACKGROUND

- Brain SPECT with I-123 ioflupane is approved by the US FDA in January 2011 (DaTscan, GE Healthcare, Princeton, NJ) and is used to detect presynaptic dopaminergic deficit in Parkinson's disease (PD) and other parkinsonian disorders.
- Visual assessment of dopamine transporter (DAT) imaging is a fast image interpretation technique and can be performed by a practicing neurologist.
- Benamer's grading criteria for visual assessment [1] have been the most widely used classification in research settings, but it has not gained popularity in routine clinical practice.
- To date, most clinicians do not use any grading classification and report the results as purely descriptive interpretation of the findings.
- Lack of a unified rating scale for visual assessment of DAT imaging limits its utility in multicenter studies and in tracking disease progression.
- Study aims:
  - To assess diagnostic reliability of I-123 ioflupane studies in PD.
  - To assess accuracy of visual assessment of I-123 ioflupane studies in routine clinical practice.
  - To assess accuracy of the Benamer's criteria for visual assessment of I-123 ioflupane studies.

METHODS

- All patients and healthy controls were examined by a movement disorders neurologist and given a clinical diagnosis prior to I-123 ioflupane study.
- 9 raters (5 neurologists and 4 non-neurologists), blinded to the clinical diagnosis, reviewed 21 I-123 ioflupane studies.
- Raters were asked to:
  - Identify abnormal scans.
  - Grade scans according to the Benamer's criteria (grades 0-3).
  - Identify the more affected side in case of asymmetric radiotracer uptake (left side, right side, both affected equally).
- All images were then reviewed again and discussed by all the raters, focusing on identifying misalignment and other technical artifacts, and final identification of normal vs abnormal scans by the raters consensus was registered.
- Statistical analysis:
  - Consensus image interpretation was used to calculate sensitivity, specificity, positive and negative predictive values.
  - Individual image interpretation was used to calculate inter-rater reliability.

RESULTS

Table 1: Subjects demographic data

	PD (n-13)	Non-PD (n-7)	Total (n-20)
Age, years (mean ± SD)	45-72 (58.14 ± 9.1)	52-72 (61.86 ± 7.6)	45-72 (59.4 ± 8.6)
Male / Female	7 / 6	4 / 3	11 / 9
MDS UPDRS III (mean ± SD)	10-42 (24.5 ± 8.33)	n/a	n/a
Disease duration, years (mean + SD)	1-9 (4.0 ± 2.22)	n/a	n/a

- PD patients were allowed to continue their PD medications prior to DAT imaging
- 1 PD patient had 2 studies withiin11 months

RESULTS (continued…)

Table 2. Diagnostic reliability of visual interpretation of I-123 ioflupane studies

Sensitivity	1.0
Specificity	0.71
Positive predictive value	0.88
Negative predictive value	1.0
False positive scans	2 (1 HC, 1 ET)
False negative scans	0
Inter-rater reliability:	
for detecting abnormal scans	0.95
for grading abnormal scans	0.90
for detecting asymmetry of abnormal scans	0.79

- 2 false positive results – 1 HC and 1 ET (mildly decreased radioligand uptake).
- Raters had difficulty deciding between Benamer's grade 1 and 2 (6 cases), and between grade 2 and 3 (3 cases). See examples of "difficult scans" in figure 1.

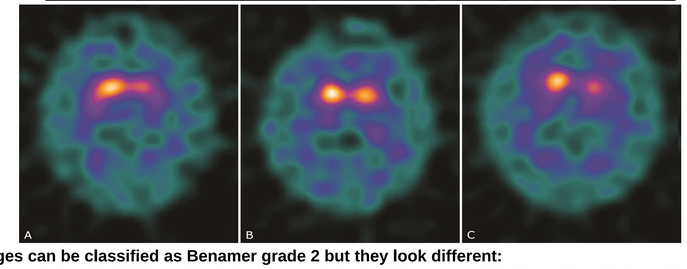
Table 3. Interpretation of I-123 ioflupane studies by neurologists and non-neurologists

	Sensitivity	Specificity	NPV	PPV
Neurologists (n-5):	1.0	0.49	1.0	0.80
Movement disorders specialists (n-2)	1.0	0.57	1.0	0.82
Postdoctoral movement disorders fellows (n-3)	1.0	0.43	1.0	0.78
Non-neurologists (n-4):	1.0	0.75	1.0	0.89
Nuclear medicine physicians (n-2)	1.0	0.71	1.0	0.88
Others (nuclear medicine technologist, research coordinator) (n-2)	1.0	0.79	1.0	0.90
Total (n-9)	1.0	0.71	1.0	0.88

DISCUSSION

- Previous studies reported sensitivity 0.52-1.0, specificity 0.7-1.0, diagnostic accuracy 0.81-0.93, and inter-rater reliability 0.49-1.0 for DAT imaging with I-123 ioflupane or Tc 99m TRODAT in parkinsonian disorders [1-10].
- Diagnostic reliability of visual assessment and semi-quantitative analysis of DAT imaging was found to be similar [3,6,8].
- Our study also demonstrated high diagnostic reliability of visual image interpretation by the raters with different background and varying levels of expertise in DAT imaging.
- Identifying previously missed misalignment and other technical artifacts during the raters consensus review improved specificity of the scans interpretation.
- Abnormal I-123 ioflupane study in one ET patient might be another illustration of a possible overlap between ET and PD [11-12] rather than false-positive study.
- All patients with clinical diagnosis of PD had abnormal DAT imaging studies indicating high accuracy of clinical diagnosis in a tertiary movement disorders referral center [13-14].
- Benamer's grading criteria fail to cover all possible patterns of abnormal radioligand uptake (see Figure 1).

Figure 1. Comparison of I-123 ioflupane study interpretation using Benamer's criteria (BC) and a new proposed grading system (NGS)



All images can be classified as Benamer grade 2 but they look different:
1A – BC grade 1 or 2; NGS– moderately abnormal study with asymmetric dopaminergic loss Grade 2A (R-1, L-3).
1B – BC grade 2 scan; NGS– moderately abnormal study with symmetric dopaminergic loss, Grade 2B (R-2, L-2).
1C – BC grade 2 or 3; NGS – markedly abnormal study with asymmetric dopaminergic loss, Grade 3A (R-2, L-3).

Benamer's classification	Definition
Normal	Tracer uptake bilaterally in putamen and caudate and largely symmetric
Abnormal grade 1	Asymmetric uptake with normal or almost normal putamen activity in one hemisphere, and with a more marked reduction in the contralateral putamen
Abnormal grade 2	Significant bilateral reduction in putamen uptake with activity confined to the caudate nuclei
Abnormal grade 3	Virtually absent uptake bilaterally affecting both putamen and caudate nuclei

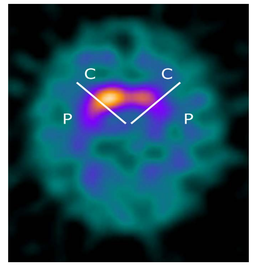
DISCUSSION (continued…)

- We propose an alternative grading system for visual assessment of DAT imaging studies:
  - Analyze caudate (C) and putamen (P) separately on each side and assign the following scores: 0 = normal uptake; 1 = decreased uptake; 2 = absent or nearly absent uptake;
  - Calculate a C+P score for each side and then calculate a total score for both sides (right C+P plus left C+P) (see Figure 2 for an example);
  - Assign Grade 0 to 4 depending on a total score calculated for both striata (Table 4);
  - For Grades 1-3, identify scans as Type A (asymmetric dopaminergic deficit) if the C+P scores are different on both sides, or Type B (symmetric dopaminergic deficit) if the C+P scores are the same on both sides.

Table 4. New grading system for visual assessment of DAT imaging studies

Grades	Description	
Grade 0	Normal scan (score 0 on both sides, total score of 0)	
Grade 1	Mildly abnormal (total score of 1-2 that can consist of score 0-1 on each side or score 2 on one side only)	Grade 1-3: Type A - score is different for two sides – asymmetric dopaminergic loss; Type B - score is the same for both sides – symmetric dopaminergic loss
Grade 2	Moderately abnormal (total score of 3-4 that can consist of score 1-2 on each side or score 3-4 on one side only)	
Grade 3	Markedly abnormal (total score of 5-6 that can consist of score 2-4 on each side)	
Grade 4	Severely abnormal (total score of 7-8)	

Figure 2. Example of interpretation of I-123 ioflupane study using new grading classification



1. Rate caudate (C) and putamen (P) separately on each side.
R side: normal uptake in caudate (score 0) and decreased uptake in putamen (score 1).
C+P score for the right side is 0+1=1.
L side: decreased uptake in caudate (score 1) and absent uptake in putamen (score 2).
C+P score for the left side is 1+2=3.
2. Total score for this image is the sum of the C+P scores on the right and on the left. It is 1+3=4.
3. Total score 4 corresponds to Grade 2.
4. Different C+P score on R and L indicates type A (asymmetric dopaminergic loss).
Report for this scan concludes: Moderately abnormal study with asymmetric dopaminergic loss, Grade 2A (R-1, L-3)

- New grading classification will need to be tested to assess its utility.
- This classification can enhance utility of visual assessment of DAT imaging in routine clinical practice, multicenter studies and in tracking progression of dopaminergic deficiency.

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