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Diagnostic accuracy of DaTSCAN in Parkinson's and clinically uncertain parkinsonism

Appraised by Kevin Galbraith, January 2016
Update due 2019

Clinical question

Is DaTSCAN an accurate diagnostic tool in Parkinson's and clinically uncertain parkinsonism?

Clinical bottom line

1. Four systematic reviews were found on the accuracy of DaTSCAN. All four were limited in terms of their search methods: all were susceptible to publication bias, and one used a single bibliographic database, raising the probability that important studies might have been missed.

2. Primary studies are difficult to compare because of:
   • recruitment, in some, of patients with prior confirmation of diagnosis
   • variation in the gold standard test used as a comparator
   • variation in the methods of DaTSCAN interpretation (visual or semiquantitative)

3. There is a lack of studies comparing DaTSCAN diagnosis with the ideal gold standard of post-mortem pathological diagnosis, despite DaTSCAN having been licensed for 15 years. There is also a lack of studies applying blinded assessment.

4. There is moderate evidence from these systematic reviews that DaTSCAN can accurately diagnose a loss of nigrostriatal dopamine transporters (DaT). It is therefore helpful in differentiating those parkinsonian conditions that are associated with nigrostriatial loss of DaT from those that are not, and from essential tremor.

5. Systematic review evidence of the accuracy of DaTSCAN in diagnosing early Parkinson's versus healthy normality reported low sensitivity from a single study of only 38%. In other words, most of those with early Parkinson's had a normal DaTSCAN. There was no clear evidence that DaTSCAN is accurate in diagnosing early Parkinson's.

Background

Parkinson's can be difficult to differentiate from other parkinsonian syndromes or essential tremor. DaTSCAN, which measures the density of nigrostriatal dopamine transporter sites, may in some cases help the clinician make the correct diagnosis. However, its clinical utility has been questioned, as most evaluations have compared DaTSCAN with clinical examination, which has itself been found to be incorrect in 6% to 25% of cases. [1] The ideal gold standard comparator would be neuropathological diagnosis at post mortem.

Search terms

Nervous System Diseases / [Radionuclide imaging] AND (Tomography, Emission-Computed, Single-Photon / OR DaTSCAN OR dopaminergic imaging OR FP-CIT OR ioflupane OR Tropanes / [Diagnostic Use] OR tropanes) AND (Sensitivity And Specificity / OR sensitivity OR specificity OR accuracy)

Search strategy

Ovid Medline, adapted for Embase and Cochrane Library, and Web of Science (all databases). All searches up to December 2015.

Evidence

From 174 relevant articles, this CAT identified four systematic reviews addressing diagnostic accuracy of DaTSCAN,[1-4] three of which are meta-analyses.[2-4] These four studies were selected for critical appraisal as potential level 1 evidence.

Suwijn SR, van Boheemen CJ, de Haan RJ, Tissingh G, Booij J, de Bie RM. The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. EJNMMI Research. 2015;5(1):12.

Summary

Systematic review to assess the diagnostic accuracy of DAT SPECT imaging (which includes DaTSCAN). Inclusion criteria required clinical diagnosis of Parkinson's or clinically uncertain parkinsonism, and that patients had either:

- at least one DAT SPECT plus post mortem evaluation or
- at least two DAT SPECT, performed at least two years apart

Of four included studies assessing DaTSCAN, only one included patients with diagnostic uncertainty (sensitivity and specificity to detect nigrostriatial cell loss both 98%), and only one included post mortem evaluation (no calculation of sensitivity and specificity). The conclusion was that DAT SPECT imaging "seems to be accurate to detect nigrostriatial cell loss in patients with parkinsonism." The following points should be considered:

- No search was undertaken for unpublished studies, making the review susceptible to publication bias.
- The only study with neuropathological evaluation did not provide data pertaining to accuracy.

Strength of evidence: level 2

(1 = strongest; 5 = weakest)*

*OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=5653

Brigo F, Matinella A, Erro R, Tinazzi M. [123I] FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: A meta-analysis. European Journal of Neurology. 2014;21(11):1369-e90.

Summary

Meta-analysis of the accuracy of DaTSCAN in differentiating Parkinson's disease (PD) from vascular parkinsonism (VP) or drug-induced parkinsonism (DIP). Excluded studies in which enrolled patients had a clinically established diagnosis of PD, VP or DIP prior to DaTSCAN.

Five studies were included, yielding pooled sensitivity (Sn) and specificity (Sp) (95% CI) as follows:

- PD v VP Sn 0.86 (0.81 to 0.9), Sp 0.83 (0.68 to 0.93).

- PD v DIP Sn 0.86 (0.81 to 0.9), Sp 0.94 (0.70 to 1.00).

The authors concluded that DaTSCAN might accurately differentiate between early PD and secondary parkinsonian conditions (namely, vascular or drug-induced) in patients with clinically uncertain parkinsonism. However, they highlighted methodological limits of included studies, and concluded that this prevented definitive conclusions on the role of DaTSCAN in this context. The following further points should be considered:

- No search was undertaken for unpublished studies, making the review susceptible to publication bias.

- The risk of bias within included studies was high. Diagnostic criteria were unclear: in three studies it was unclear whether enrolment had been random or consecutive; four did not report the interval between DaTSCAN and clinical diagnosis at follow up; and two were unclear regarding continuation of medications. Furthermore, there was potential multiple publication bias in two studies (which could lead to overestimation of results), and possible expectation bias in three (unclear whether DaTSCANS were interpreted blind to clinical examination findings).

- There was considerable statistical heterogeneity in results. This could be due to possible demographic imbalance among subjects, or to possible unreported variation in diagnostic criteria. One might question the appropriateness of pooling results.

Strength of evidence:

level 3 (1 = strongest; 5 = weakest)*
*OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=5653

Vlaar AM, van Kroonenburgh MJ, Kessels AG, Weber WE. Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. BMC neurology. 2007;7(1):27.

Summary

A meta-analysis evaluating the diagnostic accuracy of both pre- and post-synaptic SPECT on the differential diagnosis of Parkinson's. Studies were included if subjects were in one of the following categories:

- Undergoing DaTSCAN because of clinical uncertainty.

- Already diagnosed as having a parkinsonian syndrome – DaTSCAN used as a means to differentiate between conditions.

- Known early Parkinson's in which DaTSCAN was tested as a means to provide early diagnosis versus healthy controls.

The search included only studies which defined positive scans (reduced uptake) as 2SD below health controls, or which provided sufficient data to recalculate the results using 2SD as a cut-off. The values/ranges for sensitivity (Sn) and specificity (Sp) for studies of DaTSCAN were as follows:

- Early Parkinson's disease (PD) v normal: one study, Sn 38% Sp 100%.

- PD v essential tremor (ET): four studies, Sn 80-98% Sp 93-100% (one error noted during appraisal – corrected figures presented here).

- PD v vascular parkinsonism (VP): two studies, Sn 80-88% Sp 100% in both.

- PD v atypical parkinsonian syndromes (APS – consisting here of multiple system atrophy and progressive supranuclear palsy): three studies, Sn 80-98% Sp 4-33%.

The authors concluded that SPECT with presynaptic radiotracers (such as DaTSCAN) is relatively accurate to differentiate patients with early PD from normal, PD from ET and PD from VP. The accuracy of SPECT with both presynaptic and postsynaptic tracers to differentiate between PD and APS is relatively low. The following points should also be considered:

- No search was undertaken for unpublished studies, making the review susceptible to publication bias.

- None of the five studies evaluating DaTSCAN used the ideal (neuropathological) gold standard comparator. Two used clinical criteria with follow-up, two used clinical criteria without follow-up, and one was unclear in this respect.

- The single study evaluating DaTSCAN in early PD v normal yielded what was reported in the meta-analysis as a low Sn of 38%.[5] To attempt to understand this, the full text was examined as part of this appraisal. It was found that the control group comprised patients with ET or DIP rather than no condition. However, this does not explain the low sensitivity. The data quoted in the meta-analysis were not identified, and were presumed to result from recalculation to standardise the cut-off value. No further attempt was made to clarify the data. The authors of the meta-analysis proposed referral from a tertiary centre as a possible reason for the low sensitivity. However, the case mix in the study did not appear to represent a diagnostic challenge beyond what one might expect routinely.

- In all five studies evaluating DaTSCAN, the region of interest for uptake was determined using a template. This should be considered when comparing with other studies using different techniques.

Strength of evidence:

level 3 (1 = strongest; 5 = weakest)*
*OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. www.cebm.net/index.aspx?o=5653

Papathanasiou ND, Boutsiadis A, Dickson J, Bomanji JB. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: A meta-analysis of published studies. Parkinsonism and Related Disorders. 2012;18(3):225-9.

Summary

A meta-analysis evaluating the diagnostic accuracy of DaTSCAN in dementia with Lewy bodies (DLB). The search included studies of uncertain cases in which DaTSCAN was performed to differentiate between DLB and non-DLB dementia, and studies of patients with an established diagnosis of DLB, non-DLB dementia, or normalcy, against which the diagnostic accuracy of DaTSCAN was tested. Four included studies (total 419 subjects) yielded a pooled sensitivity (95% CI) of 86.5% (72-94.1%) and specificity (95% CI) of 93.6% (88.5-96.6%) in differentiating DLB versus no DLB. The pooled Mantel-Haenszel diagnostic odds ratio (DOR) was 48.95 (95% CI 26.16-91.59). The authors concluded that: "allowing for the small number of studies included, results showed high diagnostic accuracy of DaTSCAN in DLB diagnosis, especially in terms of specificity." The following points should also be noted:

- Only one bibliographic database was searched, and there was no search for unpublished studies. Some relevant studies may have been missed, and the meta-analysis may be susceptible to publication bias. A funnel plot is reported as non-indicative of publication bias – however, there does appear to be a paucity of small studies with negative results, which characterise publication bias.
- Only one study compared diagnosis by DaTSCAN with the gold standard neuropathological diagnosis.

- The quality of included studies is not clearly reported. Only two studies employed blinding in DaTSCAN interpretation.

- One large study accounted for more than half of the meta-analysis population, and had 87% weight in the estimation of DOR. However, this study did employ blinding, and presented defined diagnostic criteria.

- Moderate heterogeneity of studies was found (though not statistically significant). Differences in reference standard, interpretation of DaTSCAN (visual or semiquantitative), diagnostic cut-off and use of blinded interpretation should be noted.

Strength of evidence:

level 3 (1 = strongest; 5 = weakest)*

* OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

References

1. Suwijn SR, van Boheemen CJ, de Haan RJ, Tissingh G, Booij J, de Bie RM. The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. EJNMMI Research. 2015;5(1):12.

2. Brigo F, Matinella A, Erro R, Tinazzi M. [123I] FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: A meta-analysis. European Journal of Neurology. 2014;21(11):1369-e90.

3. Papathanasiou ND, Boutsiadis A, Dickson J, Bomanji JB. Diagnostic accuracy of 123I-FP-CIT (DaTSCAN) in dementia with Lewy bodies: A meta-analysis of published studies. Parkinsonism and Related Disorders. 2012;18(3):225-9.

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